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(54) Title: ANTI-SIRP ALPHA ANTIBODIES

(57) Abstract: The present invention relates to anti-SIRPa antibodies, as well as use of these antibodies in the treatment of diseases such as cancer and infectious disease.

ANTI-SIRP alpha ANTIBODIES

[0001] The present application claims the benefit of Netherlands Patent Application 2018708, filed April 13, 2017, and of Netherlands Patent Application 2019166, filed July 3, 2017, each of which is hereby incorporated by reference in its entirety including all tables, figures, and claims.

FIELD OF THE INVENTION

[0002] The present invention relates to anti-SIRPa antibodies, as well as use of these antibodies in the treatment of diseases.

BACKGROUND OF THE INVENTION

[0003] Signal regulatory protein alpha (SIRPα) is membrane glycoprotein from the SIRP family. Members of the SIRP family share certain common structural motifs. These include a transmembrane segment and an N-terminal extracellular domain that contains three Ig-like loops connected by three pairs of disulfide bonds. The C-terminal intracellular domain, however, differs between SIRP family members. SIRPa has an extended intracellular domain containing four tyrosine residues that form two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), while SIRPβ1 contains a lysine residue in the transmembrane domain followed by a short intracellular tail lacking ITIMs serving as a receptor for DAP12. Eight SIRPa single nucleotide polymorphisms have been identified, with the most prevalent being SIRPaV1 and SIRPaV2 (Takenaka et al., *Nat. Immunol.* 2007, 8:1313-23).

[0004] "Eat-me" signals (i.e. "altered self") are extracellular players specifically produced by and displayed on the surface of apoptotic cells, but not healthy cells, and are key to the initiation of phagocytosis by activating phagocytic receptors and subsequent signaling cascades. Eat-me signals require extracellular trafficking in order to be displayed on apoptotic cells. A particular category of eat-me signals is provided by membrane-anchored proteins such as phosphatidylserine (PtdSer) and calreticulin (CRT). Externalized PtdSer binds to its receptors on phagocytes to facilitate clearance of apoptotic cells (a process known as efferocytosis). Likewise, CRT is upregulated on the surface of apoptotic cells and binds to LDL-receptor-related protein 1 (LRP1) on the phagocyte thereby mediating engulfment.

[0005] SIRPa is broadly expressed on phagocytes (e.g., macrophages, granulocytes, and dendritic cells) and acts as an inhibitory receptor through its interaction with a transmembrane protein CD47. This interaction mediates a response referred to as the "don't eat me" signal. This interaction negatively regulates effector function of innate immune cells such as host cell phagocytosis. As CD47 is often present on tumor cells, this "don't eat me" signal is thought to contribute to the resistance of tumors to phagocyte-dependent clearance. Despite the similarities in the extracellular domains of SIRPa and SIRPpi functional differences exist among the SIRP family members. For example, SIRPβ1 does not bind CD47 at detectable levels and so does not mediate the "don't eat me" signal. Instead, SIRPpi is involved in the activation of myeloid cells.

[0006] Disruption of CD47-SIRPa signalling (e.g., by antagonistic monoclonal antibodies that bind to either CD47 or SIRPa) reportedly results in enhanced phagocytosis of both solid and hematopoietic tumor cells, including increased phagocytosis of glioblastoma cells in vitro and significant anti-tumor activity *in vivo.*

SUMMARY OF THE INVENTION

[0007] In a first aspect, the invention provides anti-SIRPa antibodies and antigen binding fragments thereof comprising the structural and functional features specified below.

[0008] In various embodiments, the invention provides an antibody or antigen binding fragment thereof that binds to human SIRPa comprising one, two, or all three of (i), (ii) and (iii): (i) a heavy chain variable region CDRl comprising the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, 3, or more conservative substitutions; (ii) a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, 3, or more conservative substitutions; and/or (iii) a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, 3, or more conservative substitutions.

[0009] In various other embodiments, the invention provides an antibody or antigen binding fragment thereof that binds to human SIRPa comprising one, two, or all three of (i), (ii) and (iii): (i) a heavy chain variable region CDRl comprising the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, 3, or more conservative substitutions; (ii) a heavy chain variable region CDR2 comprising the amino acid sequence of

SEQ ID NO: 70 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, 3, or more conservative substitutions; and/or (iii) a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 71 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, 3, or more conservative substitutions.

[0010] In certain embodiments, the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 75 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 78 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 80 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 82 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 84 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 86 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 88 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 102 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 7 or an amino acid sequence at least 90%, 95%, 97%, 98%', or 99% similar or identical thereto,

SEQ ID NO: 10 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto.

SEQ ID NO: 12 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 14 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 16 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 18 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 30 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto.

[0011] In various embodiments, the invention also provides an antibody or antigen binding fragment thereof that binds to human SIRPa comprising one, two, or all three of (i), (ii) and (iii): (i) a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, 3, or more conservative substitutions; (ii) a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 5 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, 3, or more conservative substitutions; and/or (iii) a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, 3, or more conservative substitutions.

[0012] In various otherembodiments, the invention also provides an antibody or antigen binding fragment thereof that binds to human SIRPa comprising one, two, or all three of (i), (ii) and (iii): (i) a light chain variable region CDRl comprising the amino acid sequence of SEQ ID NO: 72 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, 3, or more conservative substitutions; (ii) a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, 3, or more conservative substitutions; and/or (iii) a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, 3, or more conservative substitutions.

[0013] In certain embodiments, the antibody or antigen binding fragment thereof comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 76 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 90 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 92 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 94 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 96 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 98 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 100 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 104 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 8 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 20 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 22 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 24 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 26 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 28 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 32 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto.

[0014] In various embodiments, the invention provides an antibody or antigen binding fragment thereof that binds to human SIRPa comprising:

(i) a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, 3, or more conservative substitutions; (ii) a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, 3, or more conservative substitutions; and/or (iii) a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, 3, or more conservative substitutions;

and

(iv) a light chain variable region CDRl comprising the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, 3, or more conservative substitutions; (v) a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 5 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, 3, or more conservative substitutions; and/or (vi) a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, 3, or more conservative substitutions.

[0015] In various other embodiments, the invention provides an antibody or antigen binding fragment thereof that binds to human SIRPa comprising:

(i) a heavy chain variable region CDRl comprising the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, 3, or more conservative substitutions; (ii) a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 70 or an amino acid sequence differing from SEQ ID NO:

2 by 1, 2, 3, or more conservative substitutions; and/or (iii) a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 71 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, 3, or more conservative substitutions;

and

(iv) a light chain variable region CDRl comprising the amino acid sequence of SEQ ID NO: 72 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, 3, or more conservative substitutions; (v) a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, 3, or more conservative substitutions; and/or (vi) a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence differing from SEQ ID NO: 74 by 1, 2, 3, or more conservative substitutions.

[0016] In still other embodiments, the invention provides an antibody or antigen binding fragment thereof that binds to human SIRPα comprising:

a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 7 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 10 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 12 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 14 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 16 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 18 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 30 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto;

and

a light chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 8 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 20 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 22 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 24 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 26 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 28 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 32 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto.

[0017] In still other embodiments, the invention provides an antibody or antigen binding fragment thereof that binds to human SIRPa comprising:

a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 75 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 78 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 80 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 82 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 84 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 86 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 88 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto; and

SEQ ID NO: 102 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

and

a light chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 76 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 90 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 92 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 94 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 96 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 98 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 100 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 104 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[001 8] In this context, "sequence similarity" is based on the extent of identity combined with the extent of conservative changes. The percentage of "sequence similarity" is the percentage of amino acids or nucleotides which is either identical or conservatively changed viz. "sequence similarity" = percent sequence identity) + percent conservative changes). Thus, for the purpose of this invention "conservative changes" and "identity" are considered to be species of the broader term "similarity". Thus, whenever the term sequence "similarity" is used it embraces sequence "identity" and "conservative changes". According to certain embodiments the conservative changes are disregarded and the percent sequence similarity refers to percent sequence identity. In certain embodiments, the changes in a sequence permitted by the referenced percent sequence identity are all or nearly all conservative changes; that is, when a sequence is 90% identical, the remaining 10% are all or nearly all conservative changes. The term "nearly all" in this context refers to at least 75% of the permitted sequence changes are conservative changes, more preferably at least 85%, still more preferably at least 90%, and most preferably at least 95%. In certain embodiments of antibody heavy and/or light chains, the permitted sequence changes are within the framework regions and not in the CDRs.

[0019] Preferably said antibody has a heavy chain according to SEQ ID NO: 7. Further preferably said antibody has a light chain according to SEQ ID NO: 8. More preferably, the heavy chain is chosen from any of SEQ ID NO: 10, 12, 14, 16, 18, or 30. More preferably, the light chain is chosen from any of SEQ ID NO: 20, 22, 24, 26, 28, or 32.

[0020] Alternatively, said antibody has a heavy chain according to SEQ ID NO: 75. Further preferably said antibody has a light chain according to SEQ ID NO: 76. More preferably, the heavy chain is chosen from any of SEQ ID NO: 78, 80, 82, 84, 86, 88 or 102. More preferably, the light chain is chosen from any of SEQ ID NO: 90, 92, 94, 96, 98, 100 or 104.

[0021] In any of the above embodiments, the antibody or antigen binding fragment thereof may be isolated, as that term is defined herein.

[0022] In any of the above embodiments, the antibody or antigen binding fragment thereof is a recombinant antibody, as that term is defined herein.

[0023] In any of the above embodiments, the antibody or antigen binding fragment thereof is a full-length antibody, as that term is defined herein.

[0024] Antibodies or antigen binding fragments of the present invention may be obtained from a variety of species. For example, the antibodies of the present invention may comprise immunoglobulin sequences which are rabbit, mouse, rat, guinea pig, chicken, goal, sheep, donkey, human, llama or camelid sequences, or combinations of such sequences (so-called chimeric antibodies). Most preferably, the antibodies or antigen binding fragments are human or humanized antibodies or antigen binding fragments.

[0025] The term antibody includes antigen-binding portions, i.e., "antigen binding sites," (e.g., fragments, subsequences, complementarity determining regions (CDRs)) that retain capacity to bind antigen, including (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_Hl domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_Hl domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Single chain antibodies are also included by reference in the term "antibody." Preferred therapeutic antibodies are intact IgG antibodies. The term "intact IgG" as used herein is meant as a polypeptide belonging to the class of antibodies that are substantially encoded by a recognized immunoglobulin gamma gene. In humans this class comprises IgGl, IgG2, IgG3, and IgG4. In mice this class comprises IgGl, IgG2a, IgG2b, and IgG3. The known Ig domains in the IgG class of antibodies are V_H, Cyl, Cy2, Cy3, V_L, and C_L.

[0026] In any of the above embodiments, the antibody or antigen binding fragment thereof is a human or humanized antibody comprising two heavy chains and two light chains. In one embodiment, the antibody is an IgG. In preferred embodiments, antibody is an IgGl, IgG2, or IgG4, and preferably a human IgGl, IgG2, or IgG4.

[0027] In any of the above-mentioned embodiments, the antibody or antigen binding fragment thereof of the invention can comprise any of the light chain variable regions described

above and a human kappa or lambda light chain constant domain and an IgGl, IgG2, or IgG4 heavy chain constant domain. Exemplary light (kappa) and heavy (IgG2 and IgG4) constant region sequences which may be used in accordance with the invention are recited in SEQ ID NOs: 63, 65, 67 (each a nucleotide sequence), 64, 66, and 68 (each a polypeptide sequence).

[0028] By way of example only, in various embodiments such antibody or antigen binding fragment thereof comprises one of the following combinations of heavy chain sequence / light chain variable region sequences:

SEQ ID NO: 10 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.HlLl)

SEQ ID NO: 10 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.HlL2)

SEQ ID NO: 10 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.HlL3)

SEQ ID NO: 10 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.HlL4)

SEQ ID NO: 10 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.HlL5)

SEQ ID NO: 12 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H2Ll)

SEQ ID NO: 12 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H2L2)

SEQ ID NO: 12 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H2L3)

SEQ ID NO: 12 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H2L4)

SEQ ID NO: 12 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H2L5)

SEQ ID NO: 14 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H3Ll)

SEQ ID NO: 14 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H3L2)

SEQ ID NO: 14 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H3L3)

SEQ ID NO: 14 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H3L4)

SEQ ID NO: 14 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H3L5)

SEQ ID NO: 16 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H4Ll)

SEQ ID NO: 16 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H4L2)

SEQ ID NO: 16 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H4L3)

SEQ ID NO: 16 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H4L4)

SEQ ID NO: 16 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H4L5)

SEQ ID NO: 18 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H5Ll)

SEQ ID NO: 18 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H5L2)

SEQ ID NO: 18 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H5L3)

SEQ ID NO: 18 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H5L4)

SEQ ID NO: 18 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H5L5)

SEQ ID NO: 78 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.HlLl)

SEQ ID NO: 78 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.HlL2)

SEQ ID NO: 78 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.HlL3)

SEQ ID NO: 78 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.HlL4)

SEQ ID NO: 78 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.HlL5)

SEQ ID NO: 78 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.HlL6)

SEQ ID NO: 80 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H2Ll)

SEQ ID NO: 80 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H2L2)

SEQ ID NO: 80 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H2L3)

SEQ ID NO: 80 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H2L4)

SEQ ID NO: 80 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H2L5)

SEQ ID NO: 80 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H2L6)

SEQ ID NO: 82 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H3Ll)

SEQ ID NO: 82 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H3L2)

SEQ ID NO: 82 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H3L3)

SEQ ID NO: 82 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H3L4)

SEQ ID NO: 82 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H3L5)

SEQ ID NO: 82 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H3L6)

SEQ ID NO: 84 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H4Ll)

SEQ ID NO: 84 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H4L2)

SEQ ID NO: 84 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H4L3)

SEQ ID NO: 84 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H4L4)

SEQ ID NO: 84 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H4L5)

SEQ ID NO: 84 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H4L6)

SEQ ID NO: 86 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H5Ll)

SEQ ID NO: 86 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H5L2)

SEQ ID NO: 86 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H5L3)

SEQ ID NO: 86 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H5L4)

SEQ ID NO: 86 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H5L5)

SEQ ID NO: 86 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H5L6)

SEQ ID NO: 88 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H6Ll)

SEQ ID NO: 88 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H6L2)

SEQ ID NO: 88 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H6L3)

SEQ ID NO: 88 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H6L4)

SEQ ID NO: 88 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H6L5)

SEQ ID NO: 88 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H6L6)

or, in each case, at least 90%, 95%, 97%, 98%, or 99% similar or identical to a respective SEQ ID NO.

[0029] In some preferred embodiments, the antibody or antigen binding fragment is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 10 and each light chain comprises SEQ ID NO: 20, or, in each case, at least 90%, 95%, 97%, 98%, or 99% similar or identical to a respective SEQ ID NO, and

most preferably each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgGl, IgG2, or IgG4 constant region.

[0030] In other preferred embodiments, the antibody or antigen binding fragment is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 16 and each light chain comprises SEQ ID NO: 28, or, in each case, at least 90%, 95%, 97%, 98%, or 99% similar or identical to a respective SEQ ID NO, and most preferably each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgGl, IgG2, or IgG4 constant region.

[0031] In still other preferred embodiments, the antibody or antigen binding fragment is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 18 and each light chain comprises SEQ ID NO: 20, or, in each case, at least 90%, 95%, 97%, 98%, or 99% similar or identical to a respective SEQ ID NO, and most preferably each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgGl, IgG2, or IgG4 constant region.

[0032] In some preferred embodiments, the antibody or antigen binding fragment is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 90, or, in each case, at least 90%, 95%, 97%, 98%, or 99% similar or identical to a respective SEQ ID NO, and most preferably each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgGl, IgG2, or IgG4 constant region.

[0033] In some preferred embodiments, the antibody or antigen binding fragment is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 92, or, in each case, at least 90%, 95%, 97%, 98%, or 99% similar or identical to a respective SEQ ID NO, and most preferably each light chain comprises a human kappa light chain or a human lambda light

chain constant domain; and each heavy chain comprises a human IgGl, IgG2, or IgG4 constant region.

[0034] In some preferred embodiments, the antibody or antigen binding fragment is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 96, or, in each case, at least 90%, 95%, 97%, 98%, or 99% similar or identical to a respective SEQ ID NO, and most preferably each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgGl, IgG2, or IgG4 constant region.

[0035] In one embodiment, the anti-SIRPa antibody of the invention comprises a full length antibody structure having two light chains and two heavy chains as recited above, wherein each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgGl constant region.

[0036] In one embodiment, the anti-SIRPa antibody of the invention comprises a full length antibody structure having two light chains and two heavy chains as recited above, wherein each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgG2 constant region.

[0037] In one embodiment, the anti-SIRPa antibody of the invention comprises a full-length antibody structure having two light chains and two heavy chains as recited above, wherein each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgG4 constant region.

[0038] In certain embodiments, the antibodies or antigen binding fragments of the present invention have one, two, three, four, or more, and preferably each of, the following functional characteristics:

binds human SIRPaVl protein having the sequence of SEQ ID NO: 34 with an EC_{50} < 1 nM; and exhibits at least a 100-fold higher EC_{50} for SIRPaVl(P74A) having the sequence of SEQ ID NO: 62; and optionally also at least a 100-fold higher EC_{50} for human SIRPpi protein having the sequence of SEQ ID NO: 38 (in each case wherein the reduced EC_{50} is relative to the EC_{50} for human SIRPaVl protein having the sequence of SEQ ID NO: 34, and in each case preferably when measured by cellular ELISA (CELISA) as described hereinafter;

binds to a cell expressing human SIRPaVl protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3nM or less;
binds to a cell expressing human SIRPaV2 protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3nM or less;
does not appreciably bind to SIRPpi protein at an antibody concentration of 50 nM, preferably 67 nM, and more preferably 100 nM; or alternatively at a concentration that is 10-fold greater, preferably 50-fold greater, more preferably 100-fold greater, and still more preferably 200-fold greater than the antibody's EC_{50} for SIRPaVl or SIRPaV2;
inhibits binding between human SIRPa and CD47 with an IC_{50} < 10.0 nM, more preferably < 5.0 nM, still more preferably < 2.5 nM, and most preferably about 1.0 nM or less; and
exhibits a T20 "humanness" score of at least 79, and more preferably 85.

[0039] Preferably, the anti-SIRPa antibodies or antigen binding fragments of the invention do not appreciably bind to one or both of SIRPaVl(P74A) and SIRPpi protein at an antibody concentration of 100 nM or alternatively at an antibody concentration that is 200-fold greater than the antibody's EC_{50} for SIRPaVl or SIRPaV2, while binding to a cell expressing human SIRPaVl protein with an EC50 < 10 nM. Most preferably, each light chain comprises a human kappa light chain or a human lambda light chain constant domain; and each heavy chain comprises a human IgGl, IgG2, or IgG4constant region.

[0040] In certain embodiments, the anti-SIRPa antibody or antigen binding fragment thereof of the invention can be conjugated to at least one therapeutic agent. In one embodiment, the therapeutic agent is a second antibody or fragment thereof, an immunomodulator, a hormone, a cytotoxic agent, an enzyme, a radionuclide, or a second antibody conjugated to at least one immunomodulator, enzyme, radioactive label, hormone, antisense oligonucleotide, or cytotoxic agent, or a combination thereof.

[0041] The invention also provides isolated polypeptides comprising the amino acid sequence of any one of SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 76, 90, 92, 94, 96, 98, 100, 102, 104, 7, 10, 12, 14, 16, 18, 30, 8, 20, 22, 24, 26, 28, and 32 or a fragment of any said sequences, or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0042] The invention also provides isolated nucleic acids encoding anyone of the anti-SIRPa antibodies or antigen binding fragments of the invention.

[0043] In one embodiment, the invention provides an isolated nucleic acid which encodes an amino acid sequence selected from the group consisting of:

SEQ ID NO: 75 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 78 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 80 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 82 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 84 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 86 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 88 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 102 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 10 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 12 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 14 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 16 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 18 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 30 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto.

[0044] In certain embodiments, the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 9 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0045] In certain embodiments, the amino acid sequence of SEQ ID NO: 12 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 11 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0046] In certain embodiments, the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 13 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0047] In certain embodiments, the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 15 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0048] In certain embodiments, the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 17 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0049] In certain embodiments, the amino acid sequence of SEQ ID NO: 30 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 29 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0050] In certain embodiments, the amino acid sequence of SEQ ID NO: 78 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a

nucleic acid sequence of SEQ ID NO: 77 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[005 1] In certain embodiments, the amino acid sequence of SEQ ID NO: 80 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 79 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0052] In certain embodiments, the amino acid sequence of SEQ ID NO: 82 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 8 1 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0053] In certain embodiments, the amino acid sequence of SEQ ID NO: 84 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 83 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0054] In certain embodiments, the amino acid sequence of SEQ ID NO: 86 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 85 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0055] In certain embodiments, the amino acid sequence of SEQ ID NO: 88 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 87 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0056] In certain embodiments, the amino acid sequence of SEQ ID NO: 102 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 101 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0057] In one embodiment, the invention provides an isolated nucleic acid which encodes an amino acid sequence selected from the group consisting of:

SEQ ID NO: 76 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 90 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 92 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 94 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 96 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 98 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 100 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 104 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 8 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 20 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 22 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 24 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 26 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto,

SEQ ID NO: 28 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto, and

SEQ ID NO: 32 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto.

[0058] In certain embodiments, the amino acid sequence of SEQ ID NO: 20 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 19 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0059] In certain embodiments, the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 21 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0060] In certain embodiments, the amino acid sequence of SEQ ID NO: 24 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 23 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0061] In certain embodiments, the amino acid sequence of SEQ ID NO: 26 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 25 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0062] In certain embodiments, the amino acid sequence of SEQ ID NO: 28 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 27 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0063] In certain embodiments, the amino acid sequence of SEQ ID NO: 32 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 31 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0064] In certain embodiments, the amino acid sequence of SEQ ID NO: 90 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 89 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0065] In certain embodiments, the amino acid sequence of SEQ ID NO: 92 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 91 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0066] In certain embodiments, the amino acid sequence of SEQ ID NO: 94 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 93 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0067] In certain embodiments, the amino acid sequence of SEQ ID NO: 96 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 95 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0068] In certain embodiments, the amino acid sequence of SEQ ID NO: 98 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 97 or a nucleic acid sequence at least 90%·, 95%, 97%, 98%, or 99% identical thereto.

[0069] In certain embodiments, the amino acid sequence of SEQ ID NO: 100 or an amino acid sequence at least 90%, 95%·, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 99 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0070] In certain embodiments, the amino acid sequence of SEQ ID NO: 104 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% similar or identical thereto is encoded by a nucleic acid sequence of SEQ ID NO: 103 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0071] In certain embodiments, the isolated nucleic acids of the present invention can optionally comprise a leader sequence.

[0072] Such nucleic acids can comprise one or more of the following nucleic acid sequences:

a nucleic acid sequence of SEQ ID NO: 77 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 79 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 81 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 83 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 85 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 87 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 101 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 89 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 91 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 93 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 95 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 97 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 99 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 101 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 103 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 9 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 11 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 13 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 15 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 17 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 29 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 19 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 21 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 23 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 25 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 27 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and/or

a nucleic acid sequence of SEQ ID NO: 31 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0073] In certain embodiments, the nucleic acid can encode a human or humanized antibody, and includes nucleic acid sequences for both heavy and light chains. In one embodiment, the antibody is an IgG. In preferred embodiments, antibody is an IgGl, IgG2, or IgG4, and preferably a human IgGl, IgG2, or IgG4. In certain embodiments, the light chain sequence comprises a human kappa light chain or a human lambda light chain constant domain sequence; and each heavy chain sequence comprises a human IgGl, IgG2, or IgG4 constant region sequence.

[0074] Preferably, such nucleic acids comprise the following combination heavy chain and light chain variable region nucleic acid sequences:

SEQ ID NO: 9 / SEQ ID NO: 19 (referred to herein as hSIRPa.50A.HlLl)

SEQ ID NO: 9 / SEQ ID NO: 21 (referred to herein as hSIRPa.50A.HlL2)

SEQ ID NO: 9 / SEQ ID NO: 23 (referred to herein as hSIRPa.50A.HlL3)

SEQ ID NO: 9 / SEQ ID NO: 25 (referred to herein as hSIRPa.50A.HlL4)

SEQ ID NO: 9 / SEQ ID NO: 27 (referred to herein as hSIRPa.50A.HlL5)

SEQ ID NO: 11 / SEQ ID NO: 19 (referred to herein as hSIRPa.50A.H2Ll)

SEQ ID NO: 11 / SEQ ID NO: 21 (referred to herein as hSIRPa.50A.H2L2)

SEQ ID NO: 11 / SEQ ID NO: 23 (referred to herein as hSIRPa.50A.H2L3)

SEQ ID NO: 11 / SEQ ID NO: 25 (referred to herein as hSIRPa.50A.H2L4)

SEQ ID NO: 11 / SEQ ID NO: 27 (referred to herein as hSIRPa.50A.H2L5)

SEQ ID NO: 13 / SEQ ID NO: 19 (referred to herein as hSIRPa.50A.H3Ll)

SEQ ID NO: 13 / SEQ ID NO: 21 (referred to herein as hSIRPa.50A.H3L2)

SEQ ID NO: 13 / SEQ ID NO: 23 (referred to herein as hSIRPa.50A.H3L3)

SEQ ID NO: 13 / SEQ ID NO: 25 (referred to herein as hSIRPa.50A.H3L4)

SEQ ID NO: 13 / SEQ ID NO: 27 (referred to herein as hSIRPa.50A.H3L5)

SEQ ID NO: 15 / SEQ ID NO: 19 (referred to herein as hSIRPa.50A.H4Ll)

SEQ ID NO: 15 / SEQ ID NO: 21 (referred to herein as hSIRPa.50A.H4L2)

SEQ ID NO: 15 / SEQ ID NO: 23 (referred to herein as hSIRPa.50A.H4L3)

SEQ ID NO: 15 / SEQ ID NO: 25 (referred to herein as hSIRPa.50A.H4L4)

SEQ ID NO: 15 / SEQ ID NO: 27 (referred to herein as hSIRPa.50A.H4L5)

SEQ ID NO: 17 / SEQ ID NO: 19 (referred to herein as hSIRPa.50A.H5Ll)

SEQ ID NO: 17 / SEQ ID NO: 21 (referred to herein as hSIRPa.50A.H5L2)

SEQ ID NO: 17 / SEQ ID NO: 23 (referred to herein as hSIRPa.50A.H5L3)

SEQ ID NO: 17 / SEQ ID NO: 25 (referred to herein as hSIRPa.50A.H5L4)

SEQ ID NO: 17 / SEQ ID NO: 27 (referred to herein as hSIRPa.50A.H5L5)

SEQ ID NO: 77 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.HlLl)

SEQ ID NO: 77 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.HlL2)

SEQ ID NO: 77 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.HlL3)

SEQ ID NO: 77 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.HlL4)

SEQ ID NO: 77 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.HlL5)

SEQ ID NO: 77 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.HlL6)

SEQ ID NO: 79 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H2Ll)

SEQ ID NO: 79 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H2L2)

SEQ ID NO: 79 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H2L3)

SEQ ID NO: 79 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H2L4)

SEQ ID NO: 79 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H2L5)

SEQ ID NO: 79 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H2L6)

SEQ ID NO: 81 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H3Ll)

SEQ ID NO: 81 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H3L2)

SEQ ID NO: 81 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H3L3)

SEQ ID NO: 81 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H3L4)

SEQ ID NO: 81 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H3L5)

SEQ ID NO: 81 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H3L6)

SEQ ID NO: 83 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H4Ll)

SEQ ID NO: 83 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H4L2)

SEQ ID NO: 83 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H4L3)

SEQ ID NO: 83 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H4L4)

SEQ ID NO: 83 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H4L5)

SEQ ID NO: 83 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H4L6)

SEQ ID NO: 85 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H5Ll)

SEQ ID NO: 85 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H5L2)

SEQ ID NO: 85 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H5L3)

SEQ ID NO: 85 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H5L4)

SEQ ID NO: 85 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H5L5)

SEQ ID NO: 85 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H5L6)

SEQ ID NO: 87 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H6Ll)

SEQ ID NO: 87 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H6L2)

SEQ ID NO: 87 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H6L3)

SEQ ID NO: 87 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H6L4)

SEQ ID NO: 87 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H6L5)

SEQ ID NO: 87 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H6L6)

or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0075] In some preferred embodiments, the nucleic acid comprises SEQ ID NO: 9 and SEQ ID NO: 19 or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0076] In some preferred embodiments, the nucleic acid comprises SEQ ID NO: 15 and SEQ ID NO: 27 or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0077] In some preferred embodiments, the nucleic acid comprises SEQ ID NO: 17 and SEQ ID NO: 19 or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0078] In some preferred embodiments, the nucleic acid comprises SEQ ID NO: 79 and SEQ ID NO: 89 or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0079] In some preferred embodiments, the nucleic acid comprises SEQ ID NO: 79 and SEQ ID NO: 91 or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0080] In some preferred embodiments, the nucleic acid comprises SEQ ID NO: 79 and SEQ ID NO: 95 or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0081] The invention also provides expression vectors comprising one or more nucleic acids of the present invention. An expression vector is a DNA molecule comprising the regulatory elements necessary for transcription of a target nucleic acid in a host cell. Typically, the target nucleic acid is placed under the control of certain regulatory elements including constitutive or inducible promoters, tissue-specific regulatory elements, and enhancer elements. Such a target nucleic acid is said to be "operably linked to" the regulatory elements when the regulating element controls the expression of the gene.

[0082] These isolated nucleic acids and the expression vectors comprising them may be used to express the antibodies of the invention or antigen binding fragments thereof in recombinant

host cells. Thus, the invention also provides host cells comprising an expression vector of the present invention.

[0083] Such expression vectors can comprise one or more of the following nucleic acid sequences operably linked to regulatory elements:

a nucleic acid sequence of SEQ ID NO: 77 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 79 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 81 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 83 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 85 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 87 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 101 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 89 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 91 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 93 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 95 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 97 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 99 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 103 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 11 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 13 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 15 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 17 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 29 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 19 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 21 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 23 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 25 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 27 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and/or

a nucleic acid sequence of SEQ ID NO: 31 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

[0084] In certain embodiments, the expression vector comprises nucleic acid sequences encoding both a heavy chain sequence and a light chain sequence of an anti-SIRPa antibody of the present invention. Preferably, such expression vectors comprise the following combination heavy chain and light chain variable region nucleic acid sequences:

SEQ ID NO: 9 / SEQ ID NO: 19 (referred to herein as hSIRPα.50A.H1L1)

SEQ ID NO: 9 / SEQ ID NO: 21 (referred to herein as hSIRPα.50A.H1L2)

SEQ ID NO: 9 / SEQ ID NO: 23 (referred to herein as hSIRPα.50A.H1L3)

SEQ ID NO: 9 / SEQ ID NO: 25 (referred to herein as hSIRPα.50A.H1L4)

SEQ ID NO: 9 / SEQ ID NO: 27 (referred to herein as hSIRPα.50A.H1L5)

SEQ ID NO: 11 / SEQ ID NO: 19 (referred to herein as hSIRPα.50A.H2L1)

SEQ ID NO: 11 / SEQ ID NO: 21 (referred to herein as hSIRPα.50A.H2L2)

SEQ ID NO: 11/ SEQ ID NO: 23 (referred to herein as hSIRPα.50A.H2L3)

SEQ ID NO: 11 / SEQ ID NO: 25 (referred to herein as hSIRPα.50A.H2L4)

SEQ ID NO: 11 / SEQ ID NO: 27 (referred to herein as hSIRPα.50A.H2L5)

SEQ ID NO: 13 / SEQ ID NO: 19 (referred to herein as hSIRPα.50A.H3L1)

SEQ ID NO: 13 / SEQ ID NO: 21 (referred to herein as hSIRPα.50A.H3L2)

SEQ ID NO: 13 / SEQ ID NO: 23 (referred to herein as hSIRPα.50A.H3L3)

SEQ ID NO: 13 / SEQ ID NO: 25 (referred to herein as hSIRPα.50A.H3L4)

SEQ ID NO: 13 / SEQ ID NO: 27 (referred to herein as hSIRPα.50A.H3L5)

SEQ ID NO: 15 / SEQ ID NO: 19 (referred to herein as hSIRPα.50A.H4L1)

SEQ ID NO: 15 / SEQ ID NO: 21 (referred to herein as hSIRPα.50A.H4L2)

SEQ ID NO: 15 / SEQ ID NO: 23 (referred to herein as hSIRPα.50A.H4L3)

SEQ ID NO: 15 / SEQ ID NO: 25 (referred to herein as hSIRPα.50A.H4L4)

SEQ ID NO: 15 / SEQ ID NO: 27 (referred to herein as hSIRPa.50A.H4L5)

SEQ ID NO: 17 / SEQ ID NO: 19 (referred to herein as hSIRPa.50A.H5Ll)

SEQ ID NO: 17 / SEQ ID NO: 21 (referred to herein as hSIRPa.50A.H5L2)

SEQ ID NO: 17 / SEQ ID NO: 23 (referred to herein as hSIRPa.50A.H5L3)

SEQ ID NO: 17 / SEQ ID NO: 25 (referred to herein as hSIRPa.50A.H5L4)

SEQ ID NO: 17 / SEQ ID NO: 27 (referred to herein as hSIRPa.50A.H5L5)

SEQ ID NO: 77 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.HlLl)

SEQ ID NO: 77 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.HlL2)

SEQ ID NO: 77 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.HlL3)

SEQ ID NO: 77 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.HlL4)

SEQ ID NO: 77 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.HlL5)

SEQ ID NO: 77 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.HlL6)

SEQ ID NO: 79 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H2Ll)

SEQ ID NO: 79 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H2L2)

SEQ ID NO: 79 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H2L3)

SEQ ID NO: 79 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H2L4)

SEQ ID NO: 79 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H2L5)

SEQ ID NO: 79 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H2L6)

SEQ ID NO: 81 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H3Ll)

SEQ ID NO: 81 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H3L2)

SEQ ID NO: 81 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H3L3)

SEQ ID NO: 81 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H3L4)

SEQ ID NO: 81 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H3L5)

SEQ ID NO: 81 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H3L6)

SEQ ID NO: 83 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H4Ll)

SEQ ID NO: 83 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H4L2)

SEQ ID NO: 83 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H4L3)

SEQ ID NO: 83 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H4L4)

SEQ ID NO: 83 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H4L5)

SEQ ID NO: 83 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H4L6)

SEQ ID NO: 85 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H5Ll)

SEQ ID NO: 85 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H5L2)

SEQ ID NO: 85 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H5L3)

SEQ ID NO: 85 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H5L4)

SEQ ID NO: 85 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H5L5)

SEQ ID NO: 85 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H5L6)

SEQ ID NO: 87 / SEQ ID NO: 89 (referred to herein as hSIRPa.40A.H6Ll)

SEQ ID NO: 87 / SEQ ID NO: 91 (referred to herein as hSIRPa.40A.H6L2)

SEQ ID NO: 87 / SEQ ID NO: 93 (referred to herein as hSIRPa.40A.H6L3)

SEQ ID NO: 87 / SEQ ID NO: 95 (referred to herein as hSIRPa.40A.H6L4)

SEQ ID NO: 87 / SEQ ID NO: 97 (referred to herein as hSIRPa.40A.H6L5)

SEQ ID NO: 87 / SEQ ID NO: 99 (referred to herein as hSIRPa.40A.H6L6)

or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

[0085] In any of the above embodiments, the expression vector can encode for expression a human or humanized antibody, and includes nucleic acid sequences for both heavy and light chains. In one embodiment, the antibody is an IgG. In preferred embodiments, antibody is an IgGl, IgG2, or IgG4, and preferably a human IgGl, IgG2, or IgG4. In certain embodiments, the light chain sequence comprises a human kappa light chain or a human lambda light chain constant domain sequence; and each heavy chain sequence comprises a human IgG4 constant region sequence.

[0086] In some preferred embodiments, the expression vector encodes for expression a human or humanized antibody, wherein the heavy chain nucleic acid sequence comprises SEQ ID NO: 9 and the light chain nucleic acid sequence comprises SEQ ID NO: 19, or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO, and is most preferably an IgG1, IgG2, or IgG4 isotype.

[0087] In some preferred embodiments, the expression vector encodes for expression a human or humanized antibody, wherein the heavy chain nucleic acid sequence comprises SEQ ID NO: 15 and the light chain nucleic acid sequence comprises SEQ ID NO: 27, or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO, and is most preferably an IgGl , IgG2, or IgG4 isotype.

[0088] In some preferred embodiments, the expression vector encodes for expression a human or humanized antibody, wherein the heavy chain nucleic acid sequence comprises SEQ ID NO: 17 and the light chain nucleic acid sequence comprises SEQ ID NO: 19, or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO, and is most preferably an IgGl, IgG2, or IgG4 isotype.

[0089] In some preferred embodiments, the expression vector encodes for expression a human or humanized antibody, wherein the heavy chain nucleic acid sequence comprises SEQ ID NO: 79 and the light chain nucleic acid sequence comprises SEQ ID NO: 89, or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO, and is most preferably an IgGl, IgG2, or IgG4 isotype.

[0090] In some preferred embodiments, the expression vector encodes for expression a human or humanized antibody, wherein the heavy chain nucleic acid sequence comprises SEQ ID NO: 79 and the light chain nucleic acid sequence comprises SEQ ID NO: 91, or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO, and is most preferably an IgGl , IgG2, or IgG4 isotype.

[0091] In some preferred embodiments, the expression vector encodes for expression a human or humanized antibody, wherein the heavy chain nucleic acid sequence comprises SEQ ID NO: 79 and the light chain nucleic acid sequence comprises SEQ ID NO: 95, or, in each case,

at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO, and is most preferably an IgGl, IgG2, or IgG4 isotype.

[0092] In one embodiment, the host cell is Chinese hamster ovary (CHO) cell. In one embodiment, the host cell is a mammalian cell (e.g., a human cell such as an HEK293 cell, a hamster cell such as a CHO cell, etc.), a bacterial cell (e.g., an *E. coli* cell) a yeast cell (e.g., a *Pichia pastoris* cell, etc.), a plant cell (e.g., *a Nicotiana bentharniana* cell), etc.. Mammalian cells are preferred due to glycosylation patterns that are most favorable.

[0093] The invention also provides pharmaceutical compositions comprising an antibody or antigen binding fragment of the invention and a pharmaceutically acceptable carrier or diluent.

[0094] In one embodiment, the composition comprises one or more further therapeutic agents. In one embodiment, the further therapeutic agent is selected from the group consisting of: an anti-CD27 antibody or an antigen binding fragment thereof; an anti-LAG3 antibody or an antigen binding fragment thereof; an anli-APRIL antibody or an antigen binding fragment thereof; an anti-TIGIT antibody or antigen biding fragment thereof; an anti-VISTA antibody or an antigen binding fragment thereof; an anti-BTLA antibody or an antigen binding fragment thereof; an anti-TIM3 antibody or an antigen binding fragment thereof; an anti-CTLA4 antibody or an antigen binding fragment thereof; an anti-HVEM antibody or an antigen binding fragment thereof; an anti-CD70 antibody or an antigen binding fragment thereof; an anti-CD 137 antibody or an antigen binding fragment thereof; an anti-OX4() antibody or an antigen binding fragment thereof; an anti-CD28 antibody or an antigen binding fragment thereof; thereof; an anti-PDl antibody or an antigen binding fragment thereof; an anti-PDLl antibody or an antigen binding fragment thereof; an anli-PDL2 antibody or an antigen binding fragment thereof; an anti-GITR antibody or an antigen binding fragment thereof; an anti-ICOS antibody or an antigen binding fragment thereof; an anli-rLT2 antibody or antigen binding fragment thereof; an anti-ILT3 antibody or antigen binding fragment thereof; an anti-ILT4 antibody or antigen binding fragment thereof; and an anti-ILT5 antibody or an antigen binding fragment thereof; an anti 4-1BB antibody or an antigen binding fragment thereof; an anti- NKG2A antibody or an antigen binding fragment thereof; an anti-NKG2C antibody or an antigen binding fragment thereof; an anti-NKG2E antibody or an antigen binding fragment thereof; an anti-TSLP antibody or an antigen binding fragment thereof; an anti-IL-10 antibody or an antigen binding fragment thereof; IL-10

or PEGylated IL-10; an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of a TNF receptor protein; an Immunoglobulin-like protein; a cytokine receptor; an integrin; a signaling lymphocytic activation molecules (SLAM proteins); an activating NK cell receptor; a Toll like receptor; OX40; CD2; CD7; CD27; CD28; CD30; CD40; ICAM-1; LFA-1 (CD1 la/CD 18); 4-1BB (CD137); B7-H3; ICOS (CD278); GITR; BAFFR; LIGHT; HVEM (LIGHTR); KIRDS2; SLAMF7; NKp80 (KLRFl); NKp44; NKp30; NKp46; CD19; CD4; CDSalpha; CD8beta; IL2R beta; IL2R gamma; IL7R alpha; ITGA4; VLA1; CD49a; ITGA4; IA4; CD49D; ITGA6; VLA-6; CD49f; ITGAD; CD1 Id; ITGAE; CD103; ITGAL; ITGAM; CD1 lb; ITGAX; CDl lc; ITGB1; CD29; ITGB2; CD18; ITGB7; NKG2D; NKG2C; TNFR2; TRANCE/RANKL; DNAM1 (CD226); SLAMF4 (CD244; 2B4); CD84; CD96 (Tactile); CEACAM1; CRTAM; Ly9 (CD229); CD160 (BY55); PSGL1; CDIOO (SEMA4D); CD69; SLAMF6 (NTB-A; Lyl08); SLAM (SLAMF1, CDl 50, IPO-3); SLAM7; BLAME (SLAMF8); SELPLG (CD162); LTBR; LAT; GADS; PAG/Cbp; CD19a; a ligand that specifically binds with CD83; an inhibitor of CD47, PD-1, PD-L1; PD-L2; CTLA4; TIM3; LAG3; CEACAM (e.g.; CEACAM-1. -3 and/or -5); VISTA; BTLA; TIGIT; LAIR1; IDO; TDO; CD160; TGFR beta; and a cyclic dinculeotide or other STING pathway agonist.

[0095] The invention also comprises a combination comprising an antibody or antigen binding iragment of the invention and a second antibody that induces ADCC, wherein said antibody or antigen binding fragment of the invention enhances the antibody-mediated destruction of cells by the second antibody. Antibody-dependent cell-mediated cytotoxicity (ADCC) is a mechanism of cell-mediated immune defense whereby an effector cell of the immune system actively lyses a target cell, whose membrane-surface antigens have been bound by specific antibodies. ADCC is often thought of as being mediated by natural killer (NK) cells, but dendritic cells, macrophages, monocytes, and granulocytes can also mediate ADCC.

[0096] The invention also comprises a combination comprising an antibody or antigen binding iragment of the invention and a second antibody that induces ADCP, wherein said antibody or antigen binding fragment of the invention enhances the antibody-mediated phagocytosis of cells by the second antibody. Antibody-dependent cell-mediated phagocytosis (ADCP) is a mechanism of cell-mediated immune defense whereby target cells are killed via granulocyte, monocyte, dendritic cell, or macrophage-mediated phagocytosis.

[0097] Natural killer (NK) cells play a major role in cancer immunotherapies that involve tumor-antigen targeting by monoclonal antibodies (mAbs). In the context of targeting cells, NK cells can be "specifically activated" through certain Fc receptors that are expressed on their cell surface. NK cells can express FcyRniA and/or FcyRIIC, which can bind to the Fc portion of immunoglobulins, transmitting activating signals within NK cells. Once activated through Fc receptors by antibodies bound to target cells, NK cells are able to lyse target cells without priming, and secrete cytokines like interferon gamma to recruit adaptive immune cells. Likewise, tumor-associated macrophages (TAMs) express surface receptors that bind the Fc fragment of antibodies and enable them to engage in Ab-dependent cellular cytotoxicity/ phagocytosis (ADCC/ADCP). Because SIRPα/CD47 signalling induces a "don't eat me" response that reduces ADCC/ADCP, blocking of this signaling by the anti-SIRPa antibodies or antigen binding fragments of the invention can enhance ADCC of tumor cells bearing the antigenic determinant to which the therapeutic antibody is directed.

[0098] This ADCC/ADCP as a mode of action may be utilized in the treatment of various cancers and infectious diseases. An exemplary list of ADCC/ADCP- inducing antibodies and antibody conjugates that can be combined with the antibodies or antigen binding fragments of the present invention includes, but is not limited to, Riluximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinutuzumab, ADCT-502, Hul4.18K322A, Hu3F8, Dinituximab, Trastuzumab, Cetuximab, Rituximab-RLI, c.60C3-RLI, Hul4.1 8-IL2, KM2812, AFM13, and $(CD20)_2$xCD16, erlotinib (Tarceva), daratumumab, alemtuzumab, pertuzumab, brentuximab, elotuzumab, ibritumomab, ifabotuzumab, farletuzumab, otiertuzumab, carotuximab, epratuzumab, inebilizumab, lumretuzumab, 4G7SDIE, AFM21, AFM22, LY-3022855, SNDX-6352, AFM-13. BI-836826, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, leukotuximab, isatuximab, DS-8895, FPA144, GM102, GSK-2857916. IGN523. IT1208, ADC-1013, CAN-04, XOMA-213, PankoMab-GEX, chKM-4927, IGN003, IGN004, IGN005. MDX-1097, MOR202, MOR-208, oportuzumab, ensituximab, vedotin (Adcetris), ibritumomab tiuxetan, ABBV-838, HuMax-AXL-ADC, and ado-trastuzumab emtansine (Kadcyla). An exemplary list of target antigens for such ADCC/ADCP- inducing antibodies includes, but is not limited to, AMHR2, AXL, BCMA, CA IX, CD4, CD16, CD19, CD20, CD22, CD30, CD37, CD38, CD40, CD52, CD98, CSF1R, GD2, CCR4, CS1 . EpCam, EGFR, EGFRvIII, Endoglin,

EPHA2, EphA3, FGFR2b, folate receptor alpha, fucosyl-GMl, HER2, HER3, IL1RAP, kappa myeloma antigen, MS4A1, prolactin receptor, TA-MUC1, and PSMA.

[0099] In certain embodiments, the second antibody or antigen binding fragment thereof induces ADCP. By way of example only, such antibodies may be selected from the group consisting of Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinutuzumab, Trastuzumab, Cetuximab, alemtuzumab, ibritumomab, farletuzumab, inebilizumab, lumretuzumab, 4G7SDIE, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, GM102, GSK-2857916, PankoMab-GEX, chKM-4927, MDX-1097, MOR202, and MOR-208.

[00100] In embodiments where the antibodies or antigen binding fragments of the present invention are combined with one or more ADCC/ADCP- inducing antibodies and antibody conjugates, such combinations may also be used optionally in association with a further therapeutic agent or therapeutic procedure. In one embodiment, the further therapeutic agent is selected from the group consisting of: an anti-LAG3 antibody or an antigen binding fragment thereof; an anti-APRIL antibody or an antigen binding fragment thereof; an anti-TIGIT antibody or an antigen binding fragment thereof; an anti-VISTA antibody or an antigen binding fragment thereof; an anti-BTLA antibody or an antigen binding fragment thereof; an anti-TIM3 antibody or an antigen binding fragment thereof; an anti-CTLA4 antibody or an antigen binding fragment thereof; an anti-HVEM antibody or an antigen binding fragment thereof; an anti-CD70 antibody or an antigen binding fragment thereof; an anti-CD 137 antibody or an antigen binding fragment thereof; an anti-OX40 antibody or an antigen binding fragment thereof; an anti-CD28 antibody or an antigen binding fragment thereof; thereof; an anti-PDl antibody or an antigen binding fragment thereof; an anti-PDLl antibody or an antigen binding fragment thereof; an anti-PDL2 antibody or an antigen binding fragment thereof; an anti-GITR antibody or an antigen binding fragment thereof; an anti-ICOS antibody or an antigen binding fragment thereof; an anti-ILT2 antibody or antigen binding fragment thereof; an anti-ILT3 antibody or antigen binding fragment thereof; an anti-ILT4 antibody or antigen binding fragment thereof; an anti-ILT5 antibody or an antigen binding fragment thereof; and an anti-4-lBB antibody or an antigen binding fragment thereof; an anti- NKG2A antibody or an antigen binding fragment thereof; an anti-NKG2C antibody or an antigen binding fragment thereof; an anti-NKG2E antibody or an antgien binding fragment thereof; an anti-TSLP antibody or an antigen binding fragment thereof; an anti-IL-10 antibody or an antigen binding fragment thereof; and IL-10 or PEGylated IL-10.

[00101] The invention also provides a vessel or injection device comprising anyone of the anti-SIRPa antibodies or antigen binding fragments of the invention.

[00102] The invention also provides a method of producing an anti-SIRPa antibody or antigen binding fragment of the invention comprising: culturing a host cell comprising a polynucleotide encoding a heavy chain and/or light chain of an antibody of the invention (or an antigen binding fragment thereof) under conditions favorable to expression of the polynucleotide; and optionally, recovering the antibody or antigen binding fragment from the host cell and/or culture medium. In one embodiment, the polynucleotide encoding the heavy chain and the polynucleotide encoding the light chain are in a single vector. In another embodiment, the polynucleotide encoding the heavy chain and the polynucleotide encoding the light chain are in different vectors.

[00103] The invention also provides a method of treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of an anti-SIRPa antibody or antigen binding fragment of the invention, optionally in association with a further therapeutic agent or therapeutic procedure.

[00104] In one embodiment, the subject to be treated is a human subject. In one embodiment, the further therapeutic agent is selected from the group consisting of: an anti-LAG3 antibody or an antigen binding fragment thereof; an anti-APRIL antibody or an antigen binding fragment thereof; an an anti-TIGIT antibody or an antigen binding fragment thereof; an anti-VISTA antibody or an antigen binding fragment thereof; an anti-BTLA antibody or an antigen binding fragment thereof; an anti-TIM3 antibody or an antigen binding fragment thereof; an anti-CTLA4 antibody or an antigen binding fragment thereof; an anti-HVEM antibody or an antigen binding fragment thereof; an anti-CD70 antibody or an antigen binding fragment thereof; an anti-CD 137 antibody or an antigen binding fragment thereof; an anti-OX40 antibody or an antigen binding fragment thereof; an anti-CD28 antibody or an antigen binding fragment thereof; thereof; an anti-PDl antibody or an antigen binding fragment thereof; an anti-PDLl antibody or an antigen binding fragment thereof; an anti-PDL2 antibody or an antigen binding fragment thereof; an anti-GITR antibody or an antigen binding fragment thereof; an anti-ICOS antibody or an antigen binding fragment thereof; an anti-ILT2 antibody or antigen binding fragment thereof; an anti-ILT3 antibody or antigen binding fragment thereof; an anti-ILT4 antibody or antigen binding

fragment thereof; an anti-ILT5 antibody or an antigen binding fragment thereof; and an anti-4-1BB antibody or an antigen binding fragment thereof; an anti- NKG2A antibody or an antigen binding fragment thereof; an anti-NKG2C antibody or an antigen binding fragment thereof; an anti-NKG2E antibody or an antgien binding fragment thereof; an anti-TSLP antibody or an antigen binding fragment thereof; an anti-IL-10 antibody or an antigen binding fragment thereof; and IL-10 or PEGylated IL-10.

[00105] The invention also provides a method of treating an infection or infectious disease in a subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment of the invention, optionally in association with a further therapeutic agent or therapeutic procedure. In one embodiment, the subject to be treated is a human subject.

[00106] In one embodiment, the further therapeutic agent is selected from the group consisting of: an anti-LAG3 antibody or an antigen binding fragment thereof; an anti-APRIL antibody or an antigen binding fragment thereof; an an anti-TIGIT antibody or an antigen binding fragment thereof; an anti-VISTA antibody or an antigen binding fragment thereof; an anti-BTLA antibody or an antigen binding fragment thereof; an anti-TIM3 antibody or an antigen binding fragment thereof; an anti-CTLA4 antibody or an antigen binding fragment thereof; an anti-HVEM antibody or an antigen binding fragment thereof; an anti-CD70 antibody or an antigen binding fragment thereof; an anti-CD 137 antibody or an antigen binding fragment thereof; an anti-OX4() antibody or an antigen binding fragment thereof; an anti-CD28 antibody or an antigen binding fragment thereof; thereof; an anti-PDl antibody or an antigen binding fragment thereof; an anti-PDLl antibody or an antigen binding fragment thereof; an anti-PDL2 antibody or an antigen binding fragment thereof; an anti-GITR antibody or an antigen binding fragment thereof; an anti-ICOS antibody or an antigen binding fragment thereof; an anti-ILT2 antibody or antigen binding fragment thereof; an anti-ILT3 antibody or antigen binding fragment thereof; an anti-ILT4 antibody or antigen binding fragment thereof; an anti-ILT5 antibody or an antigen binding fragment thereof; and an anti-4-lBB antibody or an antigen binding fragment thereof; an anti- NKG2A antibody or an antigen binding fragment thereof; an anti-NKG2C antibody or an antigen binding fragment thereof; an anti-NKG2E antibody or an antien binding fragment thereof; an anti-TSLP antibody or an antigen binding fragment thereof; an anti-IL-10 antibody or an antigen binding fragment thereof; and IL-10 or PEGylated IL-10.

[00107] The invention also provides a method for detecting the presence of a SIRPa peptide or a fragment thereof in a sample comprising contacting the sample with an antibody or antigen binding fragment thereof of the invention and detecting the presence of a complex between the antibody or fragment and the peptide; wherein detection of the complex indicates the presence of the SIRPa peptide.

BRIEF DESCRIPTION OF THE FIGURES

[00108] Fig. 1 depicts cross-reactivity of commercially available anti-hSIRPa antibodies with hSIRPpl and allele-specific binding to hSIRPaVl and hSIRPaV2.

[00109] Fig. 2 depicts reactivity of KWAR23 antibody with hSIRPaVl , hSIRPaV2, hSIRPpl , and hS!RPy.

[001 10] Fig. 3 depicts reactivity of antibody clone hSIRPa. 50A for various hSIRPa alleles.

[001 11] Fig. 4 depicts the ability of hSIRPa.5()A antibody to block recombinant hCD47/Fc-protein binding to cell surface expressed hSIRPa.

[001 12] Fig. 5A and Fig. 5B depicts binding of hSIRPa.50A antibody to primary human CD 14+ enriched monocytes.

[001 13] Fig. 5C and Fig. 5D depicts the ability of hSIRPa. 50A antibody to block hCD47 binding to to primary human CD 14+ enriched monocytes.

[001 14] Fig. 6A depicts binding of hSIRPa. 50A antibody to primary human granulocytes.

[001 15] Fig. 6B depicts phagocytosis of tumor cells by primary human granulocytes in the presence of rituximab plus or minus the hSIRPa.5()A antibody.

[001 16] Fig. 6C depicts phagocytosis of tumor cells by primary human granulocytes in the presence of daratumumab plus or minus the hSIRPa.5()A antibody.

[001 17] Fig. 6D depicts phagocytosis of tumor cells by primary human granulocytes in the presence of alemtuzumab plus or minus the hSIRPa.5()A antibody.

[001 18] Fig. 6E depicts phagocytosis of tumor cells by primary human granulocytes in the presence of celuximab plus or minus the hSIRPa.SOA antibody.

[001 19] Fig. 7 depicts phagocytosis of tumor cells by human macrophages in the presence of the indicated antibody (rituximab or daratumumab) plus or minus the hSIRPa.50A antibody.

[00120] Fig. 8 depicts blocking of the hSIRPa/hCD47 interaction bymouse hSIRPa.50A and humanized hSIRPa.50A antibodies to hSIRPa.

[00121] Fig. 9 depicts depicts hSIRPa.50A antibody binding to hSIRPaVl, hSIRPaV2, hSIRPpi, hSIRPa-VpClaC2a, hSIRPa-VaCipC2a, and hSIRPa-VaClaC2p.

[00122] Fig. 10A depicts an alignment of the hSIRPa and hSIRPpi IgV domain amino acid sequences.

[00123] Fig. 10B depicts loss of hSIRPa.50A antibody binding to hSIRPaV 1(P74A).

[00124] Fig. 11 depicts binding of hSIRPa.40A and hSIRPa.50A antibodies to hSIRPaVl, hSIRPa V2, hSIRPpi, hSIRPpL, and hSIRPy.

[00125] Fig. 12 depicts binding of hSIRPa.40A and hSIRPa.50A antibodies to hSIRPaVl, hSIRPaV2, hSlRPaV3, hSIRPaV4, hSIRPaV5, hSIRPaV6, hSIRPaV8, and hSIRPaV9.

[00126] Fig. 13 depicts the ability of hSIRPa.4()A and hSIRPa.50A antibodies to block recombinant hCD47/Fc -protein binding to cell surface expressed hSIRPa.

[00127] Fig. 14A and Fig. 14B depicts binding of hSIRPa.40A antibody to primary human CD14+ enriched monocytes.

[00128] Fig. 14C and Fig. 14D depicts the ability of hSIRPa.40A antibody to block hCD47 binding to to primary human CD14+ enriched monocytes.

[00129] Fig. 15A depicts binding of hSIRPa.40A and hSIRPa.5()A antibodies to primary human granulocytes.

[00130] Fig. 15B depicts phagocytosis of Ramos cells by primary human granulocytes in the presence of rituximab plus or minus the hSIRPa.40A and hSIRPa.50A antibodies.

[00131] Fig. 16 depicts enhancement of rituximab-induced Raji cell phagocytosis by hSIRPa.40A and hSIRPa.50A antibodies.

[001 32] Fig. 17 depicts binding of mouse hSIRPa.40A and humanized hSIRPa.40A antibodies to hSIRPa.

[00133] Fig. 18 depicts the blockade of hCD47 binding to hSIRPa in the presence of humanized hSIRPa.40A antibody variants.

[00134] Fig. 19 depicts binding of hSIRPa.40A and hSIRPa.50A antibodies to hSIRPaVl, hSIRPaV2, hSIRPpl, hSIRP-VyClpC2p, hSIRP-VpClyC2p, and hSIRP-VpClpC2y.

[001 35] Fig. 20 depicts loss of hSIRPa.40A and hSIRPa.50A antibody binding to hSIRPaVl(P74A).

[001 36] Fig. 21 depicts the ability of chimeric hSIRPa.4()A antibody variants to affect rituximab-mediated phagocytosis.

[001 37] Fig. 22 depicts the ability of humanized hSIRPa.40A antibody variants to affect rituximab-mediated phagocytosis.

[001 38] Fig. 23A depicts the ability of mouse hSIRPa.50A and chimeric hSIRPa.50A hIgG2 and hIgG4 antibody variants to affect rituximab-mediated phagocytosis.

[001 39] Fig. 23B depicts the ability of chimeric hSIRPa.50A hIgG2 and hIgG4 antibody variants to affect rituximab-mediated phagocytosis.

[001 40] Fig. 23C depicts the ability of chimerichSIRPa.SOA hIgG2 and hIgG4 antibody variants to affect daratumumab-mediated phagocytosis.

[001 4 1] Fig. 23D depicts the ability of mouse hSIRPa.50A and chimeric hSIRPa.50A hIgG2 antibody variants to affect rituximab-mediated phagocytosis in granulocytes.

[001 42] Fig. 24A depicts the ability of mouse hSIRPa.5()A and chimeric hSIRPa.50A.hIgGl.N297Q, hSIRPa.5()A.hIgG4.N297Q or hSIRPa.50A.hIgG2 antibody variants to affect rituximab-mediated phagocytosis.

[00143] Fig. 24B depicts the ability of mouse hSIRPa.50A and chimeric hSIRPa.50A.hIgGl.N297Q, hSIRPa.50A.hIgG4.N297Q or hSIRPa.50A.MgG2 antibody variants to affect daratumumab-mediated phagocytosis.

[00144] Fig. 25 depicts the ability of chimeric hSIRPa.50A.hIgGl.N297Q, hSIRPa.50A hIgGl.L234A.L235A.P329G, and hSIRPa.5()A MgG2 or hIgG4 antibody variants to affect rituximab-mediated phagocytosis.

DETAILED DESCRIPTION

Abbreviations

[00145] Throughout the detailed description and examples of the invention the following abbreviations will be used:

ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
CDC	Complement-dependent cytotoxicity
CDR	Complementarity determining region in the immunoglobulin variable regions, defined using the Kabat numbering system
CHO	Chinese hamster ovary
EC50	Concentration at which 50% of the total binding signal is observed
ELISA	Enzyme-linked immunosorbant assay
FR	Antibody framework region: the immunoglobulin variable regions excluding the CDR regions.
HRP	Horseradish peroxidase
IFN	interferon
IC50	concentration resulting in 50% inhibition
IgG	Immunoglobulin G
Kabat	An immunoglobulin alignment and numbering system pioneered by Elvin A. Kabat ((1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.)
mAb or Mab or MAb	Monoclonal antibody
SEB	Staphylococcus Enterotoxin B
TT	Tetanus toxoid
V region	The segment of Ig chains which is variable in sequence between different antibodies. It extends to Kabat residue 109 in the light chain and 113 in the heavy chain.
VH	Immunoglobulin heavy chain variable region
VK	Immunoglobulin kappa light chain variable region
VL	Immunoglobulin light chain variable region

Definitions

[00146] So that the invention may be more readily understood, certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[00147] As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

[00148] "Administration" and "treatment," as it applies to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, refers to contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. "Administration" and "treatment" also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell.

[00149] "Treat" or "treating" means to administer a therapeutic agent, such as a composition containing any of the antibodies or antigen-binding fragments of the present invention, internally or externally to a subject or patient having one or more disease symptoms, or being suspected of having a disease, for which the agent has therapeutic activity. Typically, the agent is administered in an amount effective to alleviate one or more disease symptoms in the treated subject or population, whether by inducing the regression of or inhibiting the progression of such symptom(s) by any clinically measurable degree. The amount of a therapeutic agent that is effective to alleviate any particular disease symptom may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the drug to elicit a desired response in the subject. Whether a disease symptom has been alleviated can be assessed by any clinical measurement typically used by physicians or other skilled healthcare providers to assess the severity or progression status of that symptom.

[00150] "Recombinant expression" of a protein means the transcription and translation of an exogenous gene in a host organism to generate the protein, which is referred to herein as a "recombinant protein."

SIRPa and associated proteins

[00151] SIRPa belongs to a class of membrane proteins known as "paired receptors" that contain several genes coding for proteins (e.g., SIRPa, SIRPpi, and SIRPy) with similar extracellular regions but different transmembrane and/or cytoplasmic regions having opposite (activating or inhibitory) signaling abilities. Like SIRPa, there are several examples of paired receptors on NK cells and some on myeloid cells, including the SIRP and CD200 receptor families (Hatherley *et al, Mol Cell, 2008; 31: 266-277).*

[00152] SIRPa contains an extracellular region that can be subdivided into three separate domains: the Ig-like (immunoglobulin-like) V-type (IgV), Ig-like Cl-type (IgCl), and Ig-like C2-type (IgC2) domain. The IgV domain is also known as the ligand-binding N-terminal domain of SIRPa. Like SIRPa, also the related proteins SIRPpi and SIRPy comprise an extracellular region that can be subdivided into an IgV, IgCl, and IgC2 domain. However, SIRPa, SIRPpi and SIRPy have different cytoplasmic regions. SIRPpi has a very short cytoplasmic region of only 6 amino acids and lacks signalling motifs for association with phosphatases. Instead, this protein associates with DNAX activation protein 12 (DAP12), a dimeric adaptor protein that binds an amino acid with a basic side chain in the transmembrane region of SIRPpi and is able to transmit activating signals through its immunoreceptor tyrosine-based activation motif (ITAM). SIRPy also has a short cytoplasmic region of 4 amino acids, but it lacks a charged amino-acid side chain in the transmembrane region and therefore does not associate with DAP12. Hence, SIRPy is annotated as a non-signalling protein (Barclay, A.N. and Brown, M.H., *Nat Rev Immunol. 2006; 6: 457-464).*

[001 53] The major ligand of SIRPa is CD47, which consists of one extracellular IgV domain, a five times transmembrane-spanning domain, and a short cytoplasmic tail. CD47 functions as a cellular ligand with binding mediated through the NH2-terminal IgV domain of SIRPa. Evidence that CD47 contributes to recognition of self comes from the observation that splenic macrophages derived from CD47-expressing mice clear infused blood cells from $CD47^{-/-}$ mice (Oldenborg *et al, Science.* 2000; 288: 2051-2054).

[001 54] In addition to CD47, two other SIRPa ligands have been reported, known as surfactant proteins A and D (Sp-A and Sp-D), both of which belong to the collectin family. Sp-D has been reported to bind to the membrane-proximal IgC2 domain of SIRPa in a calcium- and

saccharide-dependeiit manner. It is thought that Sp-A and Sp-D help maintain an anti-inflammatory environment in the lung by stimulating SIRPa on alveolar macrophages (Gardai *et al, Cell* 2003; 115: 13-23).

[00155] The amino acid sequence of eight human SIRPa valiants are listed in SEQ ID NOs: 34, 36, 44, 46, 48, 50, 52, and 54; exemplary nucleic acid sequences encoding these variants are listed in SEQ ID NOs: 33, 35, 43, 45, 47, 49, 51, and 53, respectively.

[00156] For comparison, the amino acid sequence of human SIRPβ1 and SIRPy are listed in SEQ ID NOs: 38 and 40, respectively, and exemplary nucleic acid sequences in SEQ ID NOs: 37 and 39, respectively.

[00157] The amino acid sequence of human CD47 is listed in SEQ ID NO: 42, and an exemplary nucleic acid sequence in SEQ ID NO: 41.

[00158] Modified SIRPa polypeptides hSIRPa-VpClaC2a, hSIRPa-VaCl pC2a, hSIRPa-VaClaC2p, and hSIRPaVl(P74A) discussed hereinafter are listed in SEQ IDNOs: 56, 58, 60, and 62; exemplary nucleic acid sequences encoding these variants are listed in SEQ ID NOs: 55, 57, 59, and 61, respectively.

Anti-SIRPa Antibodies and Antigen-Binding Fragments Thereof

[00159] The present invention provides antibodies or antigen-binding fragments thereof that bind human SIRPa and uses of such antibodies or fragments. In some embodiments, the anti-SIRPa antibodies are isolated.

[00160] Whether an antibody specifically binds to a polypeptide sequence (e.g., human SIRPa, hSIRPpi, etc.) can be determined using any assay known in the art. Examples of assays known in the art to determining binding affinity include surface plasmon resonance (e.g., BIACORE) or a similar technique (e.g. KinExa or OCTET).

[00161] As used herein, the term "antibody" refers to any form of antibody that exhibits the desired biological activity. The term antibody includes antigen-binding portions, i.e., "antigen binding sites," (e.g., fragments, subsequences, complementarity determining regions (CDRs)) that retain capacity to bind antigen, including (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_Hl domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd

fragment consisting of the V_H and C_H1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341 :544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Single chain antibodies are also included by reference in the term "antibody." Preferred therapeutic antibodies are intact IgG antibodies. The term "intact IgG" as used herein is meant as a polypeptide belonging to the class of antibodies that are substantially encoded by a recognized immunoglobulin gamma gene. In humans this class comprises IgGl, IgG2, IgG3, and IgG4. In mice this class comprises IgGl, IgG2a, IgG2b, IgG3. The known Ig domains in the IgG class of antibodies are V_H, $C\gamma1$, Cy2, $C\gamma3$, V_L, and CL.

[00162] The present invention includes anti-SIRPa antigen-binding fragments and methods of use thereof.

[00163] As used herein, a "full length antibody" is, in the case of an IgG, a bivalent molecule comprising two heavy chains and two light chains. Each heavy chain comprises a V_H domain followed by a constant domain (CHI), a hinge region, and two more constant (C_{H_2} and C_{H_3}) domains; while each light chain comprises one V_L domain and one constant (CL) domain. A full length antibody in the case of an IgM is a decavalent or dodecavalent molecule comprising 5 or 6 linked immunoglobulins in which immunoglobulin each monomer has two antigen binding sites formed of a heavy and light chain.

[00164] As used herein, unless otherwise indicated, "antibody fragment" or "antigen-binding fragment" refers to antigen-binding fragments of antibodies, *i.e.* antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, *e.g.* fragments that retain one or more CDR regions. Examples of antigen-binding fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules, *e.g.*, sc-Fv; nanobodies and multispecific antibodies formed from antibody fragments.

[00165] The present invention includes anti-SIRPa Fab fragments and methods of use thereof. A "Fab fragment" is comprised of one light chain and the C_H1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule. A "Fab fragment" can be the product of papain cleavage of an antibody.

[00166] The present invention includes anti-SIRPa antibodies and antigen-binding fragments thereof which comprise an Fc region and methods of use thereof. An "Fc" region contains two heavy chain fragments comprising the C_H3 and C_H2 domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_H3 domains.

[00167] The present invention includes anti-SIRPa Fab' fragments and methods of use thereof. A "Fab' fragment" contains one light chain and a portion or fragment of one heavy chain that contains the V_H domain and the C_H1 domain and also the region between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form a $F(ab')_2$ molecule.

[00168] The present invention includes anti-SIRPa $F(ab')_2$ fragments and methods of use thereof. A "$F(ab')_2$ fragment" contains two light chains and two heavy chains containing a portion of the constant region between the C_{H1} and C_{H_2} domains, such that an interchain disulfide bond is formed between the two heavy chains. A $F(ab')_2$ fragment thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains. An "$F(ab')_2$ fragment" can be the product of pepsin cleavage of an antibody.

[00169] The present invention includes anti-SIRPa Fv fragments and methods of use thereof. The "Fv region" comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

[00170] The present invention includes anti-SIRPa scFv fragments and methods of use thereof. The term "single-chain Fv" or "scFv" antibody refers to antibody fragments comprising the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen-binding. For a review of scFv, see Pluckthun (1994) THE PHARMACOLOGY OF MONOCLONAL ANTIBODIES, vol. 113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315. See also, International Patent Application Publication No. WO 88/01649 and U.S. Pat. Nos. 4,946, 778 and 5,260,203.

[00171] The present invention includes anti-SIRPa domain antibodies and methods of use thereof. A "domain antibody" is an immunologically functional immunoglobulin fragment

containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody may target the same or different antigens.

[00172] The present invention includes anli-SIRPa bivalent antibodies and methods of use thereof. A "bivalent antibody" comprises two antigen-binding sites. In some instances, the two binding sites have the same antigen specificities. However, bivalent antibodies may be bispecific (see below).

[00173] The present invention includes anli-SIRPa diabodies and methods of use thereof. As used herein, the term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain (V_H-V_L or V_L-V_H). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, *e.g.*, EP 404,097; WO 93/1 l 161; and Holliger *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90: 6444-6448. Duobodies are described in Labrijn et al., 2013, Proc. Natl. Acad. Sci. USA 110 (13): 5145-5150. For a review of engineered antibody variants generally see Holliger and Hudson (2005) *Nat. Biotechnol.* 23:1 126-1136.

[00174] Typically, an antibody or antigen-binding fragment of the invention which is modified in some way retains at least 10% of its binding activity (when compared to the parental antibody) when that activity is expressed on a molar basis. Preferably, an antibody or antigen-binding fragment of the invention retains at least 20%, 50%, 70%, 80%, 90%, 95% or 100% or more of the SIRPa binding affinity as the parental antibody. It is also intended that an antibody or antigen-binding fragment of the invention can include conservative or non-conservative amino acid substitutions (referred to as "conservative variants" or "function conserved variants" of the antibody) that do not substantially alter its biologic activity.

[00175] The present invention includes isolated anti-SIRPa antibodies and antigen-binding fragments thereof and methods of use thereof. Herein, the term "isolated" is not intended to refer to a complete absence of such biological molecules or to an absence of water, buffers, or salts or to components of a pharmaceutical formulation that includes the antibodies or fragments. An

"isolated" antibody, antigen-binding fragment, nucleic acid, etc., is one which has been identified and separated and/or recovered from one or more components of its natural environment. In preferred embodiments, the antibody, antigen-binding fragment, nucleic acid, etc., is purified to 75% by weight or more, more preferably to 90% by weight or more, still more preferably to 95%· by weight or more, an still more preferably to 98% by weight or more. Thus, "isolated" biological molecules are at least partially free of other biological molecules from the cells or cell cultures in which they are produced. Such biological molecules include nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth medium. An isolated antibody or antigen-binding fragment may further be at least partially free of expression system components such as biological molecules from a host cell or of the growth medium thereof.

[00176] The present invention includes anti-SIRPa chimeric antibodies (e.g., human constant domain/mouse variable domain) and methods of use thereof. As used herein, a "chimeric antibody" is an antibody having the variable domain from a first antibody and the constant domain from a second antibody, where the first and second antibodies are from different species. (U.S. Pat. No. 4,816,567; and Morrison *et al.* (1984) *Proc. Natl. Acad. Sci. USA* 81: 6851-6855). Typically, the variable domains are obtained from an antibody from an experimental animal (the "parental antibody"), such as a rodent, and the constant domain sequences are obtained from human antibodies, so that the resulting chimeric antibody will be less likely to elicit an adverse immune response in a human subject than the parental *(e.g.,* mouse) antibody.

[00177] The present invention includes anti-SIRPa humanized antibodies and antigen-binding fragments thereof *(e.g.,* rat or mouse antibodies that have been humanized) and methods of use thereof. As used herein, the term "humanized antibody" refers to forms of antibodies that contain sequences from both human and non-human *(e.g.,* mouse or rat) antibodies. In general, the humanized antibody will comprise substantially 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, and all or substantially all of the framework (FR) regions are those of a human immunoglobulin sequence. The humanized antibody may optionally comprise at least a portion of a human immunoglobulin constant region (Fc). For more details about humanized antibodies, see, e.g., Jones et al., *Nature,* 321:522-525 (1986); Reichmann et al., *Nature,*

332:323-329 (1988); Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992); and Clark, *Immunol. Today* 21: 397-402 (2000).

[00178] In general, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989).

[00179] The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. Except in Afunctional or bispecific antibodies, the two binding sites are, in general, the same.

[00180] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FRl, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest. Kabat, *etal;* National Institutes of Health, Bethesda, MD; 5* ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) *Adv. Prot. Chem.* 32:1-75; Kabat, *et al,* (1977) *J. Biol. Chem,* 252:6609-6616; Chothia, *et al,* (1987) *J Mol. Biol.* 196:901-917 or Chothia, *et al.,* (1989) *Nature* 342:878-883.

[00181] As used herein, the term "hypervariable region" refers to the amino acid residues of an antibody or antigen-binding fragment thereof that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining

region" or "CDR" *(i.e.* CDRL1, CDRL2 and CDRL3 in the light chain variable domain and CDRH1, CDRH2 and CDRH3 in the heavy chain variable domain). See Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (defining the CDR regions of an antibody by sequence); see also Chothia and Lesk (1987) *J. Mol. Biol.* 196: 901-917 (defining the CDR regions of an antibody by structure). As used herein, the term "framework" or "FR" residues refers to those variable domain residues other than the hypervariable region residues defined herein as CDR residues.

[00182] "Isolated nucleic acid molecule" or "isolated polynucleotide" means a DNA or RNA of genomic, mRNA, cDNA, or synthetic origin or some combination thereof which is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, or is linked to a polynucleotide to which it is not linked in nature. For purposes of this disclosure, it should be understood that "a nucleic acid molecule comprising" a particular nucleotide sequence does not encompass intact chromosomes. Isolated nucleic acid molecules "comprising" specified nucleic acid sequences may include, in addition to the specified sequences, coding sequences for up to ten or even up to twenty or more other proteins or portions or fragments thereof, or may include operably linked regulatory sequences that control expression of the coding region of the recited nucleic acid sequences, and/or may include vector sequences.

[00183] The phrase "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to use promoters, polyadenylation signals, and enhancers.

[00184] A nucleic acid or polynucleotide is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate

translation. Generally, but not always, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

[00185] As used herein, the expressions "cell," "cell line," and "cell culture" are used interchangeably and all such designations include progeny. Thus, the words "transformants" and "transformed cells" include the primary subject cell and cultures derived therefrom without regard for the number of transfers. It is also understood that not all progeny will have precisely identical DNA content, due to deliberate or inadvertent mutations. Mutant progeny that have the same function or biological activity as screened for in the originally transformed cell are included. Where distinct designations are intended, it will be clear from the context.

[00186] As used herein, "germline sequence" refers to a sequence of unrearranged immunoglobulin DNA sequences. Any suitable source of unrearranged immunoglobulin sequences may be used. Human germline sequences may be obtained, for example, from JOINSOLVER germline databases on the website for the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the United States National Institutes of Health. Mouse germline sequences may be obtained, for example, as described in Giudicelli *et al.* (2005) *Nucleic Acids Res.* 33: D256-D261.

Physical and Functional Properties of the Exemplary Anti-SIRPa Antibodies

[00187] The present invention provides anti-SIRPa antibodies and antigen-binding fragments thereof having specified structural and functional features, and methods of use of the antibodies or antigen-binding fragments thereof in the treatment or prevention of disease (e.g., cancer or infectious disease).

[00188] As staled above, antibodies and fragments that bind to the same epitope as any of the anti-SIRPa antibodies or antigen-binding fragments thereof of the present invention also form part of the present invention. In one embodiment, the invention provides an antibody or antigen binding fragment thereof that binds to the same epitope of human SIRPa as an antibody comprising one of the following combinations of heavy chain sequence / light chain sequence (or in each case an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto):

SEQ ID NO: 10 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.HlLl)

SEQ ID NO: 10 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.HlL2)

SEQ ID NO: 10 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.HlL3)

SEQ ID NO: 10 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.HlL4)

SEQ ID NO: 10 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.HlL5)

SEQ ID NO: 12 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H2Ll)

SEQ ID NO: 12 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H2L2)

SEQ ID NO: 12 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H2L3)

SEQ ID NO: 12 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H2L4)

SEQ ID NO: 12 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H2L5)

SEQ ID NO: 14 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H3Ll)

SEQ ID NO: 14 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H3L2)

SEQ ID NO: 14 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H3L3)

SEQ ID NO: 14 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H3L4)

SEQ ID NO: 14 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H3L5)

SEQ ID NO: 16 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H4Ll)

SEQ ID NO: 16 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H4L2)

SEQ ID NO: 16 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H4L3)

SEQ ID NO: 16 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H4L4)

SEQ ID NO: 16 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H4L5)

SEQ ID NO: 18 / SEQ ID NO: 20 (referred to herein as hSIRPa.50A.H5Ll)

SEQ ID NO: 18 / SEQ ID NO: 22 (referred to herein as hSIRPa.50A.H5L2)

SEQ ID NO: 18 / SEQ ID NO: 24 (referred to herein as hSIRPa.50A.H5L3)

SEQ ID NO: 18 / SEQ ID NO: 26 (referred to herein as hSIRPa.50A.H5L4)

SEQ ID NO: 18 / SEQ ID NO: 28 (referred to herein as hSIRPa.50A.H5L5)

SEQ ID NO: 78 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.HlLl)

SEQ ID NO: 78 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.HlL2)

SEQ ID NO: 78 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.HlL3)

SEQ ID NO: 78 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.HlL4)

SEQ ID NO: 78 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.HlL5)

SEQ ID NO: 78 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.HlL6)

SEQ ID NO: 80 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H2Ll)

SEQ ID NO: 80 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H2L2)

SEQ ID NO: 80 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H2L3)

SEQ ID NO: 80 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H2L4)

SEQ ID NO: 80 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H2L5)

SEQ ID NO: 80 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H2L6)

SEQ ID NO: 82 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H3Ll)

SEQ ID NO: 82 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H3L2)

SEQ ID NO: 82 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H3L3)

SEQ ID NO: 82 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H3L4)

SEQ ID NO: 82 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H3L5)

SEQ ID NO: 82 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H3L6)

SEQ ID NO: 84 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H4Ll)

SEQ ID NO: 84 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H4L2)

SEQ ID NO: 84 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H4L3)

SEQ ID NO: 84 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H4L4)

SEQ ID NO: 84 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H4L5)

SEQ ID NO: 84 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H4L6)

SEQ ID NO: 86 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H5Ll)

SEQ ID NO: 86 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H5L2)

SEQ ID NO: 86 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H5L3)

SEQ ID NO: 86 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H5L4)

SEQ ID NO: 86 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H5L5)

SEQ ID NO: 86 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H5L6)

SEQ ID NO: 88 / SEQ ID NO: 90 (referred to herein as hSIRPa.40A.H6Ll)

SEQ ID NO: 88 / SEQ ID NO: 92 (referred to herein as hSIRPa.40A.H6L2)

SEQ ID NO: 88 / SEQ ID NO: 94 (referred to herein as hSIRPa.40A.H6L3)

SEQ ID NO: 88 / SEQ ID NO: 96 (referred to herein as hSIRPa.40A.H6L4)

SEQ ID NO: 88 / SEQ ID NO: 98 (referred to herein as hSIRPa.40A.H6L5)

SEQ ID NO: 88 / SEQ ID NO: 100 (referred to herein as hSIRPa.40A.H6L6) .

[00189] There are several methods available for mapping antibody epitopes on target antigens, including: H/D-Ex mass spectrometry, crosslinking coupled mass spectrometry, X-ray crystallography, pepscan analysis and site directed mutagenesis. For example, HDX (Hydrogen Deuterium Exchange) coupled with proteolysis and mass spectrometry can be used to determine the epitope of an antibody on a specific antigen Y. HDX-MS relies on the accurate measurement and comparison of the degree of deuterium incorporation by an antigen when incubated in D_2O on its own and in presence of its antibody at various time intervals. Deuterium is exchanged with hydrogen on the amide backbone of the proteins in exposed areas whereas regions of the antigen bound to the antibody will be protected and will show less or no exchange after analysis by LC-MS/MS of proteolytic fragments., Crosslinking coupled mass spectrometry begins by binding the antibody and the antigen with a mass labeled chemical crosslinker. Next the presence of the complex is confirmed using high mass MALDI detection. Because after crosslinking chemistry the Ab/Ag complex is extremely stable, many various enzymes and digestion conditions can be applied to the complex to provide many different overlapping peptides.

Identification of these peptides is performed using high *resolution* mass spectrometry and MS/MS techniques. Identification of the crosslinked peptides is determined using mass tag linked to the cross-linking reagents. After MS/MS fragmentation and data analysis, both epitope and paratope are determined in the same experiment.

[00190] The scope of the present invention also includes isolated anti-SIRPa antibodies and antigen-binding fragments thereof *(e.g.,* humanized antibodies), comprising a variant of an immunoglobulin chain set forth herein, wherein the variant exhibits one or more of the following properties:

binds human SIRPaVl protein having the sequence of SEQ ID NO: 34 with an EC_{50} < 1 nM; and exhibits at least a 100-fold higher EC_{50} for SIRPaV 1(P74A) having the sequence of SEQ ID NO: 62; and optionally also at least a 100-fold higher EC_{50} for human SIRPpi protein having the sequence of SEQ ID NO: 38 (in each case wherein the reduced EC_{50} is relative to the EC_{50} for human SIRPaVl protein having the sequence of SEQ ID NO: 34, and in each case preferably when measured by cellular ELISA (CELISA) as described hereinafter;

binds to a cell expressing human SIRPaVl protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3nM or less;

binds to a cell expressing human SIRPaV2 protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3nM or less;

does not appreciably bind to SIRPpi protein at an antibody concentration of 50 nM, preferably 67 nM, and more preferably 100 nM; or alternatively at a concentration that is 10-fold greater, preferably 50-fold greater, more preferably 100-fold greater, and still more preferably 200-fold greater than the antibody's EC_{50} for SIRPaVl or SIRPaV2;

inhibits binding between human SIRPa and CD47 with an IC_{50} < 10.0 nM, more preferably < 5.0 nM, still more preferably < 2.5 nM, and most preferably about 1.0 nM or less; and

exhibits a T20 "humanness" of at least 79, and more preferably 85%.

[00191] In other embodiments, the invention provides antibodies or antigen-binding fragment thereof that bind human SIRPa *(e.g.,* humanized antibodies) and have V_H domains and V_L domains with at least 90% sequence identity with SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 102, 7, 10, 12, 14, 16, 18, and 30; and 76, 90, 92, 94, 96, 98, 100, 104, 8, 20, 22, 24, 26, 28, and 32. In other embodiments, the invention provides antibodies or antigen-binding fragment thereof that bind human SIRPa *(e.g.,* humanized antibodies) and have V_H domains and V_L domains with at least 95%. sequence identity with SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 102, 7, 10, 12, 14, 16, 18, and 30; and 76, 90, 92, 94, 96, 98, 100. 104, 8, 20, 22, 24, 26, 28, and 32. In other

embodiments, the invention provides antibodies or antigen-binding fragment thereof that bind human SIRPa *(e.g.,* humanized antibodies) and have V_H domains and V_L domains with at least 97% sequence identity with SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 102, 7, 10, 12, 14, 16, 18, and 30; and 76, 90, 92, 94, 96, 98, 100, 104, 8, 20, 22, 24, 26, 28, and 32. In other embodiments, the invention provides antibodies or antigen-binding fragment thereof that bind human SIRPa *(e.g.,* humanized antibodies) and have V_H domains and V_L domains with at least 98% sequence identity with SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 102, 7, 10, 12, 14, 16, 18, and 30; and 76, 90, 92, 94, 96, 98, 100, 104. 8, 20, 22, 24, 26, 28, and 32. In other embodiments, the invention provides antibodies or antigen-binding fragment thereof that bind human SIRPa *(e.g.,* humanized antibodies) and have V_H domains and V_L domains with at least 99% sequence identity with SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 102, 7, 10, 12, 14, 16, 18, and 30; and 76, 90, 92, 94, 96, 98, 100, 104, 8, 20, 22, 24, 26, 28, and 32. Preferably, in each case, the sequence differences between SEQ ID NOs: 75, 78, 80. 82, 84, 86, 88, 102, 7, 10, 12. 14, 16, 18, and 30; and 76, 90, 92, 94, 96, 98, 100, 104, 8. 20, 22, 24, 26, 28, and 32 and the variants consist of conservative substitutions and are most preferably limited to substitutions within the framework residues.

[00192] The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Camacho, C. et al. (2009): *BMC Bioinformatics* 10:421; Altschul et al. (2005) *FEBS* J. 272(20): 5101-5109; Altschul, S.F., *et al.,* (1990) *J. Mol. Biol.* 215:403-410; Gish, W., *et al.*. (1993) *Nature Genet.* 3:266-272; Madden, T.L., *et al.,* (1996) *Meth. Enzymol.* 266:131-141; Altschul, S.F., *et al.,* (1997) *Nucleic Acids Res.* 25:3389-3402; Zhang. J., *et al,* (1997) *Genome Res.* 7:649-656; Wootton, J.C., *et al* , (1993) *Comput. Chem.* 17:149-163; Hancock, J.M. *et al,* (1994) *Comput. Appl. Biosci.* 10:67-70; ALIGNMENT SCORING SYSTEMS: Dayhoff, M.O., *et al,* "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, *Natl. Bioined. Res. Found,* Washington, DC; Schwartz, R.M., *et al,* "Matrices for detecting distant relationships." in *Atlas of Protein Sequence and Structure,* (1978) vol. 5, suppl. 3." M.O. Dayhoff (ed.), pp. 353-358, *Natl. Biomed. Res. Found.,* Washington. DC; Altschul, S.F., (1991) J. Mol. Biol. 219:555-565; States. D.J., *et al,* (1991) *Methods* 3:66-70; Henikoff, S., *et al,* (1992) *Proc. Natl. Acad. Sci. USA* 89:10915-10919; Altschul, S.F., *etal,* (1993) J. Mol. Evol. 36:290-300; ALIGNMENT STATISTICS: Karlin, S., *et al,* (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268; Karlin, S., *etal,* (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877; Dembo, A., *et*

al, (1994) *Ann. Prob.* 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in *Theoretical and Computational Methods in Genome Research* (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York. In the present application, percent identity comparisons are preferably performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences (e.g. expect threshold: 10; word size: 6; max matches in a query range: 0; BLOSUM 62 matrix; gap costs: existence 11, extension 1; conditional compositional score matrix adjustment).

[00193] "Conservatively modified variants" or "conservative substitution" refers to substitutions of amino acids in a protein with other amino acids having similar characteristics *(e.g.* charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.), such that the changes can frequently be made without altering the biological activity of the protein. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity *(see, e.g.,* Watson *et al.* (1987) *Molecular Biology of the Gene,* The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity. Exemplary conservative substitutions are set forth the following Table 1.

TABLE 1. Exemplary Conservative Amino Acid Substitutions

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys; His
Asn (N)	Gln; His
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; His
Met (M)	Leu; Ile; Tyr
Phe (F)	Tyr; Met; Leu
Pro (P)	Ala

Original residue	Conservative substitution
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

[00194] Function-conservative variants of the antibodies of the invention are also contemplated by the present invention. "Function-conservative variants," as used herein, refers to antibodies or fragments in which one or more amino acid residues have been changed without altering a desired property, such an antigen affinity and/or specificity. Such variants include, but are not limited to, replacement of an amino acid with one having similar properties, such as the conservative amino acid substitutions of Table 1. Also provided are isolated polypeptides comprising the V_L domains of the anti-SIRPa antibodies of the invention *(e.g.,* SEQ ID NOs: 76, 90, 92, 94, 96, 98, 100, 8, 20, 22, 24, 26, 28, and 32), and isolated polypeptides comprising the V_H domains of the anti-SIRPa antibodies of the invention *(e.g.*, SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 7, 10, 12, 14, 16, 18, and 30) having up to 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid substitutions, and preferably conservative substitutions.

[001 95] The present invention further comprises the polynucleotides encoding any of the polypeptides or immunoglobulin chains of anti-SIRPa antibodies and antigen-binding fragments thereof of the invention. For example, the present invention includes the polynucleotides encoding the amino acids described in any one of SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 102, 7, 10, 12, 14, 16, 18, and 30; and SEQ ID NOs: 76, 90, 92, 94, 96, 98, 100, 104, 8, 20, 22, 24, 26, 28, and 32.

[001 96] In one embodiment, an isolated polynucleotide, for example DNA, encoding the polypeptide chains of the isolated antibodies or antigen-binding fragments set forth herein is provided. In one embodiment, the isolated polynucleotide encodes an antibody or antigen-binding fragment thereof comprising at least one mature immunoglobulin light chain variable (VL) domain according to the invention and/or at least one mature immunoglobulin heavy chain variable (VH) domain according to the invention. In some embodiments, the isolated polynucleotide encodes both a light chain and a heavy chain on a single polynucleotide molecule, and in other embodiments the light and heavy chains are encoded on separate

polynucleotide molecules. In another embodiment, the polynucleotides further encodes a signal sequence.

[00197] This present invention also provides vectors, *e.g.*, expression vectors, such as plasmids, comprising the isolated polynucleotides of the invention, wherein the polynucleotide is operably linked to control sequences that are recognized by a host cell when the host cell is transfected with the vector. Also provided are host cells comprising a vector of the present invention and methods for producing the antibody or antigen-binding fragment thereof or polypeptide disclosed herein comprising culturing a host cell harboring an expression vector or a nucleic acid encoding the immunoglobulin chains of the antibody or antigen-binding fragment thereof in culture medium, and isolating the antigen or antigen-binding fragment thereof from the host cell or culture medium.

Binding Affinity

[00198] By way of example, and not limitation, the antibodies and antigen-binding fragments disclosed herein may bind human SIRPa bivalently with a K_D value of 10 x 10^{-9} M or lower) as determined by surface plasmon resonance (e.g., BIACORE) or a similar technique (e.g. KinExa or bio-layer interferometry (OCTET)). In one embodiment, the antibodies and antigen-binding fragments disclosed herein may bind human SIRPa or bivalently with a K_D value of about 5-10 x 10^{-9} M as determined by surface plasmon resonance (e.g., BIACORE) or a similar technique (e.g. KinExa or OCTET). Affinity is calculated as $K_D = k_{off}/k_{on}$ (k_{off} is the dissociation rate constant, K_{on} is the association rate constant and K_D is the equilibrium constant). Affinity can be determined at equilibrium by measuring the fraction bound (r) of labeled ligand at various concentrations (c). The data are graphed using the Scatchard equation: r/c = K(n-r): where r = moles of bound ligand/mole of receptor at equilibrium; c = free ligand concentration at equilibrium; K = equilibrium association constant; and n = number of ligand binding sites per receptor molecule. By graphical analysis, r/c is plotted on the Y-axis versus r on the X-axis, thus producing a Scatchard plot. Antibody affinity measurement by Scatchard analysis is well known in the art. *See, e.g.*, van Erp *et ai, J. Immunoassay* 12: 425-43, 1991; Nelson and Griswold, *Compiit. Methods Programs Biomed.* 27: 65-8, 1988.

Humanness

[00199] For purposes of this document, "humanness" is measured using the T20 score analyzer to quantify the humanness of the variable region of monoclonal antibodies as described in Gao SH, Huang K, Tu H, Adler AS. Monoclonal antibody humanness score and its applications. *BMC Biotechnology*. 2013: 13:55. doi:10.1 186/1472-6750-13-55).

[00200] A web-based tool is provided to calculate the T20 score of antibody sequences using the T20 Cutoff Human Databases: http://abAnalyzer.lakepharma.com. In computing a T20 score, an input VH, VK, or VL variable region protein sequence is first assigned Kabat numbering, and CDR residues are identified. The full-length sequence or the framework only sequence (with CDR residues removed) is compared to every sequence in a respective antibody database using the blastp protein-protein BLAST algorithm. The sequence identity between each pairwise comparison is isolated, and after every sequence in the database has been analyzed, the sequences are sorted from high to low based on the sequence identity to the input sequence. The percent identity of the Top 20 matched sequences is averaged to obtain the T20 score.

[00201] For each chain type (VH, VK, VL) and sequence length (full-length or framework only) in the "All Human Databases," each antibody sequence was scored with its respective database using the T20 score analyzer. The T20 score was obtained for the top 20 matched sequences after the input sequence itself was excluded (the percent identity of sequences 2 through 2 1 were averaged since sequence 1 was always the input antibody itself). The T20 scores for each group were sorted from high to low. The decrease in score was roughly linear for most of the sequences; however the T20 scores for the bottom -15% of antibodies started decreasing sharply. Therefore, the bottom 15 percent of sequences were removed and the remaining sequences formed the T20 Cutoff Human Databases, where the T20 score cutoff indicates the lowest T20 score of a sequence in the new database.

[00202] As used herein, a "Human" antibody is one that has a T20 humanness score of at least 79%, and more preferably at least 85%.

Ability of Anti-hSIRPa Antibodies to Block Binding to CD47

[00203] In some embodiments, the anti-SIRPa antibodies or antigen binding fragments of the invention are able to block binding of human SIRPa to human CD47. The ability to block binding of human SIRPa to human CD47 can be determined using any method known in the art.

In one embodiment, the ability of the antibodies to block binding of human SIRPa to human CD47 is determined using an ELISA assay.

Methods of Making Antibodies and Antigen-binding Fragments Thereof

[00204] Thus, the present invention includes methods for making an anti-SIRPa antibody or antigen-binding fragment thereof of the present invention comprising culturing a hybridoma cell that expresses the antibody or fragment under condition favorable to such expression and, optionally, isolating the antibody or fragment from the hybridoma and/or the growth medium (e.g. cell culture medium).

[00205] The anti-SIRPa antibodies disclosed herein may also be produced recombinantly *(e.g.,* in an *E. coli*/YI expression system, a mammalian cell expression system or a lower eukaryote expression system). In this embodiment, nucleic acids encoding the antibody immunoglobulin molecules of the invention *(e.g.*, V_H or V_L) may be inserted into a pET-based plasmid and expressed in the *E. coli*/T7 system. For example, the present invention includes methods for expressing an antibody or antigen-binding fragment thereof or immunoglobulin chain thereof in a host cell *(e.g.,* bacterial host cell such as *E.coli* such as BL21 or BL21DE3) comprising expressing T7 RNA polymerase in the cell which also includes a polynucleotide encoding an immunoglobulin chain that is operably linked to a T7 promoter. For example, in an embodiment of the invention, a bacterial host cell, such as a *E. coli,* includes a polynucleotide encoding the T7 RNA polymerase gene operably linked to a *lac* promoter and expression of the polymerase and the chain is induced by incubation of the host cell with IPTG (isopropyl-beta-D-thiogalactopyranoside).

[00206] There are several methods by which to produce recombinant antibodies which are known in the art. One example of a method for recombinant production of antibodies is disclosed in U.S. Patent No. 4,816,567.

[00207] Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-medialed transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral

vectors. Methods of transforming cells are well known in the art. See, for example, U.S. Patent Nos. 4,399,216; 4,912,040; 4,740,461 and 4,959,455.

[00208] Thus, the present invention includes recombinant methods for making an anti-SIRPa antibody or antigen-binding fragment thereof of the present invention, or an immunoglobulin chain thereof, comprising introducing a polynucleotide encoding one or more immunoglobulin chains of the antibody or fragment *(e.g.,* heavy and/or light immunoglobulin chain); culturing the host cell *(e.g.,* CHO or *Pichia* or *Pichia pastoris)* under condition favorable to such expression and, optionally, isolating the antibody or fragment or chain from the host cell and/or medium in which the host cell is grown.

[00209] Anti-SIRPa antibodies can also be synthesized by any of the methods set forth in U.S. Patent No. 6,331,415.

[00210] Eukaryotic and prokaryotic host cells, including mammalian cells as hosts for expression of the antibodies or fragments or immunoglobulin chains disclosed herein are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, *inter alia,* Chinese hamster ovary (CHO) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells *(e.g..* Hep G2), A549 cells, 3T3 cells, HEK-293 cells and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Cell lines of particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells and fungal cells. Fungal cells include yeast and filamentous fungus cells including, for example, *Pichia pastoris, Pichia finlandica, Pichia trehalophila, Pichia koclamae, Pichia membranaefaciens, Pichia minuta (Ogataea minuta, Pichia lindneri), Pichia opuntiae, Pichia thermotolerans, Pichia salictaria, Pichia guercuum, Pichia pijperi, Pichia stiptis, Pichia methanolica, Pichia* sp., *Saccharomyces* ***cerevisiae,*** *Saccharomyces* sp., *Hansenula polymorpha, Kluyveromyces sp., Kluyveromyces lactis, Candida albicans, Aspergillus nidulans, Aspergillus niger, Aspergillus oryzae,* ***Trichoderma*** *reesei, Chrysosporium luckfwweti.se, Fusarium* sp., *Fusarium gramineum, Fusarium venenatum, Physcomitrella patens* and *Neurospora crassa. Pichia sp.,* any *Saccharomyces sp., Hansenula polymorpha,* any *Kluyveromyces sp., Candida albicans,* any

Aspergillus sp., Trichoderma reesei, Chrysospoiium lucknowense, any *Fusarium sp., Yarrowia Upolytica,* and *Neurospora crassa.* When recombinant expression vectors encoding the heavy chain or antigen-binding portion or fragment thereof, and/or the light chain or antigen-binding fragment thereof are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody or fragment or chain in the host cells or secretion into the culture medium in which the host cells are grown.

[00211] Antibodies and antigen-binding fragments thereof and immunoglobulin chains can be recovered from the culture medium using standard protein purification methods. Further, expression of antibodies and antigen-binding fragments thereof and immunoglobulin chains of the invention (or other moieties therefrom) from production cell lines can be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common approach for enhancing expression under certain conditions. The GS system is discussed in whole or part in connection with European Patent Nos. 0216846, 0256055, and 0323997 and 0338841. Thus, in an embodiment of the invention, the mammalian host cells *(e.g.,* CHO) lack a glutamine synthetase gene and are grown in the absence of glutamine in the medium wherein, however, the polynucleotide encoding the immunoglobulin chain comprises a glutamine synthetase gene which complements the lack of the gene in the host cell.

[00212] The present invention includes methods for purifying an anti-SIRPa antibody or antigen-binding fragment thereof of the present invention comprising introducing a sample comprising the antibody or fragment to a purification medium (e.g., cation exchange medium, anion exchange medium, hydrophobic exchange medium, affinity purification medium (e.g., protein-A, protein-G, protein-A/G, protein-L)) and either collecting purified antibody or fragment from the flow-through fraction of said sample that does not bind to the medium; or, discarding the flow-through fraction and eluting bound antibody or fragment from the medium and collecting the eluate. In an embodiment of the invention, the medium is in a column to which the sample is applied. In an embodiment of the invention, the purification method is conducted following recombinant expression of the antibody or fragment in a host cell, e.g., wherein the host cell is first lysed and, optionally, the lysate is purified of insoluble materials prior to purification on a medium.

[00213] In general, glycoproteins produced in a particular cell line or transgenic animal will have a glycosylation pattern that is characteristic for glycoproteins produced in the cell line or transgenic animal. Therefore, the particular glycosylation pattern of an antibody will depend on the particular cell line or transgenic animal used to produce the antibody. However, all antibodies encoded by the nucleic acid molecules provided herein, or comprising the amino acid sequences provided herein, comprise the instant invention, independent of the glycosylation pattern the antibodies may have. Similarly, in particular embodiments, antibodies with a glycosylation pattern comprising only non-fucosylated *N*-glycans may be advantageous, because these antibodies have been shown to typically exhibit more potent efficacy than their fucosylated counterparts both *in vitro* and *in vivo (See* for example, Shinkawa *et al., J. Biol. Chem.* 278: 3466-3473 (2003); U.S. Patent Nos. 6,946,292 and 7,214,775). These antibodies with non-fucosylated *N*-glycans are not likely to be immunogenic because their carbohydrate structures are a normal component of the population that exists in human serum IgG.

[00214] The present invention includes bispecific and bifunctional antibodies and antigen-binding fragments having a binding specificity for SIRPa and another antigen such as, for example, CD19, CD20, CD22, CD24, CD25, CD30, CD33, CD38, CD44, CD52, CD56, CD70, CD96, CD97, CD99, CD117, CD123, c-Met, CEA, EGFR, EpCAM, HER2, HER3, PSMA, PTHR2, mesothelin, PD-1, PD-L1, TIM3, and methods of use thereof. A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, *e.g.,* Songsivilai, *et al.,* (1990) *Clin. Exp. Immunol.* 79: 315-321, Kostelny, *et al.,* (1992) *J Immunol.* 148:1547- 1553. In addition, bispecific antibodies may be formed as "diabodies" (Holliger, *et al.,* (1993) *PNAS USA* 90:6444-6448) or as "Janusins" (Traunecker, *et al.* (1991) *EMBO J.* 10:3655-3659 and Traunecker, *et al.,* (1992) *Int. J. Cancer Suppi.* 7:51-52). Included are "Duobodies," which are bispecific antibodies with normal IgG structures (Labrijn et al., 2013, Proc. Natl. Acad. Sci. USA 110 (13): 5145-5150).

[00215] The present invention further includes anti-SIRPa antigen-binding fragments of the anti-SIRPa antibodies disclosed herein. The antibody fragments include $F(ab)_2$ fragments, which may be produced by enzymatic cleavage of an IgG by, for example, pepsin. Fab fragments may be produced by, for example, reduction of $F(ab)_2$ with dithiothreitol or mercaptoethylamine.

[00216] Immunoglobulins may be assigned to different classes depending on the amino acid sequences of the constant domain of their heavy chains. In some embodiments, different constant domains may be appended to humanized V_L and V_H regions derived from the CDRs provided herein. There are at least five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.* IgGl, IgG2, IgG3 and IgG4; IgAl and IgA2. The invention comprises antibodies and antigen-binding fragments of any of these classes or subclasses of antibodies.

[00217] In one embodiment, the antibody or antigen-binding fragment comprises a heavy chain constant region, e.g. a human constant region, such as γ1, γ2, γ3, or γ4 human heavy chain constant region or a variant thereof. In another embodiment, the antibody or antigen-binding fragment comprises a light chain constant region, *e.g. a* human light chain constant region, such as lambda or kappa human light chain region or variant thereof. By way of example, and not limitation the human heavy chain constant region can be *γ4* and the human light chain constant region can be kappa. In an alternative embodiment, the Fc region of the antibody is γ4 with a Ser228Pro mutation (Schuurman, J *et. a*/., *Mol. Immunol.* 38: 1-8, 2001).

[00218] In one embodiment, the antibody or antigen-binding fragment comprises a heavy chain constant region of the IgGl subtype. In one embodiment, the antibody or antigen-binding fragment comprises a heavy chain constant region of the IgG2 subtype. In one embodiment, the antibody or antigen-binding fragment comprises a heavy chain constant region of the IgG4 subtype.

Antibody Engineering

[00219] Further included are embodiments in which the anti-SIRPa antibodies and antigen-binding fragments thereof are engineered antibodies to include modifications to framework residues within the variable domains the antibody, *e.g.* to improve the properties of the antibody or fragment. Typically, such framework modifications are made to decrease the immunogenicity of the antibody or fragment. This is usually accomplished by replacing non-CDR residues in the variable domains *(i.e.* framework residues) in a parental *(e.g.* rodent) antibody or fragment with analogous residues from the immune repertoire of the species in which the antibody is to be used, *e.g.* human residues in the case of human therapeutics. Such an antibody or fragment is referred to as a "humanized" antibody or fragment. In some cases, it is desirable to increase the

affinity, or alter the specificity of an engineered *(e.g.* humanized) antibody. One approach is to mutate one or more framework residues to the corresponding germline sequence. More specifically, an antibody or fragment that has undergone somatic mutation can contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody or fragment framework sequences to the germline sequences from which the antibody or fragment is derived. Another approach is to revert to the original parental *(e.g.,* rodent) residue at one or more positions of the engineered *(e.g.* humanized) antibody, *e.g.* to restore binding affinity that may have been lost in the process of replacing the framework residues. (See, *e.g.,* U.S. Patent No. 5,693,762, U.S. Patent No. 5,585,089 and U.S. Patent No. 5,530,101).

[00220] In certain embodiments, the anti-SIRPa antibodies and antigen-binding fragments thereof are engineered (e.g. humanized) to include modifications in the framework and/or CDRs to improve their properties. Such engineered changes can be based on molecular modelling. A molecular model for the variable region for the parental (non-human) antibody sequence can be constructed to understand the structural features of the antibody and used to identify potential regions on the antibody that can interact with the antigen. Conventional CDRs are based on alignment of immunoglobulin sequences and identifying variable regions. Kabat et al., (1991) Sequences of Proteins of Immunological Interest, Kabat, *et al.;* National Institutes of Health, Bethesda, MD; 5th ed.; NIH Publ. No. 91-3242; Kabat (1978) *Adv. Prot. Chem.* 32:1-75; Kabat, *et al.,* (1977) *J. Biol. Chem.* 252:6609-6616. Chothia and coworkers carefully examined conformations of the loops in crystal structures of antibodies and proposed hypervariable loops. Chothia, *et al,* (1987) *J Mol. Biol.* 196:901-917 or Chothia, *et al.,* (1989) *Nature* 342:878-883. There are variations between regions classified as "CDRs" and "hypervariable loops". Later studies (Raghunathan et al, (2012) *J. MolRecog.* 25, 3, 103-113) analyzed several antibody - antigen crystal complexes and observed that the antigen binding regions in antibodies do not necessarily conform strictly to the "CDR" residues or "hypervariable" loops. The molecular model for the variable region of the non-human antibody can be used to guide the selection of regions that can potentially bind to the antigen. In practice the potential antigen binding regions based on the model differ from the conventional "CDR"s or "hypervariable" loops. Commercial scientific software such as Discovery Studio (BIOVIA, Dassault Systems)) can be used for molecular modeling. Human frameworks can be selected based on best matches with the non-

human sequence both in the frameworks and in the CDRs. For FR4 (framework 4) in VH, VJ regions for the human germlines are compared with the corresponding non-human region. In the case of FR4 (framework 4) in VL, J-kappa and J-Lambda regions of human germline sequences are compared with the corresponding non-human region. Once suitable human frameworks are identified, the CDRs are grafted into the selected human frameworks. In some cases, certain residues in the VL-VH interface can be retained as in the non-human (parental) sequence. Molecular models can also be used for identifying residues that can potentially alter the CDR conformations and hence binding to antigen. In some cases, these residues are retained as in the non-human (parental) sequence. Molecular models can also be used to identify solvent exposed amino acids that can result in unwanted effects such as glycosylation, deamidation and oxidation. Developability filters can be introduced early on in the design stage to eliminate/minimize these potential problems.

[00221] Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T cell epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent No. 7,125,689.

[00222] In particular embodiments, it will be desirable to change certain amino acids containing exposed side-chains to another amino acid residue in order to provide for greater chemical stability of the final antibody, so as to avoid deamidation or isomerization. The deamidation of asparagine may occur on NG, DG, NG, NS, NA, NT, QG or QS sequences and result in the creation of an isoaspartic acid residue that introduces a kink into the polypeptide chain and decreases its stability (isoaspaitic acid effect). Isomerization can occur at DG, DS, DA or DT sequences. In certain embodiments, the antibodies of the present disclosure do not contain deamidation or asparagine isomerism sites.

[00223] For example, an asparagine (Asn) residue may be changed to Gin or Ala to reduce the potential for formation of isoaspartate at any Asn-Gly sequences, particularly within a CDR. A similar problem may occur at a Asp-Gly sequence. Reissner and Aswad (2003) *Cell, Mol. Life Sci.* 60:1281. Isoaspartate formation may debilitate or completely abrogate binding of an antibody to its target antigen. *See,* Presta (2005) *J. Allergy Clin. Immunol.* 116:731 at 734. In one embodiment, the asparagine is changed to glutamine (Gin). It may also be desirable to alter

an amino acid adjacent to an asparagine (Asn) or glutamine (Gin) residue to reduce the likelihood of deamidation, which occurs at greater rates when small amino acids occur adjacent to asparagine or glutamine. *See,* Bischoff & Kolbe (1994) *J. Chrornatog.* 662:261. In addition, any methionine residues (typically solvent exposed Met) in CDRs may be changed to Lys, Leu, Ala, or Phe or other amino acids in order to reduce the possibility that the methionine sulfur would oxidize, which could reduce antigen-binding affinity and also contribute to molecular heterogeneity in the final antibody preparation. *Id.* Additionally, in order to prevent or minimize potential scissile Asn-Pro peptide bonds, it may be desirable to alter any Asn-Pro combinations found in a CDR to Gin-Pro, Ala-Pro, or Asn-Ala. Antibodies with such substitutions are subsequently screened to ensure that the substitutions do not decrease the affinity or specificity of the antibody for SIRPa, or other desired biological activity to unacceptable levels.

TABLE 2. Exemplary stabilizing CDR variants

CDR Residue	Stabilizing Variant Sequence
Asn-Gly (N-G)	Gln-Gly, Ala-Gly, or Asn-Ala (Q-G), (A-G), or (N-A)
Asp-Gly (D-G)	Glu-Gly, Ala-Gly or Asp-Ala (E-G), (A-G), or (D-A)
Met (M)	Lys, Leu, Ala, or Phe (K), (L), (A), or (F)
Asn (N)	Gln or Ala (Q) or (A)
Asn-Pro (N-P)	Gln-Pro, Ala-Pro, or Asn-Ala (Q-P), (A-P), or (N-A)

[00224] Another type of framework modification involves mutating one or more residues within the framework regions to prevent aggregation. The risk of an antibody to aggregate can be assessed using the spatial aggregation propensity -*See,* Chennamsetty, N et al (2010) *./. Phys. Chem.* 114, 6614-6624. The method requires the calculation of the Solvent Accessible Area (SAA) for each atom. The molecular aggregation score is then calculated as the sum of all atomic scores. For a given radius and size of molecule, this is an approximate indication of its overall tendency to aggregate. Residues with a high aggregation score are replaced by residues with a lower score (e.g. more hydrophilic amino acids).

Antibody Engineering of the Fc region

[00225] The antibodies *(e.g.,* humanized antibodies) and antigen-binding fragments thereof disclosed herein can also be engineered to include modifications within the Fc region, typically to alter one or more properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or effector function *(e.g.,* antigen-dependent cellular cytotoxicity). Furthermore, the antibodies and antigen-binding fragments thereof disclosed herein can be chemically modified *(e.g.,* one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more properties of the antibody or fragment. Each of these embodiments is described in further detail below. The numbering of residues in the Fc region is that of the EU index of Kabat.

[00226] The antibodies and antigen-binding fragments thereof disclosed herein also include antibodies and fragments with modified (or blocked) Fc regions to provide altered effector functions. See, *e.g.,* U.S. Pat. No. 5,624,821; WO2003/086310; WO20()5/120571; WO2006/0057702. Such modifications can be used to enhance or suppress various reactions of the immune system, with possible beneficial effects in diagnosis and therapy. Alterations of the Fc region include amino acid changes (substitutions, deletions and insertions), glycosylation or deglycosylation, and adding multiple Fc regions. Changes to the Fc can also alter the half-life of antibodies in therapeutic antibodies, enabling less frequent dosing and thus increased convenience and decreased use of material. *See* Presta (2005) *J. Allergy Clin. Immunol.* 116:731 at 734-35.

[00227] In one embodiment, the antibody or antigen-binding fragment of the invention is an IgG4 isotype antibody or fragment comprising a Serine to Proline mutation at a position corresponding to position 228 (S228P; EU index; SEQ ID NO: 66) in the hinge region of the heavy chain constant region. This mutation has been reported to abolish the heterogeneity of inter-heavy chain disulfide bridges in the hinge region (Aiigal *et al* (1993). *Mol, Immunol.* 30:105-108; position 241 is based on the Kabat numbering system).

[00228] In one embodiment of the invention, the hinge region of CHI is modified such that the number of cysteine residues in the hinge region is increased or decreased. This approach is described further in U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge

region of CHI is altered, for example, to facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[00229] In another embodiment, the Fc hinge region of an antibody or antigen-binding fragment of the invention is mutated to decrease the biological half-life of the antibody or fragment. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody or fragment has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Patent No. 6,165,745.

[00230] In another embodiment, the antibody or antigen-binding fragment of the invention is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375. Alternatively, to increase the biological half-life, the antibody can be altered within the CHI or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022.

[00231] In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector function(s) of the antibody or antigen-binding fragment. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322 can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand and retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260.

[00232] In another example, one or more amino acids selected from amino acid residues 329, 331 and 322 can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent No. 6,194,551 .

[00233] In another example, one or more amino acid residues within amino acid positions 231 and 239 are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351.

[00234] The proteins of the invention, which are preferably antibodies and most preferably IgG antibodies or fragments thereof, may have altered (e.g., relative to an unmodified antibody) FcyR binding properties (examples of binding properties include but are not limited to, binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (k_{off} and k_{on} respectively), binding affinity and/or avidity) and that certain alterations are more or less desirable. It is known in the art that the equilibrium dissociation constant (¾) is defined as k_{off}¾ ₃n, and K_a is the reciprocal of K_D.

[00235] The affinities and binding properties of an Fc region for its ligand, may be determined by a variety of in vitro assay methods (biochemical or immunological based assays) known in the art for determining Fc-FcyR interactions, i.e., specific binding of an Fc region to an FcyR including but not limited to, equilibrium methods (e.g., enzyme-linked immuno absorbent assay (ELISA) or radioimmunoassay (RIA)), or kinetics (e.g. BIACORE©, Octet®, or KinExa® analysis), and other methods such as indirect binding assays, competitive inhibition assays, fluorescence resonance energy transfer (FRET), gel electrophoresis and chromatography (e.g., gel filtration). These and other methods may utilize a label on one or more of the components being examined and/or employ a variety of detection methods including but not limited to chromogenic, fluorescent, luminescent, or isotopic labels.

[00236] In certain embodiments, the proteins of the present invention bind to one or more human FcyRs selected from the group consisting of FcyRI, FcyRIIB, FcyRIIC, FCYRIIIA-F 158, and FcyRrnA-V158 with an affinity at least 10-fold, preferably at least 30-fold, and more preferably at least 100-fold, less than equivalent protein having a wild-type human IgGl heavy chain constant domain (SEQ ID NO: 119) Fc region or a wild-type human IgG4 heavy chain constant domain (SEQ ID NO: 66) Fc region.

[00237] In various embodiments, the proteins of the invention comprise an immunoglobulin Fc region comprising an immunoglobulin C2 region and an immunoglobulin C3 region and an immunoglobulin hinge region. By way of example, the immunoglobulin Fc region may be an IgG Fc region, an IgE Fc region, or an IgA Fc region. In certain preferred embodiments, the protein comprises two immunoglobulin Fc regions, each immunoglobulin Fc region comprising an immunoglobulin C2 region and an immunoglobulin C3 region and an immunoglobulin hinge region, wherein the hinge region of one of the immunoglobulin Fc regions is bound to the hinge

region of the other immunoglobulin Fc region to form a dimeric Fc structure. Most preferably, such a protein is a human or humanized IgG protein.

[00238] In certain embodiments, the proteins of the invention comprise a mutated IgG4 Fc region, and preferably the protein is an IgG comprising two mutated IgG4 Fc regions to form a dimeric Fc structure. By way of example, a mutated IgG4 Fc region may comprise one of the mutations, or mutational combinations, recited in Table 3. The numbering system of the constant region referred to in this table is that of the EU index as set forth in Kabat *et al.* (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). In the table, the first letter and number represent the unmodified amino acid and its position and the second letter represents the substituted amino acid at said position. For those entries that include combinations of more than one mutation, each mutation in the combination is separated by a "/".

Table 3:

N297Q	L235E	N297Q/L235E
F234A	Q268A	F234A/L235A/G237A/P238A
F234A/L235A/ΔG236 /G237A/P238A	F234A/L235A/G237A /P238A/Q268A	F234A/L235A/ΔG236/G237A /P238A/Q268A
F234A/L235A	L235E/P329G	L235A/G237A/E318A
F234A/L235A/G237A /P238S	F234A/L235A/ΔG236 /G237A/P238S	F234A/L235A/G237A /P238S/Q268A
F234A/L235A/ΔG236 /G237A/P238S/Q268A		

[00239] In certain embodiments, the proteins of the invention comprise a mutated IgGl Fc region, and preferably the protein is an IgG comprising two mutated IgGl Fc regions to form a dimeric Fc structure. By way of example, a mutated IgGl Fc region may comprise one of the mutations recited in Table 4. The numbering system of the constant region referred to in this table is that of the EU index as set forth in Kabat *et al.* (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). In the table, the first letter and number represent the unmodified amino acid and its position and the second letter represents the substituted amino acid at said position.

Table 4:

K222Y	P232K	A231K
E233N	E233Q	E233R
E233S	E233T	E233H
E233A	E233V	E233L

E233F	E233M	E233Y
E233W	E233G	L234D
L234E	L234N	L234Q
L234T	L234H	L234F
L234K	L234R	L234S
L234A	L234M	L234V
L235E	L235T	L235F
L235K	L235R	L235A
L235M	L235W	L235N
L235Q	L235H	L235V
G236A	G236N	G236R
G236H	G236L	G236F
G236P	G237A	G237E
G237N	G237Q	G237K
G237R	G237S	G237T
G237H	G237L	G237I
G237F	G237M	G237Y
G237P	P238K	P238N
P238R	P238S	P238T
P238Y	P238G	P238A
S239A	S239N	S239F
S239K	S239R	S239V
S239W	S239P	S239H
S239Y	D249H	V240A
F241W	F241L	F243W
F243L	F243E	P244H
P245A	P247V	P247G
V253I	V263I	V263T
V263M	V264D	V264E
V264K	V264F	V264M
V264H	V264W	V264G
V264Q	V264A	V264L
D265A	D265E	D265Q
D265S	D265H	D265V
D265L	D265F	D265M
D265Y	D265N	D265G
V266T	V266M	V266A
S267G	S267H	S267N
S267P	S267R	S267T
S267F	S267W	E269A
E269K	E269S	E269V
E269F	E269I	E269M
E269W	E269H	E269T
E269L	E269N	E269Y
E269R	E269P	E269G

D270A	D270N	D270E
D270Q	D270T	D270H
D270R	D270S	D270L
D270I	D270F	D270W
D270P	D270G	P271H
P271Q	P271K	P271R
P271S	P271V	P271F
P271W	D280L	D280W
D280P	E293F	E294A
E293Y	E294K	E294R
E294S	E294V	E294L
E294F	Q295A	Q295W
Q295P	Q295G	Y296E
Y296Q	Y296D	Y296N
Y296S	Y296T	Y296L
Y296I	Y296A	Y296V
Y296M	N297S	N297D
N297Q	N297A	S298T
S298N	S298K	S298R
T299A	T299H	T299D
T299E	T299N	T299Q
T299K	T299R	T299I
T299F	T299M	T299Y
T299W	T299S	T299V
T299P	T299G	Y300E
Y300K	Y300R	Y300S
Y300P	Y300W	V303A
V303D	W313F	E318A
E318V	E318Q	E318H
E318L	E318Y	K320A
K322A	K322E	N325A
N325V	N325H	N325K
N325Y	N325W	N325P
N325G	N325Q	N325D
N325E	N325L	N325I
A327Q	A327E	A327N
A327L	A327I	A327F
A327W	L328N	L328F
L328H	L328R	L328T
L328V	L328I	L328P
L328M	L328E	L328A
P329A	P329F	P329D
P329N	P329Q	P329K
P329S	P329T	P329H
P329V	P329L	P329M

P329Y	P329W	P329G
P329R	A330L	A330R
A330P	A330T	A330V
A330F	A330H	P331A
P331S	P331N	P331E
I332K	I332N	I332Q
I332T	I332H	I332Y
I332A	I332R	E333N
E333R	I336E	I336Y
S337H		

[00240] In certain embodiments, a mutated IgGl Fc region may comprise one of the mutational combinations recited in Table 5. The numbering system of the constant region referred to in this table is that of the EU index as set forth in Kabat *et al.* (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). In the table, the first letter and number represent the unmodified amino acid and its position and the second letter represents the substituted amino acid at said position. For each of the combinations of more than one mutation, each mutation in the combination is separated by a "/" and deletions are indicated by a "Δ".

Table 5:

C220S/C226S/C229S/P238S	C226S/C229S/E233P/L234V/ L235A	E233P/L234V/L235A
E233P/L234V/L235A/ΔG236	E233P/L234V/L235A/ΔG236/ A327G/A330S/P331S	L234A/L235A
L235A/G237A	L235A/G237A/E318S/K320S/ K322S	L235A/G237A/P331A
L234F/L235E	L234F/L235E/D265A	L234F/L235E/D265A/ N297Q/P331S
L234F/L235E/N297Q	L234F/L235E/P329G	L234F/L235A/K322Q/ M252Y/S254T/T256E
L234F/L235Q/K322Q/M252Y/ S254T/T256E	L234F/L235Q/P331G/M252Y/ S254T/T256E	G236R/L328R
S239D/D265I/N297D/I332E	S239D/D265L/N297D/I332E	S239D/D265F/N297D/ I332E
S239D/D265Y/N297D/I332E	S239D/D265T/N297D/I332E	S239D/N297D/A330Y/ I332E
S239D/F241S/F243H/V262T/V264T/N297D/K326E/I332E	V264E/N297D/I332E	D265A/P331S
D265A/N297Q	N297D/D265Y/T299L/I332E	N297D/D265Y/I332E
N297D/I332E/Y296D	N297D/I332E	N297D/I332E/Y296E
N297D/I332E/Y296N	N297D/I332E/Y296Q	N297D/I332E/Y296H

N297D/I332E/Y296T	N297D/1332E/T299V	N297D/1332E/T2991
N297D/I332E/T299L	N297D/I332E/T299F	N297D/I332E/T299H
N297D/1332E/T299E	N297D/1332E/A330Y	N297D/1332E/S298A/ A330Y
N297E/D265F/I332E	N297E/1332E	F241E/F243R/V262E/ V264R
F241E/F243Q/V262T/V264E	F24 1L/F243L/V262I/V264I	F241W/F243W
F241W/F243W/V262A/V264A	F24IL/V262I	F243L/V2621/V264W
F241 Y/F243Y/V262T/V264T	F241E/F243R/V262E/V 264R	F241E/F243Q/V262T/V264E
F241R/F243Q/V262T/V264R	F24 1E/F243Y/V262T/V264R	P244H/P245A/P247V
F241E/F243R/V262E/V264R/I3 32E	F24IE/F243Y/V262T/V264R	F241E/F243Y/V262T/ V264R/1332E
S239E/D265G	S239E/D265N	S239E/D265Q
M252Y/S254T/T256E	S267Q/A327S	S267L/A327S
N297S/1332E	S239N/1332N	S239N/I332Q
S239Q/I332N	S239Q/1332Q	S298N/Y300S
S298N/T299A/Y300S	N297Q/S298N/Y300S	E318S/K320S/K322S
E318S/K320S/K322S/P3 11A	L328E/I332E	L328N/I332E
L234A/L235A/G237A/P238A /H268A/A330S/P331S	L234A/L235A/G237A/P238S/H 268A/A330S/P331S	L234A/L235A/G237A/P238A/H 268A/A330S/P331S
L328Q/I332E	L328H/I332E	

[00241] In certain embodiments, the proteins of the invention comprise a wild type or mutated IgG2 Fc region, and preferably the protein is an IgG comprising two wild type or mutated IgG2 Fc regions to form a dimeric Fc structure. A mutated IgG2 Fc region may comprise one of the mutations, or mutational combinations, recited in Table 6. The numbering system of the constant region referred to in this table is that of the EU index as set forth in Kabat *et al.* (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). In the table, the first letter and number represent the unmodified amino acid and its position and the second letter represents the substituted amino acid at said position. For those entries that include combinations of more than one mutation, each mutation in the combination is separated by a "/".

Table 6:

V234A	G237A	A235E/G237A
V234A/A235E/G237A	V234A/G237A	V234A/G237A/P238S
H268Q/V309L/A330S/P331S	V234A/G237A/H268A/V309L/ A330S/P331S	V234A/G237A/H268Q/V309L/ A330S/P331S
V234A/G237A/P238S/H268A/ V309L/A330S/P331S	P233S/V234A/G237A/P238S	P233S/V234A/G237A/H268A/ V309L/A330S/P331S
P233S/V234A/G237A/H268Q/ V309L/A330S/P331S	P233S/V234A/G237A/P238S/ H268A/V309L/A330S/P331S	

Production of Antibodies with Modified Glycosylation

[00242] In still another embodiment, the antibodies or antigen-binding fragments of the invention comprise a particular glycosylation pattern. For example, an afucosylated or an aglycosylated antibody or fragment can be made *(i.e.,* the antibody lacks fucose or glycosylation, respectively). The glycosylation pattern of an antibody or fragment may be altered to, for example, increase the affinity or avidity of the antibody or fragment for a SIRPa antigen. Such modifications can be accomplished by, for example, altering one or more of the glycosylation sites within the antibody or fragment sequence. For example, one or more amino acid substitutions can be made that result in removal of one or more of the variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such deglycosylalion may increase the affinity or avidity of the antibody or fragment for antigen. *See, e.g.,* U.S. Patent Nos. 5,714,350 and 6,350,861.

[00243] Antibodies and antigen-binding fragments disclosed herein may further include those produced in lower eukaryote host cells, in particular fungal host cells such as yeast and filamentous fungi have been genetically engineered to produce glycoproteins that have mammalian- or human-like glycosylation patterns (See for example, Choi *et al,* (2003) *Proc. Natl. Acad. Sci.* 100: 5022-5027; Hamilton *et al,* (2003) *Science* 301: 1244-1246; Hamilton *et al,* (2006) *Science* 313: 1441-1443; Nett et al., *Yeast* 28(3):237-52 (2011); Hamilton et al., *Curr Opin Biotechnol.* 18(5): 387-92 (2007)). A particular advantage of these genetically modified host cells over currently used mammalian cell lines is the ability to control the glycosylation profile of glycoproteins that are produced in the cells such that compositions of glycoproteins can be produced wherein a particular *N*-glycan structure predominates (see, *e.g.,* U.S. Patent No. 7,029,872 and U.S. Patent No. 7,449,308). These genetically modified host cells have been used to produce antibodies that have predominantly particular *N*-glycan structures (See for example, Li *et al,* (2006) *Nat. Biotechnol* 24: 210-215).

[00244] In particular embodiments, the antibodies and antigen-binding fragments thereof disclosed herein further include those produced in lower eukaryotic host cells and which comprise fucosylated and non-fucosylated hybrid and complex *N*-glycans, including bisected and multiantennary species, including but not limited to *N*-glycans such as $GlcNAc_{(1-4)}Man_3GlcNAc_2$; $Gal_{(1-4)}GlcNAc_{(1-4)}Man_3GlcNAc_2$; $NANA_{(1-4)}Gal_{(1-4)}GlcNAC_{(1-4)}Man_3GlcNAc_2$.

[00245] In particular embodiments, the antibodies and antigen-binding fragments thereof provided herein may comprise antibodies or fragments having at least one hybrid *N*-glycan selected from the group consisting of GlcNAcMan$_5$GlcNAc2; GalGlcNAcMan$_5$GlcNAc2; and NANAGalGlcNAcMan5GlcNAc2. In particular aspects, the hybrid *N*-glycan is the predominant *N*-glycan species in the composition.

[00246] In particular embodiments, the antibodies and antigen-binding fragments thereof provided herein comprise antibodies and fragments having at least one complex *N*-glycan selected from the group consisting of GlcNAcMan$_3$GlcNAc2; GalGlcNAcMan$_3$GlcNAc$_2$; NANAGalGlcNAcMan$_3$GlcNAc$_2$; GlcNAc$_2$Man$_3$GlcNAc$_2$; GalGlcNAc$_2$Man$_3$GlcNAc$_2$; Gal$_2$GlcNAc$_2$Man$_3$GlcNAc2; NANAGal2GlcNAc$_2$Man$_3$GlcNAc$_2$; and NANA2Gal2GlcNAc2Man$_3$GlcNAc2. In particular aspects, the complex *N*-glycan are the predominant *N*-glycan species in the composition. In further aspects, the complex *N*-glycan is a particular *N*-glycan species that comprises about 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99%, or 100% of the complex *N*-glycans in the composition. In one embodiment, the antibody and antigen binding fragments thereof provided herein comprise complex *N*-glycans, wherein at least 50%, 60%, 70%, 80%, 90%, 95%. 97%, 98%, 99%, or 100% of the complex *N*-glycans comprise the structure NANA2Gal$_2$GlcNAc2Man$_3$GlcNAc$_2$, wherein such structure is afucosylated. Such structures can be produced, e.g., in engineered *Pichia pastoris* host cells.

[00247] In particular embodiments, the *N*-glycan is fucosylated. In general, the fucose is in an <xl,3-linkage with the GlcNAc at the reducing end of the *N*-glycan, an al,6-linkage with the GlcNAc at the reducing end of the *N*-glycan, an a 1,2-linkage with the Gal at the non-reducing end of the *N*-glycan, an al,3-linkage with the GlcNac at the non-reducing end of the *N*-glycan, or an al,4-linkage with a GlcNAc at the non-reducing end of the *N*-glycan.

[00248] Therefore, in particular aspects of the above the glycoprotein compositions, the glycoform is in an al,3-linkage or α1,6-linkage fucose to produce a glycoform selected from the group consisting of Man$_5$GlcNAc$_2$(Fuc), GlcNAcMan$_5$GlcNAc$_2$(Fuc), Man$_3$GlcNAc$_2$(Fuc), GlcNAcMan$_3$GlcNAc$_2$(Fuc), GlcNAc$_2$Man$_3$GlcNAc$_2$(Fuc), GalGlcNAc$_2$Man$_3$GlcNAc$_2$(Fuc), Gal$_2$GlcNAc$_2$Man$_3$GlcNAc$_2$(Fuc), NANAGal$_2$GlcNAc$_2$Man$_3$GlcNAc$_2$(Fuc), and NANA$_2$Gal$_2$GlcNAc$_2$Man$_3$GlcNAc$_2$(Fuc); in an al,3-linkage or al,4-linkage fucose to produce a glycoform selected from the group consisting of GlcNAc(Fuc)Man$_5$GlcNAc$_2$,

GlcNAc(Fuc)Man $_3$GlcNAc $_2$, GlcNAc $_2$(Fuc, $_2$)Man $_3$GlcNAc $_2$, GalGlcNAc $_2$(Fuc, $_2$)Man $_3$GlcNAc $_2$, Gal $_2$GlcNAc $_2$(Fuc 1-2)Man3GlcNAc2, NANAGal2GlcNAc2(Fuc $_{1-2}$)Man $_3$GlcNAc $_2$, and NANA $_2$Gal $_2$GlcNAc2(Fuc $_{1-2}$)Man $_3$GlcNAc $_2$; or in an al,2-linkage fucose to produce a glycoform selected from the group consisting of Gal(Fuc)GlcNAc $_2$Man $_3$GlcNAc $_2$, Gal $_2$(Fuc $_{1-2}$)GlcNAc $_2$Man $_3$GlcNAc $_2$, NANAGal $_2$(Fuci $_{1-2}$)GlcNAc $_2$Man $_3$GlcNAc $_2$, and NANA $_2$Gal $_2$(Fuci $_{1-2}$)GlcNAc $_2$Man $_3$GlcNAc $_2$.

[00249] In further aspects, the antibodies *(e.g.,* humanized antibodies) or antigen-binding fragments thereof comprise high mannose *N*-glycans, including but not limited to, Man $_8$GlcNAc $_2$, Man $_7$GlcNAc $_2$, Man $_6$GlcNAc $_2$, Man $_5$GlcNAc $_2$, Man $_4$GlcNAc $_2$, or *N*-glycans that consist of the Man3GlcNAc2 *N*-glycan structure.

[00250] In further aspects of the above, the complex *N*-glycans further include fucosylated and non-fucosylated bisected and multianlennary species.

[00251] As used herein, the terms *"N*-glycan" and "glycoform" are used interchangeably and refer to an *N*-linked oligosaccharide, for example, one that is attached by an asparagine -*N*-acetylglucosamine linkage to an asparagine residue of a polypeptide. *N*-linked glycoproteins contain an *N*-acetylglucosamine residue linked to the amide nitrogen of an asparagine residue in the protein. The predominant sugars found on glycoproteins are glucose, galactose, mannose, fucose, *N*-acetylgalactosamine (GalNAc), *N*-acelylglucosamine (GlcNAc) and sialic acid *(e.g.,* *N*-acetyl-neuraminic acid (NANA)). The processing of the sugar groups occurs co-translationally in the lumen of the ER and continues post-lranslationally in the Golgi apparatus for *N*-linked glycoproteins.

[00252] *N*-glycans have a common pentasaccharide core of Man $_3$GlcNAc $_2$ ("Man" refers to mannose; "Glc" refers to glucose; and "NAc" refers to *N*-acetyl; GlcNAc refers to *N*-acetylglucosamine). Usually, *N*-glycan structures are presented with the non-reducing end to the left and the reducing end to the right. The reducing end of the *N*-glycan is the end that is attached to the Asn residue comprising the glycosylation site on the protein. *N*-glycans differ with respect to the number of branches (antennae) comprising peripheral sugars *(e.g.,* GlcNAc, galactose, fucose and sialic acid) that are added to the Man $_3$GlcNAc $_2$ ("Man3") core structure which is also referred to as the "trimannose core", the "pentasaccharide core" or the "paucimannose core". *N*-glycans are classified according to their branched constituents *(e.g.,*

high mannose, complex or hybrid). A "high mannose" type *N*-glycan has five or more mannose residues. A "complex" type *N*-glycan typically has at least one GlcNAc attached to the 1,3 mannose arm and at least one GlcNAc attached to the 1,6 mannose arm of a "trimannose" core. Complex *N*-glycans may also have galactose ("Gal") or *N*-acetylgalactosamine ("GalNAc") residues that are optionally modified with sialic acid or derivatives *(e.g.,* "NANA" or "NeuAc", where "Neu" refers to neuraminic acid and "Ac" refers to acetyl). Complex *N*-glycans may also have intrachain substitutions comprising "bisecting" GlcNAc and core fucose ("Fuc"). Complex *N*-glycans may also have multiple antennae on the "trimannose core," often referred to as "multiple antennary glycans." A "hybrid" *N*-glycan has at least one GlcNAc on the terminal of the 1,3 mannose arm of the trimannose core and zero or more mannoses on the 1,6 mannose arm of the trimannose core. The various *N*-glycans are also referred to as "glycoforms."

[00253] With respect to complex *N*-glycans, the terms "G-2", "G-l", "GO", "Gl ", "G2", "Al", and "A2" mean the following. "G-2" refers to an *N*-glycan structure that can be characterized as Man3GlcNAc2; the term "G-l " refers to an *N*-glycan structure that can be characterized as GlcNAcMaii3GlcNAc2; the term "GO" refers to an *N*-glycan structure that can be characterized as GlcNAc2Man3GlcNAc2; the term "Gl" refers to an *N*-glycan structure that can be characterized as GalGlcNAc2Man3GlcNAc2; the term "G2" refers to an *N*-glycan structure that can be characterized as Gal2GlcNAc2Man3GlcNAc2; the term "Al" refers to an *N*-glycan structure that can be characterized as NANAGal2GlcNAc2Man3GlcNAc2; and, the term "A2" refers to an *N*-glycan structure that can be characterized as NANA2Gal2GlcNAc2Man $_3$GlcNAc2. Unless otherwise indicated, the terms G-2", "G-l", "GO", "Gl ", "G2", "Al ", and "A2" refer to *N*-glycan species that lack fucose attached to the GlcNAc residue at the reducing end of the *N*-glycan. When the term includes an "F", the "F" indicates that the *N*-glycan species contains a fucose residue on the GlcNAc residue at the reducing end of the *N*-glycan. For example, G0F, G1F, G2F, A1F, and A2F all indicate that the *N*-glycan further includes a fucose residue attached to the GlcNAc residue at the reducing end of the *N*-glycan. Lower eukaryotes such as yeast and filamentous fungi do not normally produce *N*-glycans that produce fucose.

[00254] With respect to multiantennary *N*-glycans, the term "multiantennary *N*-glycan" refers to *N*-glycans that further comprise a GlcNAc residue on the mannose residue comprising the

non-reducing end of the 1,6 arm or the 1,3 arm of the *N*-glycan or a GlcNAc residue on each of the mannose residues comprising the non-reducing end of the 1,6 arm and the 1,3 arm of the *N*-glycan. Thus, multiantennary *N*-glycans can be characterized by the formulas GlcNAc(2-4)Man3GlcNAc2, Gal(1-4)GlcNAc(2-4)Man3GlcNAc2, or NANA(i_4)Gal(i_4)GlcNAc(2_4)Man3GlcNAc2- The term "1-4" refers to 1, 2, 3, or 4 residues.

[00255] With respect to bisected *N*-glycans, the term "bisected *N*-glycan" refers to *N*-glycans in which a GlcNAc residue is linked to the mannose residue at the reducing end of the *N*-glycan. A bisected *N*-glycan can be characterized by the formula GlcNAc3Man3GlcNAc2 wherein each mannose residue is linked at its non-reducing end to a GlcNAc residue. In contrast, when a multiantennary *N*-glycan is characterized as GlcNAc3Man3GlcNAc2, the formula indicates that two GlcNAc residues are linked to the mannose residue at the non-reducing end of one of the two arms of the *N*-glycans and one GlcNAc residue is linked to the mannose residue at the non-reducing end of the other arm of the *N*-glycan.

[00256] In certain embodiments, the proteins of the invention comprise an aglycosylated Fc region. By way of example, an IgGl Fc region may be aglycosylayed by deleting or substituting residue N297.

Antibody Physical Properties

[00257] The antibodies and antigen-binding fragments thereof disclosed herein may further contain one or more glycosylation sites in either the light or heavy chain immunoglobulin variable region. Such glycosylation sites may result in increased immunogenicity of the antibody or fragment or an alteration of the pK of the antibody due to altered antigen-binding (Marshall *et al* (1972) *Annu Rev Biochem* 41:673-702; Gala and Morrison (2004) *J Immunol* 172:5489-94; Wallick *et al* (1988) *J Exp Med* 168:1099-109; Spiro (2002) *Glycobiology* 12:43R-56R; Parekh *et al* (1985) *Nature* 316:452-7; Mimura *et al* (2000) *Mo! Immunol* 37:697-706). Glycosylation has been known to occur at motifs containing an N-X-S/T sequence.

[00258] Each antibody or antigen-binding fragment will have a unique isoelectric point **(pi),** which generally falls in the pH range between 6 and 9.5. The **pi** for an IgGl antibody typically falls within the pH range of 7-9.5 and the **pi** for an IgG4 antibody typically falls within the pH range of 6-8.

[00259] Each antibody or antigen-binding fragment will have a characteristic melting temperature, with a higher melting temperature indicating greater overall stability *in vivo* (Krishnamurthy R and Manning MC (2002) *Curr Pharm Biotechnol* 3:361-71). In general, the T_{M1} (the temperature of initial unfolding) may be greater than 60°C, greater than 65°C, or greater than 70°C. The melting point of an antibody or fragment can be measured using differential scanning calorimetry (Chen *et al* (2003) *Pharm Res* 20:1952-60; Ghirlando *et al* (1999) *Immunol Lett* 68:47-52) or circular dichroism (Murray *et al.* (2002) *J. Chromatogr Sci* 40:343-9).

[00260] In a further embodiment, antibodies and antigen-binding fragments thereof are selected that do not degrade rapidly. Degradation of an antibody or fragment can be measured using capillary electrophoresis (CE) and MALDI-MS (Alexander AJ and Hughes DE (1995) *Anal Chem* 67:3626-32).

[00261] In a further embodiment, antibodies and antigen-binding fragments thereof are selected that have minimal aggregation effects, which can lead to the triggering of an unwanted immune response and/or altered or unfavorable pharmacokinetic properties. Generally, antibodies and fragments are acceptable with aggregation of 25% or less, 20% or less, 15%· or less, 10%· or less, or 5% or less. Aggregation can be measured by several techniques, including size-exclusion column (SEC), high performance liquid chromatography (HPLC), and light scattering.

Antibody Conjugates

[00262] The anti-SIRPa antibodies and antigen-binding fragments thereof disclosed herein may also be conjugated to a chemical moiety. The chemical moiety may be, *inter alia,* a polymer, a radionucleotide or a cytotoxic factor. In particular embodiments, the chemical moiety is a polymer which increases the half-life of the antibody or fragment in the body of a subject. Suitable polymers include, but are not limited to, hydrophilic polymers which include but are not limited to polyethylene glycol (PEG) *(e.g.,* PEG with a molecular weight of 2kDa, 5 kDa, 10 kDa, 12kDa, 20 kDa, 3()kDa or 40kDa), dextran and monomethoxy polyethylene glycol (mPEG). Lee, *et al,* (1999) *(Bioconj. Chem.* 10:973-981) discloses PEG conjugated single-chain antibodies. Wen, *et al.,* (2001) *(Bioconj. Chem.* 12:545-553) disclose conjugating antibodies with PEG which is attached to a radiometal chelator (diethylenetriaminpentaacetic acid (DTPA)).

[00263] The antibodies and antigen-binding fragments thereof disclosed herein may also be conjugated with labels such as ^{99}Tc, ^{90}Y, "'in, ^{3}2P, ^{1}4C, ^{125}I, ¾ ^{131}I, ^{11}C, ^{15}0 , ,^{3}N, ^{18}F, ^{3}5S, ^{51}Cr, ^{5}7To, ^{22}6Ra, ^{60}Co, ^{5}9Fe, ^{5}7Se, ^{152}Eu, ^{6}7CU, ^{2}17Ci, ^{2},, At, ^{2}1^{2}Pb, ^{4}7Sc, ,^{09}Pd, ^{23}4Th, and ^{4}0K, ,^{5}7Gd, ^{55}Mn, ^{52}Tr, and ^{5}6Fe.

[00264] The antibodies and antigen-binding fragments disclosed herein may also be PEGylated, for example to increase its biological *(e.g.,* serum) half-life. To PEGylate an antibody or fragment, the antibody or fragment, typically is reacted with a reactive form of polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. In particular embodiments, the PEGylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (CI -CIO) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody or fragment to be PEGylated is an aglycosylated antibody or fragment. Methods for PEGylating proteins are known in the art and can be applied to the antibodies of the invention. *See, e.g.,* EP 0 154 316 and EP 0 401 384.

[00265] The antibodies and antigen-binding fragments disclosed herein may also be conjugated with fluorescent or chemilluminescent labels, including fluorophores such as rare earth chelates, fluorescein and its derivatives, rhodamine and its derivatives, isothiocyanate, phycoerythrin, phycocyanin, allophycocyanin, o-phthaladehyde, fluorescamine, ^{152}Eu, dansyl, umbeiliferone, luciferin, luminal label, isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridimium salt label, an oxalate ester label, an aequorin label, 2,3-dihydrophthalazinediones, biotin/avidin, spin labels and stable free radicals.

[00266] The antibodies and antigen-binding fragments thereof of the invention may also be conjugated to a cytotoxic factor such as diptheria toxin, *Pseudomonas aeruginosa* exotoxin A chain , ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins and compounds *(e.g.,* fatty acids), dianthin proteins, *Phytolacca arnericana* proteins PAPI, PAPII, and PAP-S, *mornordica charantia* inhibitor, curcin, crotin, *saponaria officinalis* inhibitor, mitogellin, restrictocin, phenomycin, and enomycin.

[00267] Any method known in the art for conjugating the antibodies and antigen-binding fragments thereof of the invention to the various moieties may be employed, including those methods described by Hunter, *et al,* (1962) *Nature* 144:945; David, *etal,* (1974) *Biochemistry* 13:1014; Pain, *et al.,* (1981) J. Immunol. Meth. 40:219; and Nygren, J., (1982) *Histochem. and Cytochem.* 30:407. Methods for conjugating antibodies and fragments are conventional and very well known in the art.

Therapeutic Uses of Anti-SIRPa antibodies

[00268] Further provided are methods for treating subjects, including human subjects, in need of treatment with the isolated antibodies or antigen-binding fragments thereof disclosed herein. In one embodiment of the invention, such subject suffers from an infection or an infectious disease.

[00269] In another embodiment of the invention, such subject suffers from cancer. In one embodiment the cancer is , e.g., osteosarcoma, rhabdomyosarcoma, neuroblastoma, kidney cancer, leukemia, renal transitional cell cancer, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, lung cancer (e.g., non-small cell lung cancer), gastric cancer, colorectal cancer, cervical cancer, synovial sarcoma, head and neck cancer, squamous cell carcinoma, multiple myeloma, renal cell cancer, retinoblastoma, hepatoblastoma, hepatocellular carcinoma, melanoma, rhabdoid tumor of the kidney, Ewing's sarcoma, chondrosarcoma, brain cancer, glioblastoma, meningioma, pituitary adenoma, vestibular schwannoma, a primitive neuroectodermal tumor, medulloblastoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, polycythemia vera, thrombocythemia, idiopathic myelfibrosis, soft tissue sarcoma, thyroid cancer, endometrial cancer, carcinoid cancer or liver cancer, breast cancer or gastric cancer. In an embodiment of the invention, the cancer is metastatic cancer, *e.g.,* of the varieties described above.

[00270] Cancers that may be treated by the antibodies or antigen-binding fragments, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma,

bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma) colorectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma,

Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[00271] In one embodment, cancers that may be treated by the antibodies or antigen-binding fragments thereof disclosed herein, compositions and methods of the invention include, but are not limited to: breast cancer, gastric cancer, esophageal cancer, gastroesophageal junction carcinoma, colorectal cancer, head and neck cancer, non-small cell lung cancer, osteosarcoma, neuroblastoma, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, lung cancer, squamous cell carcinoma, melanoma, pancreatic cancer, prostate cancer, small cell lung cancer, kidney cancer, renal cell carcinoma, thyroid cancer, glioblastoma multiforme, fallopian tube cancer, peritoneal cancer, angiosarcoma, hepatocellular carcinoma, choriocarcinoma, soft tissue sarcoma, chronic lymphocytic leukemia, chronic myelocytic leukemia, non-Hodgkin's lymphoma, B-cell non-hodgkin's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, myelodysplastic syndrome, acute myelocytic leukemia, T~ cell lymphoma, natural killer cell lymphoma, extranodal marginal zone B-cell lymphoma, acute lymphocytic leukemia, multiple myeloma.

[00272] In one embodiment, the antibodies or antigen-binding fragments thereof disclosed herein may be used for the treatment of infections and infectious diseases. As used herein, the term "infection" refers to any state in at least one cell of an organism (i.e., a subject) is infected by an infectious agent (e.g., a subject has an intracellular pathogen infection, e.g., a chronic intracellular pathogen infection). As used herein, the term "infectious agent" refers to a foreign biological entity (i.e. a pathogen) that induces CD47 expression (e.g., increased CD47 expression) in at least one cell of the infected organism. For example, infectious agents include, but are not limited to bacteria, viruses, protozoans, and fungi.

[00273] Intracellular pathogens are of particular interest. Infectious diseases are disorders caused by infectious agents. Some infectious agents cause no recognizable symptoms or disease under certain conditions, but have the potential to cause symptoms or disease under changed conditions. The subject methods can be used in the treatment of chronic pathogen infections, for example including but not limited to viral infections, e.g. retrovirus, lentivirus, liepadna virus, herpes viruses, pox viruses, human papilloma viruses, etc.; intracellular bacterial infections, e.g.

Mycobacterium, Chlamydophila, Ehrlichia, Rickettsia, Brucella, Legionella, Francisella, Listeria, Coxiella, Neisseria, Salmonella, Yersinia sp, *Helicobacter pylori* etc.; and intracellular protozoan pathogens, e.g. *Plasmodium* sp, *Trypanosoma* sp., *Giardia* sp., *Toxoplasma* sp., *Leishmania* sp., etc.

[00274] In an embodiment, the invention provides methods for treating subjects using an anti-SIRPa antibody or antigen-binding fragment thereof of the invention, wherein the subject suffers from a viral infection. In one embodiment, the viral infection is an infection with a virus selected from the group consisting of human immunodeficiency virus (HIV), hepatitis virus (A, B, or C), herpes virus *{e.g.,* VZV, HSV-I, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovims, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, coronavirus, respiratory syncytial virus, mumps vims, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies vims, JC virus or arboviral encephalitis virus.

[00275] In an embodiment, the invention provides methods for treating subjects using an anti-SIRPa antibody or antigen-binding fragment thereof of the invention, wherein the subject suffers from a bacterial infection. In one embodiment, the bacterial infection is infection with a bacteria selected from the group consisting of *Chlamydia,* rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and gonococci, klebsiella, proleus, serratia, pseudomonas, *Legionella, Corynebacterium diphtheriae. Salmonella,* bacilli. *Vibrio cholerae, Clostridium tetan, Clostridium botulinum, Bacillus anthricis, Yersinia pestis, Mycobacterium leprae, Mycobacterium lepromatosis,* and *Borriella.*

[00276] In an embodiment, the invention provides methods for treating subjects using an anti-SIRPa antibody or antigen-binding fragment thereof of the invention, wherein the subject suffers from a fungal infection. In one embodiment, the fungal infection is an infection with a fungus selected from the group consisting of *Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.),* Genus *Mucorales (mucor, absidia, rhizopus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis* and *Histoplasma capsulatum.*

[00277] In an embodiment, the invention provides methods for treating subjects using an anti-SIRPa antibody or antigen-binding fragment thereof of the invention, wherein the subject suffers

from a parasitic infection. In one embodiment, the parasitic infection is infection with a parasite selected from the group consisting of *Entamoeba histolytica, Balantidium coli, Naegleria fowleri, **Acanthamoeba,** Giardia lambia, Cryptosporidium, Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmcmia donovani, Toxoplasma gondii* and *Nippostrongylus brasiliensis.*

[00278] A "subject" may be a mammal such as a human, dog, cat, horse, cow, mouse, rat, monkey *(e.g.,* cynomolgous monkey, *e.g., Macaca fascicularis)* or rabbit. In preferred embodiments of the invention, the subject is a human subject.

[00279] The term "in association with" indicates that the components administered in a method of the present invention *(e.g.,* an anti-SIRPa antibody *(e.g.,* humanized antibody) or antigen-binding fragment thereof along with an anti-cancer agent can be formulated into a single composition for simultaneous delivery or formulated separately into two or more compositions *(e.g.,* a kit). Each component can be administered to a subject at a different time than when the other component is administered; for example, each administration may be given non-simultaneously *(e.g.,* separately or sequentially) at several intervals over a given period of time. Moreover, the separate components may be administered to a subject by the same or by a different route.

[00280] In particular embodiments, the antibodies or antigen-binding fragments thereof disclosed herein may be used alone, or in association with other, further therapeutic agents and/or therapeutic procedures, for treating or preventing any disease such as cancer, *e.g.,* as discussed herein, in a subject in need of such treatment or prevention. Compositions, *e.g.,* pharmaceutical compositions comprising a pharmaceutically acceptable carrier, comprising such antibodies and fragments in association with further therapeutic agents are also part of the present invention.

[00281] Therefore, the present invention provides a method of treating cancer in a human subject, comprising administering to the subject an effective amount of the antibody or antigen binding fragment disclosed herein, optionally in association with a further therapeutic agent or therapeutic procedure.The present invention also provides a method of treating an infection or infectious disease in a human subject, comprising administering to the subject an effective amount of the antibody or antigen binding fragment disclosed herein, optionally in association

with a further therapeutic agent or therapeutic procedure. The present invention also provides a method of increasing the activity of an immune cell, comprising administering to a subject in need thereof an effective amount of an antibody or antigen binding fragment disclosed herein. In one embodiment, the method is used for: the treatment of cancer; the treatment of an infection or infectious disease; or as a vaccine adjuvant.

[00282] In particular embodiments, the antibodies or antigen-binding fragments thereof disclosed herein may be used alone, or in association with tumor vaccines. Examples of tumor vaccines include but are not limited to vaccines for Human Papillomavirus (HPV) infection caused cancer such as Gardasil®, Gardisil9® and Cervarix®; vaccines that prevent hepatitis B virus caused liver cancer such as Engerix-B® and Recombivax HB®; oncolytic vims therapy that triggers immune response such as Imlygic®; DNA vaccines such as Synchotrope MA2M plasmid DNA vaccine and ZYC101; mammaglobin-a DNA vaccine (see Clinical Cancer Res. 2014 20(23):5964-75); vector based vaccines such as PSA-TRICOM (prostvac), PANVAC-VF, Listeria monocytogenes-based vaccines (see, e.g., Therapeutic Advances in Vaccines, 2014, 2(5) 137-148), Listeria-based vaccines (Listeria expressing one or more cancer vaccines such as Listeria-mesothelin (e.g., CRS-207), ADXS-HPV, Axalimogene Filolisbac, Listeria-HER2/Neu, Listeria-EGFRvill), Adeno-CEA; allogeneic vaccines such as GVAX, BLP-25 (anti-Ankara-mucin 1), Belagenpumatucel-L, TG4010, CIMAvax epidermal growth factor vaccine, NY-ESO, GM.CD40L-CCL21; autologous vaccines such as:Adeno-CD40L, BCG, INGN-225, Dendritic cell vaccines such as Provenge®(Sipuleucel-T), rF-CEA-MUC 1-TRICOM (panvac-DC); antigen vaccines such as MUC-1 (stimuvax), NY-ESO-1, GP-100, MAGE-A3 (melanoma antigen encoding gene A3), INGN-225 (see Pharmacology & Therapeutics 153 (2015) 1-9).

[00283] Eat-me signals could be elevated by cytotoxic therapies like radiotherapy or chemotherapeutic agents including, but not limited to anthracyclines (doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone), oxaliplatin, bortezomib, cyclophosphamide, bleomycin, vorinostat, paclitaxel, 5-fluorouracil, cytarabine, prednisolone, docetaxel, mitomycin C, topotecan/camptothecin, etoposide, zoledronic acid, methotrexate, ibrutinib, aflibercept, bevacizumab, toremifene, vinblastine, vincristine, idelalisib, mercaptopurine, thalidomide, sorafenib. Thus, in certain embodiments, the antibodies or antigen-binding fragments thereof disclosed herein may be used in association with chemotherapeutic agents, in association with radiation therapy, etc. In particular embodiments, the antibodies or antigen-binding fragments

thereof disclosed herein may be used alone, or in association with targeted therapies. Examples of targeted therapies include: hormone therapies, signal transduction inhibitors (e.g., EGFR inhibitors, such as cetuximab (Erbitux) and erlotinib (Tarceva)); CD20 inhibitors (e.g., rituximab (Rituxan) and ofatumumab (Arzerra)); CD38 inhibitors (e.g., daratumumab (DARZALEX)); CD52 inhibitors (e.g., alemtuzumab (Campath)); HER2 inhibitors (e.g., trastuzumab (Herceptin) and pertuzumab (Perjeta)); BCR-ABL inhibitors (such as imatinib (Gleevec) and dasatinib (Sprycel)); ALK inhibitors (such as crizotinib (Xalkori) and ceritinib (Zykadia)); BRAF inhibitors (such as vemurafenib (Zelboraf) and dabrafenib (Tafinlar)), gene expression modulators (e.g., decitabine (Dacogen) and Vorinostat (Zolinza)), apoptosis inducers (e.g., bortezomib (Velcade) and carfilzomib (Kyprohs)), angiogenesis inhibitors (e.g., bevacizumab (Avastin) and ramucirumab (Cyramza)), immunomodulatory imide drugs (e.g., thalidomide, lenalidomide, pomalidomide, and apremilast), monoclonal antibodies attached to toxins (e.g., brentuximab vedotin (Adcetris) and ado-trastuzumab emtansine (Kadcyla)).

[00284] The antibodies or antigen-binding fragments thereof disclosed herein may preferably find use in association with targeted therapies in which antibodies are employed to mediate ADCC/ADCP. Functional bioassays are available to analyze the mode of action of an antibody drug and to distinguish ADCP as a mode of action from ADCC. By way of example, an antibody-dependent cell-mediated cytotoxicity (ADCC) assay typically utilizes normal human peripheral blood mononuclear cells (PBMCs) or effector cells isolated thereof. Assay variation can be reduced by using selective donor pools with defined Fey receptor Ila (FcyRIIa/CD32a), Ilia (FcYRIHa/CD16a) or Illb (FcyRIIIb/CD16b) gene copy number variation (CNV) or genotypes such as FcYRIIIa-158 V/V versus V/F or F/F, FcγRffla-131 H/H versus H/R or R/R, and the FcyRIIIb-NAl and -NA2 polymorphic variants. Alternatively, effector cells such as PBMCs, PBMC-derived natural killer (NK) cells, granulocytes, monocytes, monocyte-derived macrophages, or dendritic cells (DCs) can be replaced with a FcyRIIIa-expressing cell line (for example, engineered NK92). Killing of the target cells can be assessed by measuring the release of specific probes from pre-labelled target cells, using "chromium (Cr^{51}) or fluorescent dyes such as calcein-acetoxymethyl (calcein-AM), carboxyfluorescein succinimidyl ester (CFSE), 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein (BCECF), europium (Eu) or propidium iodide (PI), or by measuring the release of cytosolic enzymes such as lactate dehydrogenase (LDH) or the release of nucleoside triphosphate (ATP).

[00285] In contrast, antibody-dependent cellular phagocytosis (ADCP) may be assessed by measuring the destruction of target cells via granulocyte, monocyte, dendritic cell, or macrophage-mediated phagocytosis. ADCP assays use PBMC-derived cells or myeloid cell lines such as HL-60, THP-1, and U937 cells differentiated into macrophages or granulocytes. Stimuli that are commonly used to induce macrophage differentiation in monocytic cell lines include phorbol-12-myristate-13-acetate (PMA), 1,25-dihydroxyvitamin D3 (VD3), and retinoic acid (RA). RA is also known to induce terminal granulocytic differentiation of for example HL-60 cells. Phagocytosis of the target cells can be assessed by monitoring effector cells for the internalization of specific probes from target cells pre-labelled with fluorescent dyes such as cell proliferation dye eFluor450, CFSE, and pH-sensitive dyes including pHrodo and CypHerSE. Phagocytosis is measured by an increase in fluorescently labelled effector cells using flow cytometry or fluorescence microscopy. "Reporter gene" assays are also available to assess ADCP. In order to measure ADCP function in a reporter gene assay, target cells are first incubated with a titration of an antibody of interest. Once the antibody is bound to its cognate target on the target cell surface, engineered Jurkat effector cells are added. If ADCP pathway activation ensues, the Jurkat cells produce a luciferase product by expression of the reporter gene NFAT-RE-luc2. Luciferase activity is then measured following a 4-24 hour induction period, after addition of the luciferase assay reagent. The dose-dependent response in the microtiter plate-based assay can be used to quantify the relative biological activity of the therapeutic antibody compared to the dose-response curve of a suitable reference item.

[00286] In particular embodiments, the anti-SIRPa antibodies or antigen-binding fragments thereof of the invention may be used in combination with an anti-cancer therapeutic agent or immunomodulatory drug such as an immunomodulatory receptor inhibitor, *e.g.,* an antibody or antigen-binding fragment thereof that specifically binds to the receptor.

[00287] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with one or more of:

an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecules (SLAM proteins), an activating NK cell receptor, a Toll like receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40,

ICAM-1, LFA-1 (CDl la/CD 18), 4-1BB (CDl 37), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp8() (KLRFl), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl Id, ITGAE, CD 103, ITGAL, ITGAM, CDl lb, ITGAX, CDl lc, ITGB1, CD29, 1TGB2, CDl 8, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CDl 60 (BY55). PSGLl, CD 100 (SEMA4D), CD69, SLAMF6 (NTB-A, LyI08), SLAM (SLAMF1, CD150, IPO-3), SLAM7, BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, PAG/Cbp, CDl 9a, and a ligand that specifically binds with CD83; or

an inhibitor of CD47, PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, CEACAM (e.g., CEACAM-1, -3 and/or -5), VISTA, BTLA, TIGIT, LAIR1, IDO, TDO, CD 160 and/or TGFR beta.

[00288] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with one or more cyclic dinculeotides or other STING pathway agonists. STING (stimulator of interferon genes, also known as TMEM173, MITA, ERIS, and MPYS) is a transmembrane protein localized to the ER that undergoes a conformational change in response to direct binding of cyclic diniicleotides (CDNs), resulting in a downstream signaling cascade involving TBK1 activation, IRF-3 phosphorylation, and production of IFN-β and other cytokines. The STING pathway in tumor-resident host antigen presenting c3ellss is involved in the induction of a spontaneous CD8+ T cell response against tumor-derived antigens. Activation of this pathway and the subsequent production of IFN-β also reportedly contributes to the anti-tumor effect of radiation. STING agoinists and their uses are described in, for example, US20060040887, US20080286296, US20 120041057, US20 140205653, WO2014179335, WO 2014179760, US20 150056224, WO 2015185565, WO 2016096174, WO 2016145102, WO 2017011444, WO 2017027645, WO 2017027646. WO 2017123657. WO 2017123669, WO 2017175147, WO 2017175156, WO 2018045204, WO 2018009648, WO 2018006652, WO 2018013887, WO 2018013908, US201 80002369, US201 80092937, and US20 180093964.

[00289] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with one or more of: anti-CD47 antibody, anti-PD-1 antibody (e.g., nivolumab, pembrolizumab, anti-PDLl antibody, anti-TIGIT antibody, anti-APRIL antibody, anti-CTLA4 antibody, anti-CSl antibody *(e.g.* , elotuzumab), anti-KIR2DL1/2/3 antibody *(e.g.* , lirilumab), anti-CD137 antibody *(e.g.* , urelumab), anti-GITR antibody *(e.g.* , TRX518), anti-PD-Ll antibody *(e.g.* , BMS-936559, MSB0010718C or MPDL3280A), anti-PD-L2 antibody, anti-ILTl antibody, anti-ILT2 antibody, anti-ILT3 antibody, anti-ILT4 antibody, anti-ILT5 antibody, anti-ILT6 antibody, anti-ILT7 antibody, anti-ILT8 antibody, anti-CD40 antibody, anti-OX40 antibody, anti-ICOS, anti-KIR2DLl antibody, anti-KIR2DL2/3 antibody, anti~KIR2DL4 antibody, anti-KIR2DL5A antibody, anti-KIR2DL5B antibody, anti-KIR3DLl antibody, anti-KIR3DL2 antibody, anti-KIR3DL3 antibody, anti-NKG2A antibody, anti-NKG2C antibody, anti-NKG2E antibody, anti-4-lBB antibody (e.g., PF-05082566), anti-TSLP antibody, anti-IL-10 antibody. IL-10 or PEGylated IL-10, or any small organic molecule inhibitor of such targets.

[00290] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD20 antibody *(e.g.* , rituximab, ofatumimiab, ocrelizumab, obinutuzimiab, ocaratuzumab, ublituximab, veltuzimiab, ibritumomab tiuxetan, tositumomab, BVX-20, SCT-400 or PR0131921).

[00291] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD38 antibody *(e.g.* , daratumumab, isatuximab or MOR202).

[00292] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-EGFR antibody *(e.g.,* cetuximab, CetuGEX, panitumumab, nimotuzumab, depatuxizumab or AFM-21).

[00293] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-HER2 antibody *(e.g.,* trastuzumab, TrasGEX, pertuzumab, margetuximab or ADCT-502).

[00294] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-HER3 antibody *(e.g.* , lumretuzumab, patritumab or LJM7 16).

[00295] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD 19 antibody *(e.g.,* inebilizumab, blinatumomab, DI-B4, MDX-1342, MEDI-551, MOR208 or 4-G7SDIE).

[00296] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD52 antibody *(e.g.,* alemtuzumab).

[00297] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-EpCAM antibody *(e.g.,* adecatumumab, catumaxomab, edrecolomab or ING-1).

[00298] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-SLAMF7 antibody *(e.g.,* elotuzumab or ABBV-838).

[00299] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-PD-1 antibody *(e.g.,* nivolumab or pembrolizumab).

[00300] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-PD-Ll antibody *(e.g.,* BMS-936559, MSB0010718C or MPDL3280A).

[00301] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CTLA4 antibody *(e.g.,* ipilimumab or tremelimumab).

[00302] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD137 antibody *(e.g.,* urelumab).

[00303] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-GITR antibody *(e.g.,* TRX518 or FPA154).

[00304] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-OX4() antibody *(e.g.,* MED16469, MOXR0916 or INCAGN 1949).

[00305] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD40 antibody *(e.g.,* lucatumumab, dacetuzmumab, APX005M, ChiLob7/4, CP-870,893 or JNJ-64457107)In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CSl antibody.

[00306] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR2DLl/2/3 antibody.

[00307] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD 137 *(e.g.,* urelumab) antibody.

[00308] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-GITR *(e.g.,* TRX518) antibody.

[00309] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-PD-L2 antibody.

[00310] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITLl antibody.

[003 11] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITL2 antibody.

[00312] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITL3 antibody.

[00313] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITL4 antibody.

[00314] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITL5 antibody.

[00315] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITL6 antibody.

[00316] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITL7 antibody.

[003 17] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ITL8 antibody.

[003 18] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-CD40 antibody.

[003 19] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-OX4() antibody.

[00320] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR2DLl antibody.

[00321] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR2DL2/3 antibody.

[00322] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR2DL4 antibody.

[00323] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR2DL5A antibody.

[00324] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR2DL5B antibody.

[00325] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR3DLl antibody.

[00326] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR3DL2 antibody.

[00327] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-KIR3DL3 antibody.

[00328] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-NKG2A antibody.

[00329] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-NKG2C antibody.

[00330] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-ICOS antibody.

[00331] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-4-lBB antibody.

[00332] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-IL-10 antibody.

[00333] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with an anti-TSLP antibody.

[00334] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with IL-10 or PEGylated IL-10.

[00335] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with one or more of an inhibitor *(e.g.,* a small organic molecule or an antibody or antigen-binding fragment thereof) such as: an MTOR (mammalian target of rapamycin) inhibitor, a cytotoxic agent, a platinum agent, an EGFR inhibitor, a VEGF inhibitor, a microtubule stabilizer, a taxane, a CD20 inhibitor, a CD52 inhibitor, a CD30 inhibitor, a RANK (Receptor activator of nuclear factor kappa-B) inhibitor, a RANKL (Receptor activator of nuclear factor kappa-B ligand) inhibitor, an ERK inhibitor, a MAP Kinase inhibitor, an AKT inhibitor, a MEK inhibitor, a PI3K inhibitor, a HERl inhibitor, a HER2 inhibitor, a HER3 inhibitor, a HER4 inhibitor, a Bcl2 inhibitor, a CD22 inhibitor, a CD79b inhibitor, an ErbB2 inhibitor, or a farnesyl protein transferase inhibitor.

[00336] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with any one or more of: 13-cis-retinoic acid, 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, 4-hydroxytamoxifen, 5-deooxyuridine, 5'-deoxy-5-fluorouridine, 5-fluorouracil, 6-mecaptopurine, 7-hydroxystaurosporine, A-443654, abirateroneacetate, abraxane, ABT-578, acolbifene, ADS-100380, ALT-110, altretamine, amifostine, aminoglutethimide, amrubicin, Amsacrine, anagrehde, anastrozole, angiostatin, AP-23573, ARQ-197, arzoxifene, AS-252424, AS-605240, asparaginase, AT-9263, atrasentan, axitinib, AZD1 152, *Bacillus Calmette-Guerin* (BCG) vaccine, batabulin, BC-210, besodutox, bevacizumab, bicalutamide, Biol 11, BIO140,

bleomycin, BMS-214662, BMS-247550, BMS-275291, BMS-3 10705, bortezomib, buserelin, busulfan, calcitriol, camptothecin, canertinib, capecitabine, carboplatin, carmustine, CC8490, Cediranib, CG-1521, CG-781, chlamydocin, chlorambucil, chlorotoxin, cilengitide, cimitidine, cisplatin, cladribine, clodronate, COL-3, CP-724714, cyclophosphamide, cyproterone, cyproteroneacetate, cytarabine, cytosinearabinoside, dacarbazine, dacinostat, dactinomycin, dalotuzumab, danusertib, dasatanib, daunorubicin, decatanib, deguelin, denileukin, deoxycoformycin, depsipeptide, diarylpropionitrile, diethylstilbestrol, diftitox, docetaxel, dovitinib, doxorubicin, droloxifene, edotecarin, yttrium-90 labeled-edotreotide, edotreotide, EKB-569, EMD121974, endostatin, enzalutamide, enzastaurin, epirubicin, epithilone B, ERA-923, Erbitux, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, ficlatuzumab, finasteride, flavopiridol, floxuridine, fludarabine, fludrocortisone, fluoxymesterone, flutamide, FOLFOX regimen, Fulvestrant, galeterone, gefitinib, gemcitabine, gimatecan, goserelin, goserelin acetate, gossypol. GSK461364, GSK690693, HMR-3339, hydiOxyprogesteronecaproate, hydroxyurea, IC871 14, idarubicin, idoxyfene, ifosfamide, IM862, imatinib, IMC-1 C I 1, INCB24360, INOIOOI , interferon, interleukin-12, ipilimumab, irinotecan, JNJ-16241 199, ketoconazole, KRX-0402, thalidomide, lenalidomide, pomalidomide, apremilasLlapatinib, lasofoxifene, letrozole, leucovorin, leuprolide, leuprolide acetate, levamisole, liposome entrapped paclitaxel, lomustine, lonafarnib, lucanthone, LY292223, LY292696, LY293646, LY293684, LY294002, LY3 17615, marimastat, mechlorethamine, medroxyprogesteroneacetate, megestrolacetate, melphalan, mercaptopurine, mesna, methotrexate, mithramycin, mitomycin, mitotane, mitoxantrone, tozasertib, MLN8054, neovastat, Neratinib , neuradiab, nilotinib, nilutimide, nolatrexed, NVP-BEZ235, oblimersen, octreotide, ofatumumab, oregovomab, orteronel, oxaliplatin, paclitaxel, palbociclib, pamidronate, panitumumab, pazopanib, PD0325901, PD184352, PEG-interferon, pemetrexed, pentostatin, perifosine, phenylalaninemustard, PI- 103, pictilisib, PIK-75, pipendoxifene, PKI-166, plicamycin, porfimer, prednisone, procarbazine, progestins, PX-866, R-763, raloxifene, raltitrexed, razoxin, ridaforolimus, rituximab, romidepsin, RTA744, rubitecan, scriptaid, Sdxl02, seliciclib, selumetinib, semaxanib, SF1 126, sirolimus, SN36093, sorafenib, spironolactone, squalamine, SR13668, streptozocin, SU6668, suberoylanalide hydroxamic acid, sunitinib, synthetic estrogen, talampanel, talimogene laheiparepvec, tamoxifen, temozolomide, temsirolimus, teniposide, tesmilifene, testosterone, tetrandrine, TGX-221, thalidomide,

thioguanine, thiotepa, tremelimumab, tipifarnib, tivozanib, TKI-258, TLK286, topotecan, toremifene citrate, trabectedin, trastuzumab, tretinoin, trichostatin A, triciribinephosphate monohydrate, triptorelin pamoate, TSE-424, uracil mustard, valproic acid, valrubicin, vandetanib, vatalanib, VEGF trap, vinblastine, vincristine, vindesine, vinorelbine, vitaxin, vitespan, vorinostat, VX-745, wortmannin, Xr311, zanolimumab, ZK186619, ZK-304709, ZM336372, ZSTK474.

[00337] Non-limiting examples of suitable anti-cancer agents to be used in combination with an anti-SIRPa antibody or antigen-binding fragment thereof of the invention include cytostatic agents, immune modulating imide dmgs, cytotoxic agents, targeted therapeutic agents (small molecules, biologies, siRNA and microRNA) against cancer and neoplastic diseases,

1) anti-metabolites (such as methotrexate, 5-fluorouracil, gemcitabine, fludarabine, capecitabine);
2) alkylating agents, such as temozolomide, cyclophosphamide,
3) DNA interactive and DNA damaging agents, such as cisplatin, oxaliplatin, doxorubicin,
4) Ionizing irradiation, such as radiation therapy,
5) topoisomerase II inhibitors, such as etoposide, doxorubicin,
6) topoisomerase I inhibitors, such as irinotecan, topotecan,
7) tubulin interacting agents, such as paclitaxel, docetaxel, Abraxane, epothilones,
8) kinesin spindle protein inhibitors,
9) spindle checkpoint inhibitors,
10) Poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, MK-4827 and veliparib
11) Matrix metalloprotease (MMP) inhibitors
12) Protease inhibitors, such as cathepsin D and cathepsin K inhibitors
13) Proteosome or ubiquitination inhibitors, such as bortezomib,
14) Activator of mutant p53 to restore its wild-type p53 activity
15) Adenoviral-p53
16) Bcl-2 inhibitors, such as ABT-263
17) Heat shock protein (HSP) modulators, such as geldanamycin and 17-AAG
18) Histone deacetylase (HDAC) inhibitors, such as vorinostat (SAHA),
19) sex hormone modulating agents,

a. anti-estrogens, such as tamoxifen, fulvestrant,
b. selective estrogen receptor modulators (SERM), such as raloxifene,
c. anti-androgens, such as bicalutamide, flutamide
d. LHRH agonists, such as leuprolide,
e. 5a-reductase inhibitors, such as finasteride,
f. Cytochrome P450 C17 lyase (CYP45()c17, also called 17aC);
g. aromatase inhibitors, such as letrozole, anastrozole, exemestane,

20) EGFR kinase inhibitors, such as geftinib, erlotinib, laptinib

21) dual erbBl and erbB2 inhibitors, such as Lapatinib

22) multi-targeted kinases (serine/threonine and/or tyrosine kinase) inhibitors,

a. ABL kinase inhibitors, imatinib and nilotinib, dasatinib
b. VEGFR-1, VEGFR-2, PDGFR, KDR, FLT, c-Kit, Tie2, Raf, MEK and ERK inhibitors, such as sunitinib, sorafenib, Vandetanib, pazopanib, PLX-4032, Axitinib, PTK787, GSK-1 120212
c. Polo-like kinase inhibitors
d. Aurora kinase inhibitors
e. JAK inhibitor
f. c-MET kinase inhibitors
g. Cyclin-dependent kinase inhibitors, such as CDK1 and CDK2 inhibitor Dinaciclib SCH 727965 (see Parry et ał, Molecular Cancer Therapeutics 9 (8): 2344-53 (2010)) and CDK4/6 inhibitors, such as Ribociclib, Palbociclib, Abemaciclib, and Trilaciclib.
h. PI3K and mTOR inhibitors, such as GDC-0941, BEZ-235, BKM-120 and AZD-8055
i. Rapamycin and its analogs, such as Temsirolimus, everolimus, and deforolimus

23) and other anti-cancer (also know as anti-neoplastic) agents include but are not limited to ara-C, adriamycin, Cytoxan, Carboplatin, Uracil mustard, Clormethine, Ifosfsmide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Vinblastine, Vincristine, Vindesine, Vinorelbine, Navelbine,

Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, teniposide, cytarabine, pemetrexed, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide, Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Flutamide Medroxyprogesteroneacetate, Toremifene, goserelin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Drolloxafine, Hexamethylmelamine, Bexxar, Zevalin, Trisenox, Profimer, Thiotepa, Altretamine, Doxil, Ontak, Depocyt, Aranesp, Neupogen, Neulasta, Kepivance.

24) Farnesyl protein transferase inhibitors, such as, SARASAR™(4-[2-[4-[(l 1R)-3,10-dibromo-8-chloro-6, 1l-dihydro-5H-benzo[5,6]cyclohepta[l,2-b]pyridin-l 1-yl-]-l-piperidinyl]-2-oxoethyl]-piperidinecarboxamide, tipifarnib

25) interferons, such as Intron A, Peg-Intron,

26) anti-erbBl antibodies, such as cetuximab, panitumumab,

27) anti-erbB2 antibodies, such as trastuzumab,

28) anti-CD52 antibodies, such as Alemtuzumab,

29) anti-CD20 antibodies, such as Rituximab

30) anti-CD33 antibodies, such as Gemtuzumab ozogamicin

31) anti-VEGF antibodies, such as Avastin,

32) TRIAL hgands, such as Lexatumumab, mapatumumab, and AMG-655

33) anti-CTLA-4 antibodies, such as ipilimumab

34) antibodies against CTA1, CEA, CD5. CD19, CD22, CD30, CD44, CD44V6, CD55. CD56. EpCAM, FAP, MHCII, HGF, IL-6, MUC1, PSMA, TAL6, TAG-72, TRAILR, VEGFR, IGF-2, FGF,

35) anti-IGF-lR antibodies, such as dalotuzumab (MK-0646) and robatumumab (SCH 717454).

[00338] "Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-l-oxopiOpoxy-4-methyl-2-[4-[2-(l-

piperidinyl)ethoxy]phenyl]-2H-l-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4~dinitrophenyl-hydrazone, and SH646.

[00339] "Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5a-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

[00340] "Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

[00341] "Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, histone deacetylase inhibitors, inhibitors of kinases involved in mitotic progression, inhibitors of kinases involved in growth factor and cytokine signal transduction pathways, antimetabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteosome inhibitors, ubiquitin ligase inhibitors, and aurora kinase inhibitors.

[00342] Examples of cytotoxic/cytostatic agents include, but are not limited to, platinum coordinator compounds, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-l,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(1 l-dodecylamino-l()-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idambicin,

daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino- 13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

[00343] An example of a hypoxia activatable compound is tirapazamine.

[00344] Examples of proteosome inhibitors include but are not limited to lactacystin and MLN-341 (Velcade).

[00345] Examples of microtubule inhibitors/microtubule-stabilising agents include taxanes in general. Specific compounds include paclitaxel (Taxol®), vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol (Taxotere®), rhizoxin, dolaslatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMSl 84476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoiO-4-melhoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-piOline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

[00346] Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypiOpionyl-3',4'-0-exo-benzylidene-chartreusin, 9-melhoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl- 1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPIl 100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-l-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydiOfuiO(3',4':6,7)naphtho(2,3-d)-l,3-dioxol-6-one, 2,3-(melhylenedioxy)-5-melhyl-7-hydroxy-8-methoxybenzo[c]-phenanlhridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,l-de]acridin-6-one, N-[l-[2(diethylamino)elhylamino]-7-methoxy-9-oxo-9H4hioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,l-c] quinolin-7-one, and dimesna.

[00347] Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in Publications WO03/039460, WO03/050064, WO03/050122, WO03/049527, WO03/049679, WO03/049678, WO04/039774, WO03/079973, WO03/09921 1, WO03/105855, WO03/106417, WO04/037171, WO04/058148, WO04/058700, WO04/126699, WO05/018638, WO05/019206, WO05/019205, WO05/018547, WO05/017190, US2005/0176776. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

[00348] Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamflatin, PXD101, MG98 and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. *J. Med. Chem.* 46(24):5097-5 116 (2003).

[00349] "Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-Rl. An example of an "aurora kinase inhibitor" is VX-680.

[00350] "Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatm, doxifluridine, tnmetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L~manno-heptopyranosyl]adeiiine, aplidine, ecteinascidin, troxacitabine, 4-[2-amiiio-4-oxo~4,6,7,8-tetrahydro-3H-pyrinndino[5,4-b][l,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-l,l l-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-l-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

[00351] Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

[00352] "Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

[00353] Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/291 19, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/1 1917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/311 11, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer,* Vol. 35, No. 9, pp. 1394-1401 (1999).

[00354] "Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-l/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-a, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including

nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib *(PNAS,* Vol. 89, p. 7384 (1992); *JNCI,* Vol. 69, p. 475 (1982); *Arch. Opthalmol.,* Vol. 108, p.573 (1990); *Anat. Rec,* Vol. 238, p. 68 (1994); *FEBS Letters,* Vol. 372, p. 83 (1995); *Clin, Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.,* Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.,* Vol. 75, p. 105 (1997); *Cancer Res.,* Vol. 57, p. 1625 (1997); *Cell,* Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.,* Vol. 2, p. 715 (1998); *J. Biol. Chem.,* Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastalin A-4, squalamine, 6-0-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105: 141-145 (1985)), and antibodies to VEGF (see. *Nature Biotechnology,* Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature, 362,* 841-844 (1993); WO 00/44777; and WO 00/61 186).

[00355] Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-l-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-l-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-lH-l,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31 838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

[00356] Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80: 10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).

[00357] "Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the CHK11 and CHK12 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

[00358] "Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs as described by Bume-Jensen and Hunter, *Nature*, 411:355-365, 2001.

[00359] "Inhibitors of cell proliferation and survival signalling pathway" refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403 , WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469), inhibitors of Raf kinase (for example PLX-4032), inhibitors of MEK (for example Arry-162, RO-4987655 and GSK-1120212), inhibitors of mTOR (for example AZD-8055, BEZ-235 and everolimus), and inhibitors of PI3K (for example GDC-0941, BKM-120).

[00360] As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ5 integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, α,β_1, $\alpha_6\beta_1$, and $\alpha_6\beta_4$ integrins.

[00361] Some specific examples of tyrosine kinase inhibitors include N-(trifluoiOmethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol~5-yl)methylidenyl)indolin-2-one, 17-(allylamino)~17-demethoxygeldananiycin, 4-(3-chloro-4-fliiorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)piOpoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,1 1,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-lH-diindolo[l,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][l,6]benzodiazocin-l-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pynOlo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4~(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N~4~chlorophenyl~4-(4-pyridylmethyl)-l-phthalazinamine, and EMD121974.

[00362] Combinations of the instantly claimed antibodies or antigen binding fragments with PPAR-y(i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists may be useful in the treatment of certain malignancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31: 909-913; *J. Biol. Chem,* 1999; 274: 9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41: 2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. *(Arch. Ophthamol.* 2001; 119: 709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, Lynparza®, Rucaparib©, Talazoparib®, niraparib, Veliparib®, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NPOl lO, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-l,2-benzisoxazol-6-yl)oxy]-2-methylpiOpionic acid, and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid.

[00363] The antibody or antigen binding fragment of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

[00364] The antibody or antigen binding fragment of the instant invention may also be useful for treating cancer in combination with the following chemotherapeulic agents: abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumab (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bendamustine hydrochloride (Treanda®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); brefeldin A; busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Lijection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); dalteparin sodium injection (Fragmin®); daratumumab (DARZALEX©); Darbepoetin alfa (Aranesp®); dasatinib (Sprycel®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); degarelix (Firmagon®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); dexrazoxane hydrochloride (Totect®); didemnin B; 17-DMAG; docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxonibicin (Adriamycin PFS Lijection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (Dromostanolone ®); dromostanolone propionate (Masterone Injection®); eculizumab injection (Soliris®); Elliott's B Solution (Elhott's B Solution®); eltrombopag (Promacta®); epirubicin (Ellence®); Epoetin alfa (epogeii®); erlotinib (Tarceva®); estramustine (Emcyt®); ethinyl estradiol; etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); everolimus tablets (Afinitor®); exemestane (Aromasin®); ferumoxytol (Feraheme Injection®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib

(Iressa®); geldanamycin; gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiiixetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); iobenguane I 123 injection (AdreView®); irinotecan (Camptosar®); ixabepilone (Ixempra®); lapatinib tablets (Tykerb®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinefhol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); 8-methoxypsoralen; mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); mitramycin; nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); nilotinib (Tasigna®); Nofetumomab (Verluma®); ofatumumab (Arzerra®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); panitumumab (Vectibix®); pazopanib tablets (Votrienttm®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plerixafor (Mozobil®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); pralatrexate injection (Folotyn®); procarbazine (Matulane®); quinacrine (Atabrine®); rapamycin; Rasburicase (Elitek®); raloxifene hydrochloride (Evista®); Rituximab (Rituxan®); romidepsin (Istodax®); romiplostim (Nplate®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); temsirolimus (Torisel®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiopurine; thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®);

Tositumomab/I-131 tositumomab (Bexxar®); trans-retinoic acid; Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); triethylenemelamine; Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); vorinostat (Zolinza®); wortmannin; and zoledronate (Zometa®).

[00365] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is in association with one or more antiemetics including, but not limited to: casopitant (GlaxoSmithKline), Netupitant (MGI-Helsinn) and other NK-1 receptor antagonists, palonosetron (sold as Aloxi by MGI Pharma), aprepitant (sold as Emend by Merck and Co.; Railway, NJ), diphenhydramine (sold as Benadryl® by Pfizer; New York, NY), hydroxyzine (sold as Atarax® by Pfizer; New York, NY), metoclopramide (sold as Reglan® by AH Robins Co,; Richmond, VA), lorazepam (sold as Ativan® by Wyeth; Madison, NJ), alprazolam (sold as Xanax® by Pfizer; New York, NY), haloperidol (sold as Haldol® by Ortho-McNeil; Raritan, NJ), droperidol (Inapsine®), dronabinol (sold as Marinol® by Solvay Pharmaceuticals, Inc.; Marietta, GA), dexamethasone (sold as Decadron® by Merck and Co.; Railway, NJ), methylprednisolone (sold as Medrol® by Pfizer; New York, NY), prochlorperazine (sold as Compazine® by Glaxosmithkline; Research Triangle Park, NC), granisetron (sold as Kytril® by Hoffmann-La Roche Inc.; Nutley, NJ), ondansetron (sold as Zofran® by Glaxosmithkline; Research Triangle Park, NC), dolasetron (sold as Anzemet® by Sanofi-Aventis; New York, NY), tropisetron (sold as Navoban® by Novartis; East Hanover, NJ).

[00366] Other side effects of cancer treatment include red and white blood cell deficiency. Accordingly, in an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof is in association with an agent which treats or prevents such a deficiency, such as, *e.g.,* filgrastim, PEG-filgrastim, erythropoietin, epoetin alfa or darbepoetin alfa.

[00367] In an embodiment of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention is administered in association with anti-cancer radiation therapy. For example, in an embodiment of the invention, the radiation therapy is external beam therapy (EBT): a method for delivering a beam of high-energy X-rays to the location of the tumor. The beam is generated outside the patient *(e.g.,* by a linear accelerator) and is targeted at the tumor site. These X-rays can destroy the cancer cells and careful treatment planning allows the surrounding normal tissues to be spared. No radioactive sources are placed inside the

patient's body. In an embodiment of the invention, the radiation therapy is proton beam therapy: a type of confomial therapy that bombards the diseased tissue with protons instead of X-rays. In an embodiment of the invention, the radiation therapy is confomial external beam radiation therapy: a procedure that uses advanced technology to tailor the radiation therapy to an individual's body structures. In an embodiment of the invention, the radiation therapy is brachytherapy: the temporary placement of radioactive materials within the body, usually employed to give an extra dose—or boost—of radiation to an area.

[00368] In an embodiment of the invention, a surgical procedure is administered in association with an anti-SIRPa antibody or antigen-binding fragment thereof is surgical tumorectomy.

Experimental and Diagnostic Uses

[00369] The anti-SIRPa antibodies and antigen-binding fragments thereof disclosed herein may be used as affinity purification agents. In this process, the anti-SIRPa antibodies and antigen-binding fragments thereof are immobilized on a solid phase such a Sephadex, glass or agarose resin or filter paper, using methods well known in the ait. The immobilized antibody or fragment is contacted with a sample containing the SIRPa protein (or a fragment thereof) to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the SIRPa protein, which is bound to the immobilized antibody or fragment. Finally, the support is washed with a solvent which elutes the bound SIRPa *(e.g.,* protein A). Such immobilized antibodies and fragments form part of the present invention.

[00370] Further provided are antigens for generating secondary antibodies which are useful for example for performing Western blots and other immunoassays discussed herein.

[00371] Anti-SIRPa antibodies *(e.g.,* humanized antibodies) and antigen-binding fragments thereof may also be useful in diagnostic assays for SIRPa protein, *e.g.* , detecting its expression in specific cells, tissues, or serum, *e.g.,* myeloid cells such as monocytes, macrophages, neutrophils, basophils, eosinophils, and dendritic cells. Such diagnostic methods may be useful in various disease diagnoses.

[00372] The present invention includes ELISA assays (enzyme-linked immunosorbent assay) incorporating the use of an anti-SIRPa antibody or antigen-binding fragment thereof disclosed herein.

[00373] For example, such a method comprises the following steps:

(a) coat a substrate *(e.g.,* surface of a microtiter plate well, *e.g.,* a plastic plate) with anti-SIRPa antibody or antigen-binding fragment thereof;

(b) apply a sample to be tested for the presence of SIRPa to the substrate;

(c) wash the plate, so that unbound material in the sample is removed;

(d) apply detectably labeled antibodies *(e.g.,* enzyme-linked antibodies) which are also specific to the SIRPa antigen;

(e) wash the substrate, so that the unbound, labeled antibodies are removed;

(f) if the labeled antibodies are enzyme linked, apply a chemical which is converted by the enzyme into a fluorescent signal; and

(g) detect the presence of the labeled antibody.

[00374] Detection of the label associated with the substrate indicates the presence of the SIRPa protein.

[00375] In a further embodiment, the labeled antibody or antigen-binding fragment thereof is labeled with peroxidase which react with ABTS *(e.g.,* 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)) or 3,3',5,5'-Tetramethylbenzidine to produce a color change which is detectable. Alternatively, the labeled antibody or fragment is labeled with a detectable radioisotope *(e.g.,* ^{3}H) which can be detected by scintillation counter in the presence of a scintillant.

[00376] An anti-SIRPa antibody or antigen-binding fragment thereof of the invention may be used in a Western blot or immune-protein blot procedure. Such a procedure forms part of the present invention and includes *e.g. :*

(1) optionally transferring proteins from a sample to be tested for the presence of SIRPa *(e.g.,* from a PAGE or SDS-PAGE electrophoretic separation of the proteins in the sample) onto a membrane or other solid substrate using a method known in the art *(e.g.,* semi-dry blotting or tank blotting); contacting the membrane or other solid substrate to be tested for

the presence of bound SIRPa or a fragment thereof with an anti-SIRPa antibody or antigen-binding fragment thereof of the invention.

(2) washing the membrane one or more times to remove unbound anti-SIRPa antibody or fragment and other unbound substances; and

(3) detecting the bound anti-SIRPa antibody or fragment.

[00377] Such a membrane may take the form of a nitrocellulose or vinyl-based *(e.g.,* polyvinylidene fluoride (PVDF)) membrane to which the proteins to be tested for the presence of SIRPa in a non-denaturing PAGE (polyacrylamide gel electrophoresis) gel or SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) gel have been transferred *(e.g.,* following electrophoretic separation in the gel). Before contacting the membrane with the anti-SIRPa antibody or fragment, the membrane is optionally blocked, *e.g.,* with non-fat dry milk or the like so as to bind non-specific protein binding sites on the membrane.

[00378] Detection of the bound antibody or fragment indicates that the SIRPa protein is present on the membrane or substrate and in the sample. Detection of the bound antibody or fragment may be by binding the antibody or fragment with a secondary antibody (an anti-immunoglobulin antibody) which is detectably labeled and, then, detecting the presence of the secondary antibody.

[00379] The anti-SIRPa antibodies and antigen-binding fragments thereof disclosed herein may also be used for immunohistochemistry. Such a method forms part of the present invention and comprises, *e.g.,*

(1) contacting a cell *(e.g.,* a sample containing myeloid cells such as monocytes, macrophages, neutrophils, basophils, eosinophils, and dendritic cells) to be tested for the presence of SIRPa protein with an anti-SIRPa antibody or antigen-binding fragment thereof of the invention; and

(2) detecting the antibody or fragment on or in the cell.

[00380] If the antibody or fragment itself is detectably labeled, it can be detected directly. Alternatively, the antibody or fragment may be bound by a detectably labeled secondary antibody which is detected.

[00381] Certain anti-SIRPa antibodies and antigen-binding fragments thereof disclosed herein may also be used for *in vivo* tumor imaging. Such a method may include injection of a radiolabeled anti-SIRPa antibody or antigen-binding fragment thereof into the body of a patient to be tested for the presence of a tumor associated with SIRPa expression *(e.g.,* which expresses SIRPa, for example, on the tumor cell surface) followed by nuclear imaging of the body of the patient to detect the presence of the labeled antibody or fragment *e.g.,* at loci comprising a high concentration of the antibody or fragment which are bound to the tumor. The detection of the loci indicates the presence of the $SIRPa^+$ tumor and tumor cells.

[00382] Imaging techniques include SPECT imaging (single photon emission computed tomography) or PET imaging (positron emission tomography). Labels include *e.g.,* iodine-123 (^{123}I) and technetium-99m (^{99m}Tc), *e.g.,* in conjunction with SPECT imaging or ^{11}C, ^{13}N, ^{15}O or ^{18}F, *e.g.,* in conjunction with PET imaging or Indium-111 (See *e.g.,* Gordon *et al,* (2005) International Rev. Neurobiol. 67:385-440).

Pharmaceutical Compositions and Administration

[00383] To prepare pharmaceutical or sterile compositions of the anti-SIRPa antibodies and antigen-binding fragments of the invention, the antibody or antigen-binding fragment thereof is admixed with a pharmaceutically acceptable carrier or excipient. See, *e.g.. Remington's Pharmaceutical Sciences* and *U.S. Pharmacopeia: National Formulary,* Mack Publishing Company, Easton, PA (1984).

[00384] Formulations of therapeutic and diagnostic agents may be prepared by mixing with acceptable carriers, excipients, or stabilizers in the form of, *e.g.,* lyophilized powders, slurries, aqueous solutions or suspensions (see, *e.g.,* Hardman, *et al.* (2001) *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* McGraw-Hill, New York, NY; Gennaro (2000) *Remington: The Science and Practice of Pharmacy,* Lippincott, Williams, and Wilkins, New York, NY; Avis, *et al.* (eds.) (1993) *Pharmaceutical Dosage Forms: Parenteral Medications,* Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Tablets,* Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Disperse Systems,* Marcel Dekker, NY; Weiner and Kotkoskie (2000) *Excipient Toxicity and Safety,* Marcel Dekker, Inc., New York, NY).

[00385] Toxicity and therapeutic efficacy of the antibodies of the invention, administered alone or in combination with another therapeutic agent, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.,* for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index (LD_{50}/ ED_{50}). The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration.

[00386] In a further embodiment, a further therapeutic agent that is administered to a subject in association with an anti-SIRPa antibody or antigen-binding fragment thereof of the invention in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)).

[00387] The mode of administration can vary. Routes of administration include oral, rectal, transmucosal, intestinal, parenteral; intramuscular, subcutaneous, intradermal, intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intraocular, inhalation, insufflation, topical, cutaneous, transdermal, or intra-arterial.

[00388] In particular embodiments, the anti-SIRPa antibodies or antigen-binding fragments thereof of the invention can be administered by an invasive route such as by injection. In further embodiments of the invention, an anti-SIRPa antibody or antigen-binding fragment thereof, or pharmaceutical composition thereof, is administered intravenously, subcutaneously, intramuscularly, intraarterially, intratumorally, or by inhalation, aerosol delivery. Administration by non-invasive routes *(e.g.,* orally; for example, in a pill, capsule or tablet) is also within the scope of the present invention.

[00389] The present invention provides a vessel *(e.g.,* a plastic or glass vial, *e.g.,* with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising any of the antibodies or antigen-binding fragments of the invention or a pharmaceutical composition thereof. The present invention also provides an injection device comprising any of the antibodies or antigen-binding fragments of the invention or a pharmaceutical composition

thereof. An injection device is a device that introduces a substance into the body of a patient via a parenteral route, *e.g.,* intramuscular, subcutaneous or intravenous. For example, an injection device may be a syringe *(e.g.,* pre-filled with the pharmaceutical composition, such as an auto-injector) which, for example, includes a cylinder or barrel for holding fluid to be injected *(e.g.,* antibody or fragment or a pharmaceutical composition thereof), a needle for piecing skin and/or blood vessels for injection of the fluid; and a plunger for pushing the fluid out of the cylinder and through the needle bore. In an embodiment of the invention, an injection device that comprises an antibody or antigen-binding fragment thereof of the present invention or a pharmaceutical composition thereof is an intravenous (IV) injection device. Such a device includes the antibody or fragment or a pharmaceutical composition thereof in a cannula or trocar/needle which may be attached to a tube which may be attached to a bag or reservoir for holding fluid *(e.g.,* saline; or lactated ringer solution comprising NaCl, sodium lactate, KC1, $CaCl_2$ and optionally including glucose) introduced into the body of the patient through the cannula or trocar/needle. The antibody or fragment or a pharmaceutical composition thereof may, in an embodiment of the invention, be introduced into the device once the trocar and cannula are inserted into the vein of a subject and the trocar is removed from the inserted cannula. The IV device may, for example, be inserted into a peripheral vein *(e.g.,* in the hand or arm); the superior vena cava or inferior vena cava, or within the right atrium of the heart *(e.g.,* a central IV); or into a subclavian, internal jugular, or a femoral vein and, for example, advanced toward the heart until it reaches the superior vena cava or right atrium *(e.g.,* a central venous line). In an embodiment of the invention, an injection device is an autoinjector; a jet injector or an external infusion pump. A jet injector uses a high-pressure narrow jet of liquid which penetrate the epidermis to introduce the antibody or fragment or a pharmaceutical composition thereof to a patient's body. External infusion pumps are medical devices that deliver the antibody or fragment or a pharmaceutical composition thereof into a patient's body in controlled amounts. External infusion pumps may be powered electrically or mechanically. Different pumps operate in different ways, for example, a syringe pump holds fluid in the reservoir of a syringe, and a moveable piston controls fluid delivery, an elastomeric pump holds fluid in a stretchable balloon reservoir, and pressure from the elastic walls of the balloon drives fluid delivery. In a peristaltic pump, a set of rollers pinches down on a length of flexible tubing, pushing fluid forward. In a multi-channel pump, fluids can be delivered from multiple reservoirs at multiple rates.

[00390] The pharmaceutical compositions disclosed herein may also be administered with a needleless hypodermic injection device; such as the devices disclosed in U.S. Patent Nos. 6,620,135; 6,096,002; 5,399,163; 5,383,851 ; 5,312,335; 5,064,413; 4,941,880; 4,790,824 or 4,596,556. Such needleless devices comprising the pharmaceutical composition are also part of the present invention. The pharmaceutical compositions disclosed herein may also be administered by infusion. Examples of well-known implants and modules for administering the pharmaceutical compositions include those disclosed in: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent. No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments. Many other such implants, delivery systems, and modules are well known to those skilled in the art and those comprising the pharmaceutical compositions of the present invention are within the scope of the present invention.

[00391] Alternately, one may administer the anti-SIRPa antibody or antigen-binding fragment of the invention in a local rather than systemic manner, for example, via injection of the antibody or fragment directly into a tumor. Furthermore, one may administer the antibody or fragment in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody, targeting, for example, a tumor. The liposomes will be targeted to and taken up selectively by the afflicted tissue. Such methods and liposomes are part of the present invention.

[00392] The administration regimen depends on several factors, including the serum or tissue turnover rate of the therapeutic antibody or antigen-binding fragment, the level of symptoms, the immunogenicity of the therapeutic antibody, and the accessibility of the target cells in the biological matrix. Preferably, the administration regimen delivers sufficient therapeutic antibody or fragment to effect improvement in the target disease state, while simultaneously minimizing undesired side effects. Accordingly, the amount of biologic delivered depends in part on the particular therapeutic antibody and the severity of the condition being treated. Guidance in selecting appropriate doses of therapeutic antibodies or fragments is available (see, *e.g.,* Wawrzynczak (1996) *Antibody Therapy,* Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) *Monoclonal Antibodies, Cytokines and Arthritis,* Marcel Dekker, New York, NY;

Bach (ed.) (1993) *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases,* Marcel Dekker, New York, NY; Baert, *et al.* (2003) *New Engl. J. Med.* 348:601-608; Milgrom *et al.* (1999) *New Engl. J. Med,* 341:1966-1973; Slamon *et al.* (2001) *New Engl. J. Med.* 344:783-792; Beniaminovitz *et al.* (2000) *New Engl. J. Med.* 342:613-619; Ghosh *et al.* (2003) *New Engl. J. Med.* 348:24-32; Lipsky *et al.* (2000) *New Engl. J. Med.* 343: 1594-1602).

[00393] Determination of the appropriate dose is made by the clinician, *e.g.,* using parameters or factors known or suspected in the art to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of symptoms of, *e.g.,* the inflammation or level of inflammatory cytokines produced. In general, it is desirable that a biologic that will be used is derived from the same species as the animal targeted for treatment, thereby minimizing any immune response to the reagent. In the case of human subjects, for example, humanized and fully human antibodies may be desirable.

[00394] Antibodies or antigen-binding fragments thereof disclosed herein may be provided by continuous infusion, or by doses administered, *e.g.,* daily, 1-7 times per week, weekly, bi-weekly, monthly, bimonthly, quarterly, semiannually, annually etc. Doses may be provided, *e.g.,* intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, intraspinally, or by inhalation. A total weekly dose is generally at least 0.05 ng/kg body weight, more generally at least 0.2 μg/kg, 0.5 ^ig/kg, 1 μg/kg, 10 ng/kg, 100 ng/kg, 0.25 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 5.0 mg/mL, 10 mg/kg, 25 mg/kg, 50 mg/kg or more (see, *e.g.,* Yang, *et al.* (2003) *New Engl. J. Med.* 349:427-434; Herold, *et al.* (2002) *New Engl. J. Med.* 346:1692-1698; Liu, *et al.* (1999) *J. Neurol. Neurosurg. Psych,* 67: 451-456; Portielji, *et al.* (20003) *Cancer Immunol. bnmunother.* 52: 151-144). Doses may also be provided to achieve a pre-determined target concentration of anti-SIRPa antibody in the subject's serum, such as 0.1, 0.3, 1, 3, 10, 30, 100, 300 μg/mL or more. In other embodiments, An anti-SIRPa antibody of the present invention is administered, *e.g.,* subcutaneously or intravenously, on a weekly, biweekly, "every 4 weeks," monthly, bimonthly, or quarterly basis at 10, 20, 50, 80, 100, 200, 500, 1000 or 2500 mg/subject.

[00395] As used herein, the term "effective amount" refer to an amount of an anti-SIRPa or antigen-binding fragment thereof of the invention that, when administered alone or in combination with an additional therapeutic agent to a cell, tissue, or subject, is effective to cause a measurable improvement in one or more symptoms of disease, for example cancer or the progression of cancer. An effective dose further refers to that amount of the antibody or fragment sufficient to result in at least partial amelioration of symptoms, *e.g.,* tumor shrinkage or elimination, lack of tumor growth, increased survival time. When applied to an individual active ingredient administered alone, an effective dose refers to that ingredient alone. When applied to a combination, an effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. An effective amount of a therapeutic will result in an improvement of a diagnostic measure or parameter by at least 10%; usually by at least 20%; preferably at least about 30%; more preferably at least 40%, and most preferably by at least 50%. An effective amount can also result in an improvement in a subjective measure in cases where subjective measures are used to assess disease severity.

Kits

[00396] Further provided are kits comprising one or more components that include, but are not limited to, an anti-SIRPa antibody or antigen-binding fragment, as discussed herein in association with one or more additional components including, but not limited to a pharmaceutically acceptable carrier and/or a therapeutic agent, as discussed herein. The antibody or fragment and/or the therapeutic agent can be formulated as a pure composition or in combination with a pharmaceutically acceptable carrier, in a pharmaceutical composition.

[00397] In one embodiment, the kit includes an anti-SIRPa antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition thereof in one container *(e.g.,* in a sterile glass or plastic vial) and/or a therapeutic agent and a pharmaceutical composition thereof in another container *(e.g.,* in a sterile glass or plastic vial).

[00398] In another embodiment, the kit comprises a combination of the invention, including an anti-SIRPa antibody or antigen-binding fragment thereof of the invention along with a pharmaceutically acceptable carrier, optionally in combination with one or more therapeutic

agents formulated together, optionally, in a pharmaceutical composition, in a single, common container.

[00399] If the kit includes a pharmaceutical composition for parenteral administration to a subject, the kit can include a device for performing such administration. For example, the kit can include one or more hypodermic needles or other injection devices as discussed above.

[00400] The kit can include a package insert including information concerning the pharmaceutical compositions and dosage forms in the kit. Generally, such information aids patients and physicians in using the enclosed pharmaceutical compositions and dosage forms effectively and safely. For example, the following information regarding a combination of the invention may be supplied in the insert: pharmacokinetics, pharmacodynamics, clinical studies, efficacy parameters, indications and usage, contraindications, warnings, precautions, adverse reactions, overdosage, proper dosage and administration, how supplied, proper storage conditions, references, manufacturer/distributor information and patent information.

[00401] The kit can also comprise a second therapeutic, for example one or more of: anti-CD47 antibody, anti-APRIL antibody, anti-PD-1 antibody (e.g., nivolumab, pembrolizumab, anti-PDLl antibody, anti-TIGIT antibody, anti-CTLA4 antibody, anti-CSl antibody *(e.g.,* eloluzumab), anti-KIR2DL 1/2/3 antibody *(e.g.,* lirilumab), aiiti-CD137 antibody *(e.g.,* urelumab), anti-GITR antibody *(e.g.,* TRX518), anti-PD-Ll antibody *(e.g.,* BMS-936559, MSB0010718C or MPDL3280A), anti-PD-L2 antibody, anti-ILTl antibody, anti-ILT2 antibody, anti-ILT3 antibody, anti-ILT4 antibody, anti-ILT5 antibody, anti-ILT6 antibody, anti-ILT7 antibody, anti-ILT8 antibody, anti-CD40 antibody, anti-OX40 antibody, aiiti-ICOS, anti-KIR2DL1 antibody, anti-KIR2DL2/3 antibody, anti-KIR2DL4 antibody, anti-KIR2DL5A antibody, aiiti-KIR2DL5B antibody, anti-KIR3DLl antibody, anli-KIR3DL2 antibody, anti-KIR3DL3 antibody, anti-NKG2A antibody, anti-NKG2C antibody, anti-NKG2E antibody, anti-4-1BB antibody (e.g., PF-05082566), anti-TSLP antibody, anti-IL-10 antibody, IL-10 or PEGylated IL-10, or any small organic molecule inhibitor of such targets; an antibody or antigen binding fragment thereof binds to an antigen selected from the group consisting of AMHR2, AXL, BCMA, CA IX. CD4, CD16, CD19, CD20, CD22, CD30, CD37. CD38, CD40, CD52, CD98, CSF1R, GD2, CCR4, CS1, EpCam, EGFR, EGFRvIII, Endoglin, EPHA2, EphA3, FGFR2b, folate receptor alpha, fucosyl-GMl , HER2, HER3, IL1RAP, kappa myeloma antigen,

MS4A1, prolactin receptor, TA-MUC1, and PSMA; Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinutuzumab, ADCT-502, Hul4.18K322A, Hu3F8, Dinituximab, Trastuzumab, Cetuximab, Rituximab-RLI, c.60C3-RLI, Hul4.18-IL2, KM2812, AFM13, and $(CD20)_2$xCD16, erlotinib (Tarceva), daratumumab, alemtuzumab, pertuzumab, brentuximab, elotuzumab, ibritumomab, ifabotuzumab, farletuzumab, otlertuzumab, carotuximab, epratuzumab, inebilizumab, lumretuzumab, 4G7SDIE, AFM21, AFM22, LY-3022855, SNDX-6352, AFM-13, BI-836826, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, leukotuximab, isatuximab, DS-8895, FPA144, GM102, GSK-2857916, IGN523. IT1208, ADC-101 3, CAN-04, XOMA-213, PankoMab-GEX, chKM-4927, IGN003, IGN004, IGN005, MDX-1097, MOR202, MOR-208, oportuzumab, ensituximab, vedotin (Adcetris), ibritumomab tiuxetan, ABBV-838, HuMax-AXL-ADC, and ado-trastuzumab emtansine (Kadcyla); radiotherapy or chemotherapeutic agents including, but not limited to Anthracyclines (Doxorubicin, Epirubicin, Daunorubicin, Idarubicin, Mitoxantrone), Oxaliplatin, Bortezomib, Cyclophosphamide, Bleomycin, Vorinostat, Paclitaxel, 5-Fluorouracil, Cylarabine, Prednisolone, Docetaxel, Mitomycin C, Topotecan/Camptothecin, Etoposide, Zoledronic acid, Methotrexate, Ibmtinib, Aflibercept, Bevacizumab, Toremifene, Vinblastine, Vincristine, Idelalisib, Mercaptopurine, Thalidomide, Sorafenib; a cyclic dinculeotide or other STING pathway agonist; etc.

Detection Kits and Therapeutic Kits

[00402] As a matter of convenience, an anti-SIRPa antibody or antigen-binding fragment thereof of the invention can be provided in a kit, i.e., a packaged combination of reagents in predetermined amounts with instructions for performing the diagnostic or detection assay. Where the antibody or fragment is labeled with an enzyme, the kit will include substrates and cofactors required by the enzyme *(e.g.,* a substrate precursor which provides the detectable chromophore or fluorophore). In addition, other additives may be included such as stabilizers, buffers *(e.g.,* a block buffer or lysis buffer) and the like. The relative amounts of the various reagents may be varied widely to provide for concentrations in solution of the reagents which substantially optimize the sensitivity of the assay. Particularly, the reagents may be provided as dry powders, usually lyophilized, including excipients which on dissolution will provide a reagent solution having the appropriate concentration.

[00403] Also provided are diagnostic or detection reagents and kits comprising one or more such reagents for use in a variety of detection assays, including for example, immunoassays such as ELISA (sandwich-type or competitive format). The kit's components may be pre-attached to a solid support, or may be applied to the surface of a solid support when the kit is used. In some embodiments of the invention, the signal generating means may come pre-associated with an antibody or fragment of the invention or may require combination with one or more components, *e.g.,* buffers, antibody-enzyme conjugates, enzyme substrates, or the like, prior to use. Kits may also include additional reagents, *e.g.,* blocking reagents for reducing nonspecific binding to the solid phase surface, washing reagents, enzyme substrates, and the like. The solid phase surface may be in the form of a tube, a bead, a microtiter plate, a microsphere, or other materials suitable for immobilizing proteins, peptides, or polypeptides. In particular aspects, an enzyme that catalyzes the formation of a chemilluminescent or chromogenic product or the reduction of a chemilluminescent or chromogenic substrate is a component of the signal generating means. Such enzymes are well known in the art. Kits may comprise any of the capture agents and detection reagents described herein. Optionally the kit may also comprise instructions for carrying out the methods of the invention.

[00404] Also provided is a kit comprising an anti-SIRPa antibody *(e.g.,* humanized antibody) or antigen-binding fragment thereof packaged in a container, such as a vial or bottle, and further comprising a label attached to or packaged with the container, the label describing the contents of the container and providing indications and/or instructions regarding use of the contents of the container to treat one or more disease states as described herein.

[00405] In one aspect, the kit is for treating cancer and comprises an anti-SIRPa antibody (e.g., humanized antibody) or antigen-binding fragment thereof and a further therapeutic agent or a vaccine. The kit may optionally further include a syringe for parenteral, *e.g.,* intravenous, administration. In another aspect, the kit comprises an anti-SIRPa antibody *(e.g.,* humanized antibody) or antigen-binding fragment thereof and a label attached to or packaged with the container describing use of the antibody or iragment with the vaccine or further therapeutic agent. In yet another aspect, the kit comprises the vaccine or further therapeutic agent and a label attached to or packaged with the container describing use of the vaccine or further therapeutic agent with the anti-SIRPa antibody or fragment. In certain embodiments, an anti-

SIRPα antibody and vaccine or further therapeutic agent are in separate vials or are combined together in the same pharmaceutical composition.

[00406] As discussed above in the combination therapy section, concurrent administration of two therapeutic agents does not require that the agents be administered at the same time or by the same route, as long as there is an overlap in the time period during which the agents are exerting their therapeutic effect. Simultaneous or sequential administration is contemplated, as is administration on different days or weeks.

[00407] The therapeutic and detection kits disclosed herein may also be prepared that comprise at least one of the antibody, peptide, antigen-binding fragment, or polynucleotide disclosed herein and instructions for using the composition as a detection reagent or therapeutic agent. Containers for use in such kits may typically comprise at least one vial, test tube, flask, bottle, syringe or other suitable container, into which one or more of the detection and/or therapeutic composition(s) may be placed, and preferably suitably aliquoted. Where a second therapeutic agent is also provided, the kit may also contain a second distinct container into which this second detection and/or therapeutic composition may be placed. Alternatively, a plurality of compounds may be prepared in a single pharmaceutical composition, and may be packaged in a single container means, such as a vial, flask, syringe, bottle, or other suitable single container. The kits disclosed herein will also typically include a means for containing the vial(s) in close confinement for commercial sale, such as, *e.g.,* injection or blow-molded plastic containers into which the desired vial(s) are retained. Where a radiolabel, chromogenic, fluorigenic, or other type of detectable label or detecting means is included within the kit, the labeling agent may be provided either in the same container as the detection or therapeutic composition itself, or may alternatively be placed in a second distinct container means into which this second composition may be placed and suitably aliquoted. Alternatively, the detection reagent and the label may be prepared in a single container means, and in most cases, the kit will also typically include a means for containing the vial(s) in close confinement for commercial sale and/or convenient packaging and delivery.

[00408] A device or apparatus for carrying out the detection or monitoring methods described herein is also provided. Such an apparatus may include a chamber or tube into which sample can be input, a fluid handling system optionally including valves or pumps to direct flow of the

sample through the device, optionally filters to separate plasma or serum from blood, mixing chambers for the addition of capture agents or detection reagents, and optionally a detection device for detecting the amount of detectable label bound to the capture agent immunocomplex. The flow of sample may be passive *(e.g.,* by capillary, hydrostatic, or other forces that do not require further manipulation of the device once sample is applied) or active *(e.g.,* by application of force generated via mechanical pumps, electroosmotic pumps, centrifugal force, or increased air pressure), or by a combination of active and passive forces.

[00409] In further embodiments, also provided is a processor, a computer readable memory, and a routine stored on the computer readable memory and adapted to be executed on the processor to perform any of the methods described herein. Examples of suitable computing systems, environments, and/or configurations include personal computers, server computers, hand-held or laptop devices, multiprocessor systems, microprocessor-based systems, set top boxes, programmable consumer electronics, network PCs, minicomputers, mainframe computers, distributed computing environments that include any of the above systems or devices, or any other systems known in the ait.

PREFERRED EMBODIMENTS

Embodiment 1. An antibody or antigen binding fragment thereof that binds to human SIRPa, wherein the antibody or antigen binding fragment comprises one or more, and optionally each, of:

a. a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:69 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, or 3 conservative substitutions,

b. a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:70 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, or 3 conservative substitutions,

c. a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:71 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, or 3 conservative substitutions,

d. a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:72 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, or 3 conservative substitutions,

e. a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:73 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, or 3 conservative substitutions, and

f. a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:74 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, or 3 conservative substitutions.

or wherein the antibody or antigen binding fragment comprises one or more, and optionally each, of:

g. a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:l or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, or 3 conservative substitutions,

h. a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:2 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, or 3 conservative substitutions,

i. a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:3 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, or 3 conservative substitutions,

j. a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:4 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, or 3 conservative substitutions,

k. a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:5 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, or 3 conservative substitutions, and

1. a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:6 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, or 3 conservative substitutions.

Embodiment 2. The antibody or antigen binding fragment of embodiment 1, wherein the antibody or antigen binding fragment comprises

each of a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence differing from SEQ ID NO: 69 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO: 70 or an amino acid sequence differing from SEQ

ID NO: 70 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO: 71 or an amino acid sequence differing from SEQ ID NO: 71 by 1, 2, or 3 conservative substitutions;

and/or

each of a light chain sequence comprising the amino acid sequence of SEQ ID NO: 72 or an amino acid sequence differing from SEQ ID NO: 72 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence differing from SEQ ID NO: 73 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence differing from SEQ ID NO: 74 by 1, 2, or 3 conservative substitutions;

or wherein the antibody or antigen binding fragment comprises

each of a heavy chain sequence comprising the amino acid sequence of SEQ ID NO:1 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO:2 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO:3 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, or 3 conservative substitutions;

and/or

each of a light chain sequence comprising the amino acid sequence of SEQ ID NO:4 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO:5 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO:6 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, or 3 conservative substitutions.

Embodiment 3. The antibody or antigen binding fragment of embodiment 2,

wherein the antibody or antigen binding fragment comprises one or both of:

a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 75 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 78 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 80 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 82 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 84 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 86 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 88 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 102 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto;

and

a light chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 76 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 90 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 92 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 94 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 96 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 98 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 100 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 104 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto;

or wherein the antibody or antigen binding fragment comprises one or both of:

a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 7 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 10 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 12 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 14 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 16 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 18 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 30 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto;

and

a light chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 8 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 20 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 22 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 24 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 26 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 28 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 32 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 4. The antibody or antigen binding fragment of embodiment 3, wherein the antibody or fragment thereof has the following characteristics:

binds to a cell expressing human SIRPaVl protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3nM or less;

binds to a cell expressing human SIRPaV2 protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3nM or less;

does not appreciably bind to SIRPβ1 protein at an antibody concentration of 50 nM, preferably 67 nM, and more preferably 100 nM; or alternatively at a concentration that is 10-fold greater, preferably 50-fold greater, more preferably 100-fold greater, and still more preferably 200-fold greater than the antibody's EC_{50} for SIRPaVl or SIRPaV2;

inhibits binding between human SIRPα and CD47 with an IC_{50} < 10.0 nM, more preferably < 5.0 nM, still more preferably < 2.5 nM, and most preferably about 1.0 11M or less; and

exhibits a T20 "humanness" score of at least 79, and more preferably 85.

Embodiment 5. The antibody or antigen binding fragment of embodiment 1, wherein the antibody or antigen binding fragment thereof comprises one of the following combinations of heavy chain sequence / light chain sequence:

SEQ ID NO: 78 / SEQ ID NO: 90,

SEQ ID NO: 78 / SEQ ID NO: 92,

SEQ ID NO: 78 / SEQ ID NO: 94,

SEQ ID NO: 78 / SEQ ID NO: 96,

SEQ ID NO: 78 / SEQ ID NO: 98,

SEQ ID NO: 78 / SEQ ID NO: 100,

SEQ ID NO: 80 / SEQ ID NO: 90,

SEQ ID NO: 80 / SEQ ID NO: 92,

SEQ ID NO: 80 / SEQ ID NO: 94,

SEQ ID NO: 80 / SEQ ID NO: 96,

SEQ ID NO: 80 / SEQ ID NO: 98,

SEQ ID NO: 80 / SEQ ID NO: 100,

SEQ ID NO: 82 / SEQ ID NO: 90,

SEQ ID NO: 82 / SEQ ID NO: 92,

SEQ ID NO: 82 / SEQ ID NO: 94,

SEQ ID NO: 82 / SEQ ID NO: 96,

SEQ ID NO: 82 / SEQ ID NO: 98,

SEQ ID NO: 82 / SEQ ID NO: 100,

SEQ ID NO: 84 / SEQ ID NO: 90,

SEQ ID NO: 84 / SEQ ID NO: 92,

SEQ ID NO: 84 / SEQ ID NO: 94,

SEQ ID NO: 84 / SEQ ID NO: 96,

SEQ ID NO: 84 / SEQ ID NO: 98,

SEQ ID NO: 84 / SEQ ID NO: 100,

SEQ ID NO: 86 / SEQ ID NO: 90,

SEQ ID NO: 86 / SEQ ID NO: 92,

SEQ ID NO: 86 / SEQ ID NO: 94,

SEQ ID NO: 86 / SEQ ID NO: 96,

SEQ ID NO: 86 / SEQ ID NO: 98,

SEQ ID NO: 86 / SEQ ID NO: 100,

SEQ ID NO: 88 / SEQ ID NO: 90,

SEQ ID NO: 88 / SEQ ID NO: 92,

SEQ ID NO: 88 / SEQ ID NO: 94,

SEQ ID NO: 88 / SEQ ID NO: 96,

SEQ ID NO: 88 / SEQ ID NO: 98,

SEQ ID NO: 88 / SEQ ID NO: 100,

SEQ ID NO: 10 / SEQ ID NO: 20,

SEQ ID NO: 10 / SEQ ID NO: 22,

SEQ ID NO: 10 / SEQ ID NO: 24,

SEQ ID NO: 10 / SEQ ID NO: 26,

SEQ ID NO: 10 / SEQ ID NO: 28,

SEQ ID NO: 12 / SEQ ID NO: 20,

SEQ ID NO: 12 / SEQ ID NO: 22,

SEQ ID NO: 12 / SEQ ID NO: 24,

SEQ ID NO: 12 / SEQ ID NO: 26,

SEQ ID NO: 12 / SEQ ID NO: 28,

SEQ ID NO: 14 / SEQ ID NO: 20,

SEQ ID NO: 14 / SEQ ID NO: 22,

SEQ ID NO: 14 / SEQ ID NO: 24,

SEQ ID NO: 14 / SEQ ID NO: 26,

SEQ ID NO: 14 / SEQ ID NO: 28,

SEQ ID NO: 16 / SEQ ID NO: 20,

SEQ ID NO: 16 / SEQ ID NO: 22,

SEQ ID NO: 16 / SEQ ID NO: 24,

SEQ ID NO: 16 / SEQ ID NO: 26,

SEQ ID NO: 16 / SEQ ID NO: 28,

SEQ ID NO: 18 / SEQ ID NO: 20,

SEQ ID NO: 18 / SEQ ID NO: 22,

SEQ ID NO: 18 / SEQ ID NO: 24,

SEQ ID NO: 18 / SEQ ID NO: 26,

SEQ ID NO: 18 / SEQ ID NO: 28,

or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID.

Embodiment 6. The antibody or antigen binding fragment of one of embodiments 1-5, wherein the antibody is an intact IgG.

Embodiment 7. The antibody or antigen binding fragment of one of embodiments 1-6, wherein the antibody comprises a wild-type or mutated IgG2 Fc region.

Embodiment 8. The antibody or antigen binding fragment of one of embodiments 1-6, wherein the antibody comprises a mutated IgGl Fc region.

Embodiment 9. The antibody or antigen binding fragment of one of embodiments 1-6, wherein the antibody comprises a mutated IgG4 Fc region.

Embodiment 10. An antibody or antigen binding fragment thereof that binds to the same epitope of human SIRPa as an antibody as an antibody according to embodiment 5.

Embodiment 11. The antibody or antigen binding fragment of any of embodiments 1-10, wherein the antibody or antigen binding fragment is humanized.

Embodiment 12. The antibody or antigen binding fragment of any of embodiments 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 10 and each light chain comprises SEQ ID NO: 20.

Embodiment 13. The antibody or antigen binding fragment of any of embodiments 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 16 and each light chain comprises SEQ ID NO: 28.

Embodiment 14. The antibody or antigen binding fragment of any of embodiments 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 18 and each light chain comprises SEQ ID NO: 20.

Embodiment 15. The antibody or antigen binding fragment of any of embodiments 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 90.

Embodiment 16. The antibody or antigen binding fragment of any of embodiments 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 92.

Embodiment 17. The antibody or antigen binding fragment of any of embodiments 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 95.

Embodiment 18. The antibody or antigen binding fragment of any one of embodiments 1-17 that comprises a glycosylation pattern characteristic of expression by a mammalian cell, and optionally is glycosylated by expression from a CHO cell.

Embodiment 19. An isolated polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 76, 90, 92, 94, 96, 98, 100, 102, 104, 7, 10, 12, 14, 16, 18, 30, 8, 20, 22, 24, 26, 28, and 32, or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 20. An isolated nucleic acid encoding any one of the antibodies or antigen binding fragments of embodiments 1-18, or any one of the polypeptides of embodiment 19.

Embodiment 21. An isolated nucleic acid of embodiment 20 comprising:

a nucleic acid sequence of SEQ ID NO: 77 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 79 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 81 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 83 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 85 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 87 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 101 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 89 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 91 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 93 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 95 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 97 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 99 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 103 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 9 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 11 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 13 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 15 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 17 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 29 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 19 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 21 or a nucleic acid sequence at least 90%, 95%, 97%, 98%. or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 23 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 25 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 27 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and/or

a nucleic acid sequence of SEQ ID NO: 31 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 22. An expression vector comprising the isolated nucleic acid of embodiment 20 or 21.

Embodiment 23. An expression vector of embodiment 22, encoding both a heavy chain sequence and a light chain sequence of an anti-SIRPa antibody, the expression vectors comprising the following a first nucleic acid sequence / second nucleic acid sequence selected from the group consisting of:

SEQ ID NO: 77 / SEQ ID NO: 89,

SEQ ID NO: 77 / SEQ ID NO: 91,

SEQ ID NO: 77 / SEQ ID NO: 93,

SEQ ID NO: 77 / SEQ ID NO: 95,

SEQ ID NO: 77 / SEQ ID NO: 97,

SEQ ID NO: 77 / SEQ ID NO: 99,

SEQ ID NO: 79 / SEQ ID NO: 89,

SEQ ID NO: 79 / SEQ ID NO: 91,

SEQ ID NO: 79 / SEQ ID NO: 93,

SEQ ID NO: 79 / SEQ ID NO: 95,

SEQ ID NO: 79 / SEQ ID NO: 97,

SEQ ID NO: 79 / SEQ ID NO: 99,

SEQ ID NO: 81 / SEQ ID NO: 89,

SEQ ID NO: 81 / SEQ ID NO: 91,

SEQ ID NO: 81 / SEQ ID NO: 93,

SEQ ID NO: 81 / SEQ ID NO: 95,

SEQ ID NO: 81 / SEQ ID NO: 97,

SEQ ID NO: 81 / SEQ ID NO: 99,

SEQ ID NO: 83 / SEQ ID NO: 89,

SEQ ID NO: 83 / SEQ ID NO: 91,

SEQ ID NO: 83 / SEQ ID NO: 93,

SEQ ID NO: 83 / SEQ ID NO: 95,

SEQ ID NO: 83 / SEQ ID NO: 97,

SEQ ID NO: 83 / SEQ ID NO: 99,

SEQ ID NO: 85 / SEQ ID NO: 89,

SEQ ID NO: 85 / SEQ ID NO: 91,

SEQ ID NO: 85 / SEQ ID NO: 93,

SEQ ID NO: 85 / SEQ ID NO: 95,

SEQ ID NO: 85 / SEQ ID NO: 97,

SEQ ID NO: 85 / SEQ ID NO: 99,

SEQ ID NO: 87 / SEQ ID NO: 89,

SEQ ID NO: 87 / SEQ ID NO: 91,

SEQ ID NO: 87 / SEQ ID NO: 93,

SEQ ID NO: 87 / SEQ ID NO: 95,

SEQ ID NO: 87 / SEQ ID NO: 97,

SEQ ID NO: 87 / SEQ ID NO: 99,

SEQ ID NO: 9 / SEQ ID NO: 19,

SEQ ID NO: 9 / SEQ ID NO: 21,

SEQ ID NO: 9 / SEQ ID NO: 23,

SEQ ID NO: 9 / SEQ ID NO: 25,

SEQ ID NO: 9 / SEQ ID NO: 27,

SEQ ID NO: 11 / SEQ ID NO: 19,

SEQ ID NO: 11 / SEQ ID NO: 21,

SEQ ID NO: 11 / SEQ ID NO: 23,

SEQ ID NO: 11 / SEQ ID NO: 25,

SEQ ID NO: 11 / SEQ ID NO: 27,

SEQ ID NO: 13 / SEQ ID NO: 19,

SEQ ID NO: 13 / SEQ ID NO: 21,

SEQ ID NO: 13 / SEQ ID NO: 23,

SEQ ID NO: 13 / SEQ ID NO: 25,

SEQ ID NO: 13 / SEQ ID NO: 27,

SEQ ID NO: 15 / SEQ ID NO: 19,

SEQ ID NO: 15 / SEQ ID NO: 21,

SEQ ID NO: 15 / SEQ ID NO: 23,

SEQ ID NO: 15 / SEQ ID NO: 25,

SEQ ID NO: 15 / SEQ ID NO: 27,

SEQ ID NO: 17 / SEQ ID NO: 19,

SEQ ID NO: 17 / SEQ ID NO: 21,

SEQ ID NO: 17 / SEQ ID NO: 23,

SEQ ID NO: 17 / SEQ ID NO: 25, and

SEQ ID NO: 17 / SEQ ID NO: 27,

or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

Embodiment 24. A host cell comprising expression vector of embodiment 22 or 23.

Embodiment 25. A host cell of embodiment 24 which produces a full length anti-SIRPa antibody.

Embodiment 26. The host cell of one of embodiments 24 or 25, which is a bacterial cell, a human cell, a mammalian cell, a *Pichia* cell, a plant cell, an HEK293 cell, or a Chinese hamster ovary cell.

Embodiment 27. A composition comprising the antibody or antigen binding fragment of any one of embodiments 1-18 and a pharmaceutically acceptable carrier or diluent.

Embodiment 28. The composition of embodiment 27, further comprising a second antibody or antigen binding fragment thereof that induces ADCC and/or ADCP, wherein said antibody or antigen binding fragment of the invention enhances the antibody-mediated destruction of cells by the second antibody.

Embodiment 29. The composition according to embodiment 28, wherein the second antibody or antigen binding fragment thereof binds to an antigen selected from the group consisting of AMHR2, AXL, BCMA, CA IX, CD4, CD16, CD19, CD20, CD22, CD30, CD37, CD38, CD40, CD52, CD98, CSF1R, GD2, CCR4, CS1, EpCam, EGFR, EGFRvIII, Endoglin, EPHA2, EphA3, FGFR2b, folate receptor alpha, fucosyl-GMl, HER2, HER3, ILIRAP, kappa myeloma antigen, MS4A1, prolactin receptor, TA-MUC1, and PSMA.

Embodiment 30. The composition according to embodiment 29, wherein the second antibody or antigen binding fragment thereof is selected from the group consisting of Rituximab, ublituximab, margeluximab, IMGN-529, SCT400, veltuzumab, Obinutuzumab, ADCT-502, Hul4.18K322A, Hu3F8, Dinituximab, Trastuzumab, Cetuximab, Rituximab-RLI, C.60C3-RLI, Hul4.18-IL2, KM2812, AFM13, (CD2())2xCD16, erlotinib (Tarceva), daralumumab, alemtuzumab, pertuzumab, brentuximab, elotuzumab, ibritumomab, ifabotuzumab, farletuzumab, otlertuzumab, carotuximab, epratuzumab, inebilizumab, lumretuzumab, 4G7SDIE, AFM21, AFM22, LY-3022855, SNDX-6352, AFM-13, BI-836826, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, leukotuximab, isatuximab, DS-8895, FPA144, GM102, GSK-

2857916, IGN523, IT1208, ADC-1013, CAN-04, XOMA-213, PankoMab-GEX, cliKM-4927, IGN003, IGN004, IGN005, MDX-1097, MOR202, MOR-208, oportuzumab, ensituximab, vedotin (Adcetris), ibritumomab tiuxetan, ABBV-838, HuMax-AXL-ADC, and ado-trastuzumab emtansine (Kadcyla).

Embodiment 31. The composition according to embodiment 28, wherein the second antibody or antigen binding fragment thereof induces ADCP.

Embodiment 32. The composition according to embodiment 31, wherein the second antibody or antigen binding fragment thereof is selected from the group consisting of Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinutuzumab, Trastuzumab, Cetuximab, alemtuzumab, ibritumomab, farletuzumab, inebilizumab, lumretuzumab, 4G7SDIE, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, GM102, GSK-2857916, PankoMab-GEX, chKM-4927, MDX-1097, MOR202, and MOR-208.

Embodiment 33. The composition of embodiment 27, further comprising one or more agents selected from the group consisting of anti-CD27 antibody, anti-CD47 antibody, anti-APRIL antibody, anti-PD-1 antibody, anti-PD-Ll antibody, anti-TIGIT antibody, anti-CTLA4 antibody, anti-CSl antibody, anti-KIR2DL 1/2/3 antibody, anti-CD 137 antibody, anti-GITR antibody, anti-PD-L2 antibody, anti-ILTl antibody, anti-ILT2 antibody, anti-ILT3 antibody, anti-ILT4 antibody, anti-ILT5 antibody, anti-ILT6 antibody, anti-ILT7 antibody, anti-ILT8 antibody, anti-CD40 antibody, anti-OX40 antibody, anti-ICOS, anti-KIR2DLl antibody, anti-KIR2DL2/3 antibody, anti-KIR2DL4 antibody, anti-KIR2DL5A antibody, anti-KIR2DL5B antibody, anti-KIR3DLl antibody, anti-KIR3DL2 antibody, anti-KIR3DL3 antibody, anti-NKG2A antibody, anti-NKG2C antibody, anti-NKG2E antibody, anti-4-lBB antibody, anti-TSLP antibody, anti-IL-10 antibody, IL-10 PEGylated IL-10, an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecules (SLAM proteins), an activating NK cell receptor, a Toll like receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, ICAM-1, LFA-1 (CDl la/CD18), 4-lBB (CD137), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRFl), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLAl, CD49a. ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD,

CD1 Id, ITGAE, CD103, ITGAL, ITGAM, CDl lb, ITGAX, CD1 lc, ITGB1, CD29, ITGB2, CD18, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), SLAM7, BLAME (SLAMF8), SELPLG (CD 162), LTBR, LAT, GADS, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, inhibitor of CD47, an inhibitor of PD-1, an an inhibitor of PD-Ll, an inhibitor of PD-L2, an inhibitor of CTLA4, an inhibitor of TIM3, an inhibitor of LAG3, an inhibitor of CEACAM (e.g., CEACAM-1, -3 and/or -5), an inhibitor of VISTA, an inhibitor of BTLA, an inhibitor of TIGIT, an inhibitor of LAIRl, an inhibitor of IDO, an inhibitor of TDO, an inhibitor of CD160 an inhibitor of TGFR beta, and a cyclic dinculeotide or other STING pathway agonist.

Embodiment 34. A method of producing an antibody or antigen binding fragment comprising:

culturing a host cell comprising a polynucleotide encoding the heavy chain and/or the light chain of any one of the antibodies or antigen binding fragments of embodiments 1-18 under conditions favorable to expression of the polynucleotide; and optionally, recovering the antibody or antigen binding fragment from the host cell and/or culture medium.

Embodiment 35. A method for detecting the presence of a SIRPa peptide or a fragment thereof in a sample comprising contacting the sample with an antibody or fragment of any of embodiments 1-18 and detecting the presence of a complex between the antibody or fragment and the peptide; wherein detection of the complex indicates the presence of the SIRPa peptide.

Embodiment 36. An antibody or antigen binding fragment according to any one of embodiments 1-18 or a composition according to any one of embodiments 21-25, for the treatment of cancer or an infectious disease.

Embodiment 37. An antibody or antigen binding fragment of embodiments 1-18 or a composition according to any one of embodiments 27-33 for decreasing SIRPa/CD47 signalling in a human subject.

Embodiment 38. A method of treating cancer in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment of any one of embodiments 1-18, or an expression vector according to one of embodiments 22 or 23, or a host cell according to one of embodiments 24-26, or a composition according one of embodiments 27-33, optionally in association with a further therapeutic agent or therapeutic procedure.

Embodiment 39. A method of treating cancer in a human subject, comprising:

administering to the subject an effective amount of

(i) an antibody or antigen binding fragment thereof that induces ADCC and/or ADCP; and

(ii) an antibody or antigen binding fragment of any one of embodiments 1-18, or an expression vector according to one of embodiments 22 or 23, or a host cell according to one of embodiments 24-26, or a composition according one of embodiments 27-33, optionally in association with a further therapeutic agent or therapeutic procedure,

wherein the administration of (ii) enhances the antibody-mediated destruction of cells by the antibody or antigen binding fragment thereof that induces ADCC and/or ADCP.

Embodiment 40. The method according to embodiment 39, wherein the antibody or antigen binding fragment thereof that induces ADCC and/or ADCP binds to an antigen selected from the group consisting of AMHR2, AXL, BCMA, CA IX, CD4, CD16, CD19, CD20, CD22, CD30, CD37, CD38, CD40, CD52, CD98, CSF1R, GD2, CCR4, CS1, EpCam, EGFR, EGFRvIII, Endoglin, EPHA2, EphA3, FGFR2b, folate receptor alpha, fucosyl-GMl, HER2, HER3, IL1RAP, kappa myeloma antigen, MS4A1, prolactin receptor, TA-MUCl, and PSMA.

Embodiment 41. The method according to embodiment 40, wherein the antibody or antigen binding fragment thereof that induces ADCC and/or ADCP is selected from the group consisting of Rituximab, ublituximab, margetuximab, EVIGN-529, SCT400, veltuzumab, Obinutuzumab, ADCT-502, Hul4.18K322A, Hu3F8, Dinituximab, Trastuzumab, Cetuximab, Rituximab-RLI, $_{C}$.60C3-RLI, FM4.18-IL2, KM2812, AFM13, (CD20)2xCD16, erlotinib (Tarceva), daratumumab, alemtuzumab, pertuzumab, brentuximab, elotuzumab, ibritumomab, ifabotuzumab, farletuzumab, otlertuzumab, carotuximab, epratuzumab, inebilizumab, lumretuzumab, 4G7SDIE, AFM21, AFM22, LY-3022855, SNDX-6352, AFM-13, BI-836826, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, leukotuximab, isatuximab, DS-8895,

FPA144, GM102, GSK-2857916, IGN523, гг1208, ADC-1013, CAN-04, XOMA-213, PankoMab-GEX, chKM-4927, IGN003, IGN004, IGN005, MDX-1097, MOR202, MOR-208, oportuzumab, ensituximab, vedotin (Adcetris), ibritumomab tiuxetan, ABBV-838, HuMax-AXL-ADC, and ado-trastuzimiab emtansine (Kadcyla).

Embodiment 42. The method according to embodiment 39 or 40, wherein the second antibody or antigen binding fragment thereof induces ADCP.

Embodiment 43. The method according to embodiment 42, wherein the second antibody or antigen binding fragment thereof is selected from the group consisting of Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinuluzumab, Trastuzumab, Cetuximab, alemtuzumab, ibritumomab, farleluzumab, inebilizumab, lumretuzumab, 4G7SDIE, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, GM102, GSK-2857916, PankoMab-GEX, chKM-4927, MDX-1097, MOR202, and MOR-208.

Embodiment 44. A method of treating an infection or infectious disease in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment of any one of embodiments 1-18, or an expression vector according to one of embodiments 22 or 23, or a host cell according to one of embodiments 24-26, or a composition according one of embodiments 27-33, optionally in association with a further therapeutic agent or therapeutic procedure.

Embodiment 45. An antibody having one or more of the following characteristics:

binds human SIRPaVl protein having the sequence of SEQ ID NO: 34 with an EC_{50} < 1 **11M;** exhibits at least a 100-fold higher EC50 for SIRPaVl(P74A) having the sequence of SEQ ID NO: 62; and exhibits at least a 100-fold higher EC_{50} for human SIRPβ1 protein having the sequence of SEQ ID NO: 38, preferably when measured by cellular ELISA;

binds to a cell expressing human SIRPaVl protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3 nM or less;

binds to a cell expressing human SIRPaV2 protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about ().3nM or less;

does not appreciably bind to SIRPpi protein at an antibody concentration of 50 nM, preferably 67 nM, and more preferably 100 nM; or alternatively at a concentration that is 10-fold greater, preferably 50-fold greater, more preferably 100-fold greater, and still more preferably 200-fold greater than the antibody's EC_{50} for SIRPaVl or SIRPaV2;

inhibits binding between human SIRPα and CD47 with an IC_{50} < 10.0 nM, more preferably < 5.0 nM, still more preferably < 2.5 nM, and most preferably about 1.0 nM or less; and

exhibits a T20 "humanness" score of at least 79, and more preferably 85.

Embodiment 46. The antibody or antigen binding fragment of embodiment 45 that binds human SIRPaVl protein having the sequence of SEQ ID NO: 34 with an EC_{50} < 1 nM; exhibits at least a 100-fold higher EC_{50} for SIRPaVl (P74A) having the sequence of SEQ ID NO: 62; and exhibits at least a 100-fold higher EC_{50} for human SIRPpi protein having the sequence of SEQ ID NO: 38.

Embodiment 47. The antibody or antigen binding fragment of embodiment 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 20 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 10 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 48. The antibody or antigen binding fragment of embodiment 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 28 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 16 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 49. The antibody or antigen binding fragment of embodiment 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 20 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and and one or two heavy chains comprising SEQ ID NO: 18 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 50. The antibody or antigen binding fragment of embodiment 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 90 or a sequence at least 90%, 95%,

97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 80 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 51. The antibody or antigen binding fragment of embodiment 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 92 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 80 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 52. The antibody or antigen binding fragment of embodiment 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 96 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and and one or two heavy chains comprising SEQ ID NO: 80 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

Embodiment 53. The antibody or antigen binding fragment of one of embodiments 45-52, wherein the antibody is an intact IgG.

Embodiment 54. The antibody or antigen binding fragment of one of embodiments 45-52, wherein the antibody comprises a wild-type or mutated IgG2 Fc region.

Embodiment 55. The antibody or antigen binding fragment of one of embodiments 45-52, wherein the antibody comprises a mutated IgG1 Fc region.

Embodiment 56. The antibody or antigen binding fragment of one of embodiments 45-52, wherein the antibody comprises a mutated IgG4 Fc region.

Embodiment 57. An antibody or antigen binding fragment thereof that binds to the same epitope of human SIRPa as an antibody as an antibody according to one of embodiments 45-52.

Embodiment 58. The antibody or antigen binding fragment of any of embodiments 45-52, wherein the antibody or antigen binding fragment is humanized.

Embodiment 59. A composition comprising the antibody or antigen binding fragment of any one of embodiments 45-52 and a pharmaceutically acceptable carrier or diluent.

Embodiment 60. An antibody or antigen binding fragment according to any one of embodiments 45-52 or a composition according to embodiment 59, for the treatment of cancer or an infectious disease.

Embodiment 61. An antibody or antigen binding fragment according to any one of embodiments 45-52 or a composition according to embodiment 59 for decreasing SIRPα/CD47 signalling in a human subject.

Embodiment 62. A method of treating cancer in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment according to any one of embodiments 45-52 or a composition according to embodiment 59, optionally in association with a further therapeutic agent or therapeutic procedure.

Embodiment 63. A method of treating an infection or infectious disease in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment according to any one of embodiments 45-52 or a composition according to embodiment 59, optionally in association with a further therapeutic agent or therapeutic procedure.

GENERAL METHODS

[00410] Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) *Molecular Cloning, A Laboratory Manual,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Sambrook and Russell (2001) *Molecular Cloning, 3rd ed.,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Wu (1993) *Recombinant DNA,* Vol. 217, Academic Press, San Diego, CA). Standard methods also appear in Ausbel, *et al.* (2001) *Current Protocols in Molecular Biology, Vols.1-4,* John Wiley and Sons, Inc. New York, NY, which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

[00411] Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugatioii, and crystallization are described (Coligan, *et al.* (2000) *Current Protocols in Protein Science, Vol. 1,* John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (see, *e.g.,* Coligan, *et al.* (2000) *Current Protocols in Protein Science, Vol. 2,* John Wiley and Sons, Inc., New York; Ausubel, *et al.* (2001) *Current Protocols in Molecular Biology, Vol, 3,* John Wiley and Sons, Inc., NY, NY, pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) *Products for Life Science Research,* St. Louis, MO; pp. 45-89; Amersham Pharmacia Biotech (2001) *BioDirectory,* Piscataway, N.J., pp. 384-391).

Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan, *et al,* (2001) *Current Protcols in Immunology, Vol. I*, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) *Using Antibodies,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Harlow and Lane, *supra).* Standard techniques for characterizing ligand/receptor interactions are available (see, *e.g.,* Coligan, *et al.* (2001) *Current Protocols in Immunology, Vol. 4,* John Wiley, Inc., New York).

[00412] Monoclonal, polyclonal, and humanized antibodies can be prepared (see, *e.g.,* Sheperd and Dean (eds.) (2000) *Monoclonal Antibodies,* Oxford Univ. Press, New York, NY; Kontermann and Dubel (eds.) (2001) *Antibody Engineering,* Springer-Verlag, New York; Harlow and Lane (1988) *Antibodies A Laboratory Manual,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 139-243; Carpenter, *et al.* (2000) *J. Immunol.* 165:6205; He, *et al.* (1998) *J. Immunol.* 160:1029; Tang *et al.* (1999) J. Biol. Chem. 274:27371-27378; Baca *et al.* (1997) *J. Biol. Chem.* 272: 10678-10684; Chothia *et al.* (1989) *Nature* 342:877-883; Foote and Winter (1992) *J. Mol. Biol.* 224:487-499; U.S. Pat. No. 6.329,51 1).

[00413] An alternative to humanization is to use human antibody libraries displayed on phage or human antibody libraries in transgenic mice (Vaughan *et al.* (1996) *Nature* Biotechnol. 14:309-314; Barbas (1995) *Nature Medicine* 1:837-839; Mendez *et al.* (1997) *Nature Genetics* 15:146-156; Hoogenboom and Chames (2000) *Immunol, Today* 21:371-377; Barbas *et al,* (2001) *Phage Display: A Laboratory Manual,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; Kay *et al.* (1996) *Phage Display of Peptides and Proteins: A Laboratory-Manual,* Academic Press, San Diego, CA; de Bruin *et al.* (1999) *Nature Biotechnol.* 17:397-399).

[00414] Single chain antibodies and diabodies are described (see, *e.g.,* Malecki *et al,* (2002) *Proc. Natl. Acad. Sci. USA* 99:213-218; Conrath *et al.* (2001) *J. Biol. Chem.* 276:7346-7350; Desmyter *et al.* (2001) *J. Biol. Chem.* 276:26285-26290; Hudson and Kortt (1999) *J. Immunol, Methods* 231:177-189; and U.S. Pat. No. 4,946,778). Bifunctional antibodies are provided (see, *e.g.,* Mack, *et al,* (1995) *Proc. Natl. Acad, Sci. USA* 92:7021-7025; Carter (2001) *J. Immunol, Methods* 248:7-15; Volkel, *et al.* (2001) *Protein Engineering* 14:815-823; Segal, *et al.* (2001) *J. Immunol. Methods* 248:1-6; Brennan, *et al.* (1985) *Science* 229:81-83; Raso, *et al.* (1997) *J. Biol.*

Chem. 272:27623; Morrison (1985) *Science* 229: 1202-1207; Traunecker, *et al,* (1991) *EMBO J.* 10:3655-3659; and U.S. Pat. Nos. 5,932,448, 5,532,210, and 6,129,914).

[00415] Bispecific antibodies are also provided (see, *e.g.,* Azzoni *et al.* (1998) *J. Immunol.* 161:3493; Kita *et al,* (1999) *J. Immunol,* 162:6901; Merchant *et al.* (2000) *J. Biol. Chem,* 74:91 15; Pandey *et al.* (2000) *J. Biol. Chem,* 275:38633; Zheng *et al.* (2001) *J. Biol Chem.* 276:12999; Propst *et al.* (2000) *J. Immunol.* 165:2214; Long (1999) *Ann. Rev. Immunol.* 17:875).

Purification of antigen is not necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can fused with a myeloma cell line to produce a hybridoma (see, *e.g.,* Meyaard *et al.* (1997) *Immunity* 7:283-290; Wright *et al.* (2000) *Immunity* 13:233-242; Preston *et al„ supra:* Kaithamana *et al.* (1999) *J. Immunol.* 163:5157-5164).

[00416] Antibodies can be conjugated, *e.g.,* to small drug molecules, enzymes, liposomes, polyethylene glycol (PEG). Antibodies are useful for therapeutic, diagnostic, kit or other purposes, and include antibodies coupled, *e.g.,* to dyes, radioisotopes, enzymes, or metals, *e.g.,* colloidal gold (see, *e.g.,* Le Doussal *et al.* (1991) *J. Immunol.* 146:169-175; Gibellini *et al.* (1998) *J. Immunol.* 160:3891-3898; Hsing and Bishop (1999) *J. Immunol,* 162:2804-2811; Everts *et al.* (2002) J. *Immunol.* 168:883-889).

[00417] Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, *e.g.,* Owens, *et al.* (1994) *Flow Cytometry Principles for Clinical Laboratory Practice,* John Wiley and Sons, Hoboken, NJ; Givan (2001) *Flow Cytometry, 2nd ed.;* Wiley-Liss, Hoboken, NJ; Shapiro (2003) *Practical Flow Cytometry,* John Wiley and Sons, Hoboken, NJ). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, *e.g.,* as diagnostic reagents, are available (Molecular Probes (2003) *Catalogue,* Molecular Probes, Inc., Eugene, OR; Sigma-Aldrich (2003) *Catalogue,* St. Louis, MO).

[00418] Standard methods of histology of the immune system are described (see, *e.g.,* Muller-Harmelink (ed.) (1986) *Human Thymus: Histopathology and Pathology,* Springer Verlag, New York, NY; Hiatt, *et al.* (2000) *Color Atlas of Histology,* Lippincott, Williams, and Wilkins, Phila, PA; Louis, *et al.* (2002) *Basic Histology: Text and Atlas,* McGraw-Hill, New York, NY).

[00419] Software packages and databases for determining, *e.g.*, antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (see, *e.g.*, GenBank, Vector NTI® Suite (Informax, Inc, Bethesda, MD); GCG Wisconsin Package (Accelrys, Inc., San Diego, CA); DeCypher® (TimeLogic Corp., Crystal Bay, Nevada); Menne, *et al.* (2000) *Bwinfonnatics* 16: 741-742; Menne, *et al.* (2000) *Bioinformatics Applications Note* 16:741-742; Wren, *et al.* (2002) *Comput. Methods Programs Biomed.* 68:177-181; von Heijne (1983) *Eur. J. Biochem.* 133:17-21; von Heijne (1986) *Nucleic Acids Res.* 14:4683-4690).

EXAMPLES

[00420] The following examples serve to illustrate the present invention. These examples are in no way intended to limit the scope of the invention.

[00421] Example 1: Specificity of commercial hSIRPa antibodies

[00422] The specificity of various commercially available monoclonal anti-hSIRPa antibodies (Table 7) for binding to hSIRPa variant 1 (hSIRPaVl; GenBank accession: NM_0() 1040022.1) (SEQ ID NO: 34), hSIRPa variant 2 (hSIRPaV2; GenBank accession: D86043.1) (SEQ ID NO: 36), hSIRPpi (GenBank accession: NM_006065.4) (SEQ ID NO: 38), hSIRPpi transcript variant 3 / hSIRPpL (NCBI accession: NM_()()1 135844.3) (SEQ ID NO: 117), and hSIRPy (NCBI accession: NM_018556.3) (SEQ ID NO: 40) was evaluated by cellular ELISA (CELISA). Reactivity was confirmed using CHO-K1 cells (ATCC CCL-61) that had been transiently transfected, using Lipofectamine 2000, with cDNA encoding the full length open reading frame of hSIRPaVl, hSIRPaV2, hSIRPpi, hSIRPpL, and hSIRPy subcloned into the pCI-neo vector (Promega, Madison, WI). CHO-Kl.hSIRPaVl, CHO-K1 .hSIRPaV2, CHO-Kl.hSIRPpl, CHO-Kl.hSIRPpL, and CHO-K1 .hSIRPy cells were seeded in culture medium (DMEM-F12 (Gibco) supplemented with 5% New Born Calf Serum (BioWest) and Pen/Strep (Gibco)) in 96-well flat-bottom tissue culture plates and incubated at 37°C, 5% $C0_2$ and 95% humidity for 24 hours. Subsequently, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with purified hSIRPa antibodies (used at 10 **μg/mL** and dilutions thereof). Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with goat-anti-mouse IgG-HRP (Southern Biotech). Subsequently, cells were washed three times with PBS-T and immunoreactivity against hSIRPaVl, hSIRPaV2, hSIRPpi,

hSIRPpL, and hSIRPy was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm. EC50 values, the concentration at which 50% of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.).

[00423] Table 7: Commercially available hSIRPa antibodies used for comparison with antibodies generated herein.

Target	Clone	Cat.#	Company	Species	Reactivity	Isotype
hSIRPα	SE5A5	323802	Biolegend	mouse	human	IgG1
hSIRPα	7B3	LS-C340387	LifeSpan Biosciences	mouse	human	IgG1
hSIRPα	1B5	LS-C338479	LifeSpan Biosciences	mouse	human	IgG1
hSIRPα	1C6	LS-C338477	LifeSpan Biosciences	mouse	human	IgG1
hSIRPα	27	sc-136067	Santa Cruz Biotechnology	mouse	human, mouse, rat	IgG1
hSIRPα	SE7C2	sc-23863	Santa Cruz Biotechnology	mouse	human	IgG1
hSIRPα	P3C4	LS-C179629-100	CliniSciences	mouse	human	IgG2a
hSIRPα	2A4A5	W172-3	MBL International	mouse	human	IgG2a
hSIRPα	15-414	LS-C58098	LifeSpan Biosciences	mouse	human	IgG2a
hSIRPα	1H1	LS-C338476	LifeSpan Biosciences	mouse	human	IgG2a
hSIRPα	C-7	sc-376884	Santa Cruz Biotechnology	mouse	human	IgG2a
hSIRPα	03	11612-MM03-100	Sino Biological Inc.	mouse	human	IgG2b
hSIRPα	5E10	LS C83566	LifeSpan Biosciences	mouse	human	IgG2b
hSIRPα	602411	MAB4546	R&D	mouse	human	IgG2b
hSIRPα	EPR16264	ab191419	Abcam	rabbit	human, mouse, rat	IgG
hSIRPα	D6I3M	13379S	Cell Signaling Technology	rabbit	human, mouse, rat, monkey	IgG
hSIRPα	001	50956-R001_100ug	Sino Biological Inc.	rabbit	mouse, human	IgG
hSIRPα	REA144	130-099-768	Miltenyi Biotec	human	human	IgG1
hSIRPα	KWAR23	TAB-453CT	Creative Biolabs	human	human	IgG4

[00424] As depicted in Figure 1 and the following Table 8, commercially available hSIRPa antibodies cross-react with at least hSIRPpi, hSIRPpL, or hSIRPy or demonstrate allele-specific binding to hSIRPaV2. The KWAR23 antibody cross-reacts with all members of the SIRP receptor family tested: it binds to hSIRPaVl, hSIRPaV2, hSIRPpi, hSIRPpL, and hSIRPy.

[00425] Table 8:

Antibody	hSIRPaVl	hSIRPaV2	hSIRPpi	hSIRPy	hSIRPpL

	binding EC50 (nM)	binding EC50 (nM)	binding EC50 (nM)	binding EC50 (nM)	binding EC50 (nM)
hSIRPa.5()A	1.626	1.627	nd	1.475	0.639
anti-hSIRPa (clone SE5A5)	0.372	0.186	0.185	0.200	0.122
anti-hSIRPa (clone 7B3)	0.187	0.300	0.255	nd	0.206
anti-hSIRPa (clone 1B5)	nd	0.122	nd	nd	nd
anti-hSIRPa (clone 1C6)	0.739	0.167	2.965	15.589	2.008
anti-hSIRPa (clone 27)	nd	nd	nd	nd	nd
anti-hSIRPa (clone SE7C2)	1.269*	0.300	nd	1.525	26.818*
anti-hSIRPa (clone P3C4)	0.288	2.154	0.383	0.365	0.136
anti-hSIRPa (clone 2A4A5)	nd	1.005	8.633	nd	12.156*
anti-hSIRPa (clone 15-414)	nd	nd	nd	nd	nd
anti-hSIRPa (clone 1H1)	nd	0.204	nd	nd	nd
anti-hSIRPa (clone C-7)	nd	nd	nd	nd	nd
anti-hSIRPa (clone 03)	96.016*	15.059*	16.043*	17.303*	9.109*
anti-hSIRPa (clone 5E1 0)	nd	nd	nd	nd	nd
anti-hSIRPa (clone 60241 1)	0.068	nd	0.081	3.622	0.060
anti-hSIRPa (clone EPR 16264)	nd	2.450*	nd	nd	nd
anti-hSIRPa (clone D6I3M)	18.690*	8.762*	nd	nd	nd
anti-hSIRPa (clone 001)	18.081*	nd	nd	0.494	6.253*
anti-hSIRPa (clone REA144)	5.243*	3.274*	4.534*	3.212*	2.147*
KWAR23	0.067	0.062	0.140	0.043	0.097

*Values indicated with * were extrapolated; nd, not detected*

[00426] Example 2: Immunization and selection of anti-hSIRPa antibodies

[00427] To generate SIRPa antibodies that bind to all known SIRPa alleles and are not binding SIRPpi mice were immunized with a pCI-neo expression constmct encoding hSIRPaVl and hSIRPaV2. Mice were immunized by gene gun immunization using a Helios Gene gun (BioRad, Hercules, CA) and DNA coated gold bullets (BioRad) following manufacturer's instructions. Briefly, 1 μιη gold particles were coated with pCI-neo-hSIRPaV 1 or pCI-neo-hSIRPaV2 cDNA and commercial expression vectors for mouse Flt3L and mouse GM-CSF in a 2:1:1 ratio (both from Aldevron, Fargo, ND). A total of 1 μg of plasmid DNA was used to coat 500 μg of gold particles. Specifically, 7-8 weeks old female BALB/C mice (Harlan) were immunized in the ears with a gene gun, receiving 3 administration cycles in both ears.

[00428] For positive and negative B-cell selection and CELISA purposes, CHO-Kl .hSIRPaVl, CHO-Kl.hSIRPaV2, CHO-Kl.hSIRPpl, and CHO-Kl .hCD47 stable cell lines

were generated by transfecting CHO-Kl cells with pCI-neo vector encoding the full length open reading frame of hSIRPaVl, hSIRPaV2, hSIRPpi, and hCD47 (NCBI accession: NM_00 1777.3) (SEQ ID NO: 42), respectively. Stable clones were obtained by limiting dilution.

[00429] Antibody titer was assessed by CELISA, using the CHO-Kl .hSIRPaV 1 and CHO-Kl .hSIRPaV2 stable cell lines. These hSIRPa-expressing CHO-Kl cell lines were maintained in DMEM-F12 (Gibco) supplemented with 10% Fetal Bovine Serum (Hyclone) and 80U Pen/Strep (Gibco). Cells were seeded into 96-well flat-bottom tissue culture plates at 8xl0 ^{4} cells/well and cultured at 37°C, 5% C0 $_2$ and 95% humidity until cell layers were confluent. Cells were incubated with each sample of the diluted mouse sera for 1 hour at 37°C, 5% C0 $_2$ and 95% humidity. Next, cells were washed with Phosphate buffered Saline (PBS)/0.05% Tween-20 (PBS-T) and incubated with goat-anti-mouse IgG-HRP conjugate (Southern Biotech) for 1 hour at 37°C, 5% C0 $_2$ and 95% humidity. Subsequently, cells were washed three times with PBS-T and anti-hSIRPa immunoreactivity was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2S0_4 and absorbances were read at 450 and 610 nm. The anti-hSIRPa titer was higher than 1:2,500 in each individual mouse serum sample as detected after two DNA immunizations. All mice that demonstrated reactivity against hSIRPaVl and hSIRPaV2 were immunized for a final, third time and sacrificed 14 days later. Erythroeyte-depleted spleen and lymph-node cell populations were prepared as described previously *(Steenbakkers et a!., 1992, ./. Immunol. Meth. 152: 69-77; Steenbakkers et al, 1994, Mol. Biol. Rep. 19: 125-134)* and frozen at -180°C.

[00430] To select anti-hSIRPa antibody producing B-cells, a selection strategy was designed and developed that preferentially bound B-cells expressing antibodies that bind to hSIRPaVl and hSIRPaV2. Splenocytes and lymph nodes were harvested from the hSIRPaVl/V2 immunized mice and isolated cells were incubated with CHO-Kl. hSIRPpi that were seeded into T25 culture flasks and irradiated at 30 Gray. After 1 hour unbound cells were gently removed by moving the flask back and forth. Medium containing unbound cells was then transferred to a new T25 flask containing irradiated CHO-Kl. hSIRPpi cells. This procedure was followed for in total three times on ice in order to negatively select hSIRPβi -reactive B-cells. Next, medium containing unbound B-cells was incubated with CHO-Kl .hSIRPaVl and CHO-Kl .hSIRPaV2 cells that were irradiated at 3,000 Gray. After 1.5 hours incubation on ice unbound cells were removed with multiple wash steps using culture medium. Subsequently, T25 flasks containing

CHO-Kl.hSIRPaVl and CHO-Kl.hSIRPaV2 cells with bound lymphocytes were harvested with Trypsin-EDTA (Sigma). Bound B-cells were cultured, as described by *Steenbakkers et al, 1994, Mol. Biol. Rep. 19: 125-134.* Briefly, selected B-cells were mixed with 10% (v/v) T-cell supernatant and 50,000 irradiated (25 Gray) EL-4 B5 feeder cells in a final volume of 200 µl medium in 96-well flat-bottom tissue culture plates. On day eight, supernatants were screened for hSIRPaVl and hSIRPaV2 reactivity by CELISA as described below.

[00431] CHO-Kl.hSIRPaVl, CHO-K1 .hSIRPaV2, and CHO-Kl.hSIRPpl were seeded in culture medium (DMEM-F12 (Gibco) supplemented with 10% Fetal Bovine Serum (Hyclone) and 80U Pen/Strep (Gibco)) in 96-well flat-bottom tissue culture plates and cultured at 37°C, 5% $C0_2$ and 95% humidity until they were confluent. Subsequently, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity with supernatants from the B-cell cultures. Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity with goat-anti-mouse IgG-HRP conjugate (Southern Biotech). Subsequently, cells were washed three times with PBS-T and anti-hSIRPaVl, anti-hSIRPaV2, and anti-hSIRPpi immunoreactivity was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm.

[00432] Immunoreactivity to human SIRPγ was assessed by ELISA using recombinant hSIRPγ/Fc-protein (R&D Systems, Cat.# 4486-SB-050; SEQ ID NO: 108) coated 96-well MaxiSorp flat-bottom plates. Protein coated 96-well plates were blocked in PBS/1% bovine serum albumin (BSA) for 1 hour at room temperature (RT). PBS/1% BSA was removed and plates were incubated for 1 hour at RT with supernatants from the B-cell cultures. Next, plates were washed with PBS-T and incubated for 1 hour at RT with goat-anti-mouse IgG-HRP conjugate (Southern Biotech). Subsequently, wells were washed three times with PBS-T and anti-hSIRPγ immunoreactivity was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm.

[00433] B-cell clones from the hSIRPa reactive supernatants, which were not or which were minimally reactive to hSIRPpi were immortalized by mini-electrofusion following published procedures *(Steenbakkers et al., 1992, J. Immunol. Meth. 152: 69-77; Steenbakkers et al, 1994, Mol. Biol. Rep. 19:125-34)* with some minor deviations (e.g. pronase reaction was omitted).

Briefly, B-cells were mixed with 10^{f} Sp2/()-Agl4 murine myeloma cells (ATCC CRL-1581) in Electrofusion Isomolar Buffer (Eppendorf). Electrofusions were performed in a 50 µL fusion chamber by an alternating electric field of 15 s, 1 MHz, 23 Vrms AC followed by a square, high field DC pulse of 10 µ$, 180 Volt DC and again by an alternating electric field of 15 s, 1 MHz, 23 Vrms AC. Content of the chamber was transferred to hybridoma selective medium and plated in a 96-well plate under limiting dilution conditions. On day 10 following the electrofusion, hybridoma supernatants were screened for hSIRPaVl, hSIRPaV2, hSIRPpi, and hSIRPy binding activity by CELISA and ELISA, as described above. Hybridomas that secreted antibodies in the supernatant that specifically bound hSIRPaVl and hSIRPaV2 were both frozen at -180°C (-1 batch) and subcloned by limited dilution to safeguard their integrity and stability. Stable hybridomas were frozen at ~180°C (-LD1 batch) until cell layers were confluent.

[00434] Further selection of the hybridomas was performed by assessing the blocking abilities of the hSIRPaVl/hCD47 interaction in CELISA format. For the assessment of hCD47 blockade CHO-Kl.hCD47 cells were seeded in 384-well flat-bottom tissue culture plates and incubated at 37°C, 5% $C0_2$ and 95% humidity in culture medium. Recombinant hSIRPa/Fc-protein (R&D Systems, Cat.# 4546-SA-050; SEQ ID NO: 107) was pre-incubated with a dilution series of the hybridoma supernatants containing hSIRPa reactive antibodies and control antibodies (at 10 µg/ηιE and dilutions thereof) for 30 minutes at 37°C, 5% $C0_2$ and 95% humidity. Confluent CHO-Kl.hCD47 cells were washed with PBS-T and incubated for 1 hour with the mixtures containing hSIRPa reactive antibodies and recombinant hSIRPa/Fc -protein at 37°C, 5% $C0_2$ and 95% humidity. Next, cells were washed with PBS-T followed by addition of goat-anti-human IgG-HRP conjugate (Jackson Immuno Research) to the cells, which was incubated for 1 hour at 37°C, 5% C02and 95% humidity. Subsequently cells were washed three times with PBS-T and binding of hSIRPa/Fc -protein was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm.

[00435] Selected stable hybridomas were cultured in serum-free media for 7 days; supernatants were harvested and antibodies were purified using MabSelect Sure Protein A resin according to the manufacturer's instructions (GE Healthcare). Antibody concentrations were quantified using spectrophotometry. Supernatants of the hybridoma cultures were used to isotype the hybridomas. In short, isotyping was done using a mouse monoclonal antibody isotyping kit (Biorad) based on a dipstick with immobilized goat-anti-mouse antibody bands to each of the

common mouse isotypes and light chains. Recovered antibodies were all identified as mouse IgGl. Antibody sequences were elucidated by sequencing of variable regions of the mouse IgGl hybridoma material performed at LakePharma, using the following method: the total RNA of the hybridoma cells was extracted, which allowed cDNA synthesis. Rapid Amplification of cDNA Ends (RACE) was performed that allowed cloning of positive fragments in a TOPO (Thermo Fisher Scientific) vector. TOPO clones were sequenced and sequences were annotated using VBASE2 (Retter et al., VBASE2, an integrative V gene database. *Nucleic Acids Res.* 2005 Jan 1;33(Database issue):D671-4).

[00436] Example 3: Characterization of hSIRPa antibodies

[00437] The binding specificity of antibody hSIRPa.50A to hSIRPa was compared antibody KWAR23 (Canadian Patent 2939293 Al), in a CELISA format. CHO-K1 cells were transiently transfected with hSIRPaVl, hSIRPaV2, hSIRPpi, and hSIRPy (GenBank accession: NM_01 8556.3) (SEQ ID NO: 39) cDNAs. Subsequently, hSIRPa binding was assessed by CELISA using CHO-Kl.hSIRPaVl, CHO-Kl.hSIRPaV2, CHO-Kl.hSIRPpi, and CHO-Kl .hSIRPy cells. Detection of bound antibody was performed with goat-aiiti-mouse IgG-HRP (Southern Biotech) for mouse antibodies including hSIRPa.50A and control antibodies or, alternatively, with goat-anti-human IgG-HRP conjugate (Jackson Immuno Research) for the KWAR23 antibody. KWAR23 (SEQ ID NO: 130; SEQ ID NO: 131) was expressed as a chimeric human IgG4 kappa antibody in CHO cells. As shown in Figure 2 and the following Table 9, KWAR23 antibody cross-reacts with all members of the SIRP receptor family tested: it binds to hSIRPaVl, hSIRPaV2, hSIRPpi, and hSIRPy. EC50 values represent the concentration at which 50% of the total binding signal is observed (average and SD were calculated from values of two independent experiments).

[00438] Table 9:

Antibody	hSIRPαV1 binding EC50 (nM)		hSIRPαV2 binding EC50 (nM)	
	Average	SD	Average	SD
KWAR23	0,081	0,001	0,051	0,004
hSIRPα.50A	1,365	0,164	1,296	0,186
anti-hSIRPα (clone SE5A5)	0,304		0,200	
anti-hSIRPγ (clone LSB2.20)	nd		nd	
Antibody	hSIRPβ1 binding EC50 (nM)		hSIRPγ binding EC50 (nM)	
	Average	SD	Average	SD
KWAR23	0,161	0,007	0,040	0,002
hSIRPα.50A	nd	nd	1,249	0,179
anti-hSIRPα (clone SE5A5)	0,192		0,168	
anti-hSIRPγ (clone LSB2.20)	nd		0,265	

Empty squares indicate n=1 measurements. nd, not detected

[00439] In addition, the specificity of hSIRPa.50A for all known of hSIRPa alleles (allelic variants as described by Takenaka *et al,* 2007, Nat Immunol. 8:1313-1323) was further investigated by CELISA using the same strategy as above. To this end, hSIRPa.50A binding was assessed using CHO-Kl cells that were transiently transfected with cDNAs encoding full length hSIRPaVl , hSIRPaV2, hSIRPaV3 (NA07056_V3) (SEQ ID NO: 43), hSIRPa V4 (NA11832_V4) (SEQ ID NO: 45), hSIRPa V5 (NA18502JV5) (SEQ ID NO: 47), hSIRPaV6 (NA18507_V6) (SEQ ID NO: 49), hSIRPaV8 (NA18570_V8) (SEQ ID NO: 51). and hSIRPaV9 (NA18943_V9) (SEQ ID NO: 53). Figure 3 and the following Table 10 demonstrate the reactivity of antibody clone hSIRPa.50A for each of these hSIRPa alleles. EC50 values represent the concentration at which 50% of the total binding signal is observed (average and SD were calculated from values of two independent experiments).

[00440] Table 10:

		Antibody	
		hSIRPα.50A	anti-hSIRPα (clone SE5A5)
hSIRPαV1	EC50 (nM)	0,936	0,327
	SD	0,285	0,107
hSIRPαV2	EC50 (nM)	0,665	0,200
	SD	0,106	0,046
hSIRPαV3	EC50 (nM)	0,688	0,226
	SD	0,097	0,052
hSIRPαV4	EC50 (nM)	0,824	0,256
	SD	0,280	0,085
hSIRPαV5	EC50 (nM)	0,765	0,276
	SD	0,210	0,086
hSIRPαV6	EC50 (nM)	0,954	0,098
	SD	0,437	0,050
hSIRPαV8	EC50 (nM)	0,644	0,300
	SD	0,066	0,061
hSIRPαV9	EC50 (nM)	0,733	0,260
	SD	0,205	0,079

[00441] Example 4: hCD47 blocking ability of hSIRPa.50A

[00442] The hSIRPa.5()A antibody was analyzed by flow cytometry for its ability to block recombinant hCD47/Fc-protein (R&D Systems, Cat# 4670-CD-050; SEQ ID NO: 109) binding to cell surface expressed hSIRPa. For this purpose, THP-1 (ATCC TIB-202) and U-937 (ATCC CRL-1593.2) monocyte cell lines were used as the source of hSIRPa in the assay. THP-1 and U-937 cells were seeded in 96-well round bottomed tissue culture plates and incubated for 45 minutes with FcR Blocking Reagent (Miltenyi Biotec) and hSIRPa.50A antibody (200 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next cells were washed three tùnes with PBS/1% BSA and incubated with DyLight 488-labeled recombinant hCD47/Fc-protein for 30 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 μg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC).

[00443] As depicted in Figure 4 and the following Table 11, binding of recombinant hCD47 fused to an Fc domain of human IgGl was monitored in the presence of increasing amounts of

the hSIRPa.50A antibody. Antibody hSIRPa.50A blocked the hSIRPa/hCD47 interaction, using the flow cytometry-based method described above. IC50 values for the blockade of hCD47 were calculated from this data. IC50 values represent the concentration at which half of the inhibition is observed.

[00444] Table 11:

	THP-1	U-937
Antibody	IC50 (nM)	IC50 (nM)
hSIRPα.50A	4,605	7,164

[00445] Next, the binding of hSIRPa.50A to hSIRPa expressed on primary human $CD14^+$ monocytes was investigated. In addition, the ability of hSIRPa.50A to block the interaction between hSIRPa and recombinant hCD47/Fc-protein was assessed. For this purpose, CD14+ monocytes were isolated from Ficoll-purified human peripheral blood mononuclear cells (PBMCs) using RosetteSep human monocyte enrichment cocktail (Stemcell). The percentage of monocytes present after the enrichment was determined by flow cytometry on the FACSVerse (BD Biosciences) based on CD14 staining using an APC-Cy7-conjugated mouse-anti-human CD14 detection antibody (BD Biosciences). Subsequently, CD14+ enriched PBMCs were seeded in 96-well round bottomed tissue culture plates and incubated for 40 minutes with FcR Blocking Reagent (Miltenyi Biotec) containing hSIRPa.50A antibody (25 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1% BSA and incubated with a FITC-labeled goat-anti-mouse Ig (BD Biosciences) detection antibody in PBS/1% BSA for 40 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 μg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC).

[00446] Figure 5A and B and the following Table 12 indicates that hSIRPa.50A binds to primary human CD14+ enriched monocytes. EC50 values represent the concentration at which 50% of the total binding signal is observed. To assess the blocking ability of hSIRPa.50A, CD14+ enriched monocytes cells were seeded in 96-well round bottomed tissue culture plates and incubated for 45 minutes with FcR Blocking Reagent (Miltenyi Biotec) and hSIRPa.5()A antibody (200 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Thereafter, cells were

washed three times with PBS/1 % BSA and incubated with 10 μg/mL DyLight 488-labeled recombinant hCD47/Fc -protein for 45 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 μg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC). Figure 5 C and D and the following Table 12 demonstrates the ability of antibody hSIRPa.50A to block the hSIRPa/hCD47 interaction. IC50 values for the blockade of hCD47 were calculated from this data. IC50 values represent the concentration at which half of the inhibition is observed.

[00447] Table 12:

	Donor 1		Donor 2	
Antibody	EC50 (nM)	IC50 (nM)	EC50 (nM)	IC50 (nM)
hSIRPα.50A	7,381	4,618	3,081	1,035

[00448] Example 5: Functionality of hSIRPa.50A mAb in the human granulocyte phagocytosis assay

[00449] To confirm the functionality of hSIRPa.50A in primary immune cells, granulocytes (e.g. effector cells) were isolated from healthy human donor EDTA blood. First, the EDTA blood of each donor was pooled and centrifuged at 300 g for 6 minutes at 20°C. Next, plasma was removed by aspiration, and the remaining blood cells were gently resuspended. Cells were recovered in red blood cell (RBC) lysis buffer (155mM NH4C1; lOmM KHC03) and incubated for 10 minutes on ice. Next, cells were centrifuged at 300 g for 7 minutes. Supernatants containing lysed RBCs were removed by aspiration, and the remaining blood cells were gently resuspended in RBC lysis buffer and kept on ice for 1 minute. RBC lysis was neutralized by adding assay medium (IMDM (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco) and Pen/Strep (Gibco)). Blood cells were centrifuged at 300 g for 6 minutes and supernatants were removed by aspiration to remove remaining RBCs as much as possible. Subsequently, erythrocyte-lysed blood cells were resuspended in assay medium containing 10 ng/mL IFNγ and cells were incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity. Non-adherent blood cells containing human granulocytes were collected by mild washing of the tissue culture plate with assay medium (monocytes are depleted due to adherence to the plastic surface). The percentage of granulocytes present in the cell suspension was determined by flow cytometry on the

FACSCanto II (BD Biosciences) based on high forward scatter (FSC) and side scatter (SSC). Binding of hSIRPa.50A to human granulocytes was assessed by incubating the cells for 30 minutes at 4°C with hSIRPa.50A antibody (25 ng/niL and dilutions thereof) in PBS/1% BSA containing 10% autologous serum (PBS/1% BSA/10%. serum). Next, cells were washed three times with PBS/1% BSA/10%. serum and incubated for 30 minutes at 4°C with a FITC-labeled goat-anti-mouse Ig (BD Biosciences) detection antibody. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA/10% serum and analysed by flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC). Figure 6A shows that hSIRPa.50A binds to primary human granulocytes. EC50 values represent the concentration at which 50% of the total binding signal is observed.

[00450] Next, target cells were fluorescently labeled with either cell proliferation dye eFluoi-450 (eBioscience) in the case of Raji (ECACC 8501 1429), Daudi (ECACC 8501 1437), Ramos (ECACC 85030802), and BJAB (DSMZ ACC-757) lymphoma cells or, alternatively, with Vybrant DiD cell-labeling solution (Thermo Fisher Scientific) for FaDu cells. Labeling was performed according to manufacturer's instructions. Labeled target cells were co-cultured for 2-3 hours at 37°C, 5% CO: and 95% humidity with isolated primary human granulocytes in a 1:1 ratio ($7.5 * 10^4$ cells of each target and effector per well of a 96-well round bottomed tissue culture plate) in the presence of 0.1 μg/mL rituximab (anti-hCD20). In addition, cells were co-cultured with 0.1 μg/mL rituximab in presence of 10 μg/mL hSIRPa.SOA. Phagocytosis was assayed by determining the percentage of granulocytes positive for eFluor450 (or DID) using flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC).

[00451] Compared to the mouse IgG1 isotype control, hSIRPa.50A potently enhances tumor cell phagocytosis induced by rituximab (Figure 6B). The same procedure was followed with other existing therapeutic antibodies such as 0.05 μg/mL daratumumab (anti-hCD38), 0.1 μg/mL alemtuzumab (anti-hCD52), and 0.1 μg/mL cetuximab (anti-hEGFR) (Figure 6C-E). These data demonstrate that hSIRPa.50A enhances antibody-mediated tumor cell phagocytosis by human granulocytes.

[00452] Example 6: Functionality of hSIRPa.50A mAb in the human macrophage phagocytosis assay

[00453] Blockade of CD47 by hSIRPa.50A enhances the phagocytosis of human lymphoma cells tumor cells by human macrophages. Human macrophages were generated by first enriching CD14+ monocytes from Ficoll-purified human peripheral blood mononuclear cells (PBMCs) using RosetteSep human monocyte enrichment cocktail (Stemcell). Monocytes were seeded into CellCarrier 96-well flat-bottom microplates (Perkin Elmer) and cultured in macrophage medium (IMDM (Gibco) supplemented with 8.5% Fetal Bovine Serum (Gibco) and Pen/Strep (Gibco)) containing 50 ng/mL human monocyte colony stimulating factor (M-CSF) for 7 days at 37°C, 5% CO: and 95% humidity to promote differentiation into macrophages. These monocyte-derived macrophages (MDMs) become adherent allowing other cells to be washed away. Human Raji, Daudi, Ramos, and BJAB lymphoma cells were counted and labeled with cell proliferation dye eFluor450 (eBioscience) following manufacturer's instructions. After labeling, the lymphoma cells were mixed with assay medium (RPMI (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco) and Pen/Strep (Gibco)) containing 10 µg/mL anti-hSIRPa antibodies, respective isotype controls and either 0.1 µg/mL rituximab (anti-hCD20) or 0.05 µg/mL daratumumab (anti-hCD38). The lymphoma cells were then added to the individual wells containing MDMs at a ratio of 2.5: 1 tumor cells per phagocyte, mixed and incubated at 37°C, 5% $C0_2$ and 95% humidity for 2 hours. After the incubation, the wells were washed with PBS to remove most of the non-phagocytosed tumor cells, and cells were fixed with 2% formaldehyde for 10 min at RT. The wells were then washed and maintained in PBS/3% BSA in dark at 4°C overnight. Lymphoma cells present in the wells were stained with biotin-conjugated anti-human CD19 clone HIB19 (eBioscience) for 1 hour at RT, and subsequently were counterstained with Alexa Fluor 488-conjugated streptavidin (Thermo Fisher Scientific) for 1 hour at RT. Next, nuclei were stained with DRAQ5 (Thermo Fisher Scientific) for 10 minutes at RT, mixture was removed, and PBS was added to each well. Cells were analysed with the Operetta automated fluorescence microscope (Perkin Elmer). Data were processed and analysed with Columbus V2.6 software.

[00454] As shown in Figure 7, hSIRPa.50A enhances rituximab and daratumumab-mediated phagocytosis activity. The phagocytosis of human lymphoma cells was quantified using a

phagocytosis index, as follows: (number of tumor cells inside macrophages/number of macrophages) * 100; counting at least 200 macrophages per sample.

[00455] Example 7: Humanized antibody design and CDR grafting

[00456] The mouse hSIRPa.50A antibody was humanized using CDR-grafting technology *{see e.g. U.S. Patent No. 5,225,539 and Williams, D.G. el al, 2010, Antibody Engineering, volume 1, Chapter 21).*

[00457] First, human germline sequences were identified using IgBLAST (Ye J. *el al,* 2013, Nucleic Acids Res. 41:W34-40). For the hSIRPa.50A VH human germline sequence, V-gene IGHV1/OR15-2*02 was identified (75.2% identity) and for the VL human germline sequence IGKV 1-27*01 was identified (74.0% identity). These two germline sequences were used to directly graft the mouse CDRs, resulting in the following two cDNA constructs: SEQ ID NO: 17 (VH) and SEQ ID NO: 25 (VL).

[00458] Next, a database was constructed containing all human sequences available in the IMGT database (Lefranc, M.-P. *et al,* 1999, *Nucleic Acid Res.* 27:209-212) identifying 85,848 individual sequences. These sequences were queried using TBLASTN (2.2.31+) to identify template sequences that demonstrated the highest identify to the framework of hSIRPa.50A VH and VL sequences. Three VH and three VL sequences were identified that demonstrated a similarity score of 75% or higher and that displayed similar CDR lengths, preferably identical to those in hSIRPa.50A VH CDR1, CDR2, CDR3 and VL CDR1, CDR2 and CDR3, respectively.

[00459] For the heavy chain, the frameworks encoded by GenBank (Benson, D.A. *et al.,* 2013, Nucleic Acids Res. 41(D1): D36-42) accession # AB066948, AB067235, and U84168 were selected as templates for straight grafting of the hSIRPa.5()A VH CDRs, resulting in the following cDNA constructs: SEQ ID NO: 9, 11 and 13, respectively. For the light chain, the frameworks encoded by GenBank accession # JF894288, AB363321, and L12101 were selected as templates for straight grafting of the hSIRPa.5()A VL CDRs, resulting in the following cDNA constructs: SEQ ID NO: 19, 21 and 23. Framework and CDR definition were those as described by Kabat *et al,* ("Sequences of Proteins of Immunological Interest", Kabat, E., *et al.,* US Department of Health and Human Services, (1983)).

[00460] To understand the effect of humanized framework residues on the structure of the Fv, a homology model of the mouse hSIRPa.50A Fv was made using the 'Antibody Modeling Cascade' (default parameters) within Discovery Studio 4.5. The homology model was built on basis of PDB ID lCIC, for the light chain and Fv, and PDB ID 4Q0X for the heavy chain. The CDRs were grafted in silico to study residues that are close to any of the CDRs and which might affect the loop conformation, referred as Vernier residues. Residues that might affect the loop conformation, and which are within < 5Å to the CDR surface were identified and substituted with the mouse amino acid at this position. The resulting templates were checked for the presence of post translational modification (PTM) motifs using Discovery Studio 4.5 and where possible (i.e. non-CDR, non-Vemier residues) changed to prevent a PTM. For the heavy chain, removal of the predicted sequence PTM motifs and structural considerations (i.e. rigidity of the backbone) in the hSIRPa.50A VH resulted in the design of one additional construct: SEQ ID NO: 15. For the light chain the PTM removal resulted in the following construct: SEQ ID NO: 27.

[00461] CDRs were grafted on each of the identified templates, expressed as a human IgG4 (SEQ ID NO: 65), kappa (SEQ ID NO: 63) antibody cloned in the pcDNA3.1(+) vector (Thermo Fisher Scientific) and for transient transiection in FreeStyle 293-F human embryonic kidney cells (HEK293T/17, ATCC CRL-11268). In each case, an IgG4 version carrying the stabilizing Adair mutation (Angal S. *etal,* 1993, Mol Immunol. 30: 105-108), where Serine 228 is converted to Proline, was used.

[00462] Example 8: Synthesis, expression and purification of humanized constructs

[00463] Plasmids encoding the heavy chain and light chain constructs were mixed in a 1:1 ratio (30 μg in total) and transiently expressed by transiection into FreeStyle 293-F cells using 293fectin transiection reagent (Invilrogen) following the manufacturer's instructions. Supernatants (30 ml) were harvested after 7 days and antibodies were purified using MabSelect Sure Protein A resin according to the manufacturer's instructions (GE Healthcare). Buffer was exchanged for 10 mM Histidine, 100 mM NaCl pH 5.5 buffer using Zeba desalting columns (Thermo Fisher Scientific). The concentration of purified antibodies was determined based on OD280 (Nanodrop ND-1000). Endotoxin level was determined by LAL-test according to the manufacturer's instructions (Lonza).

[00464] Example 9: Binding of humanized SIRPa antibodies

[00465] Binding of the humanized antibodies to hSIRPa was studied in CELISA format. Binding of the hSIRPa antibodies to human SIRPaVl, SIRPaV2, hSIRPpl, and hSIRPy was confirmed using CHO-K1 cells that had been transiently transfected with cDNA encoding the full length open reading frame of each of these respective targets subcloned into the pCI-neo vector. CHO-Kl.hSIRPaVl, CHO-Kl.hSIRPaV2, CHO-Kl.hSIRPpl, and CHO-K1 .hSIRPy cells were seeded in culture medium (DMEM-F12 (Gibco) supplemented with 5% New Born Calf Serum (BioWest) and Pen/Strep (Gibco)) in 96-well flat-bottom tissue culture plates and incubated at 37°C, 5% CO_2 and 95% humidity until cell layers were confluent. Subsequently, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with purified hSIRPa antibodies (10 μg/mL and dilutions thereof). Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity with goat-anti-human IgG-HRP conjugate (Jackson Immuno Research) or goat-anti-mouse IgG-HRP (Southern Biotech). Subsequently, cells were washed three times with PBS-T and anti-hSIRPa immunoreactivity was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm. EC50 values, the concentration at which 50% of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.). In Table 13 the EC50 values of the humanized hSIRPa antibodies are depicted.

[00466] Table 13: Binding of humanized and parental hSIRPa.50A antibodies to CHO-Kl.hSIRPaVl, CHO-Kl.hSIRPaV2, CHO-Kl.hSIRPpi, and CHO-Kl .hSIRPy cells. EC50 values represent the concentration at which 50% of the total binding signal is observed (average and SD were calculated from values of two independent experiments).

[00467] Table 13:

	hSIRPαV1 binding EC50 (nM)		hSIRPαV2 binding EC50 (nM)		hSIRPβ1 binding EC50 (nM)		hSIRPγ binding EC50 (nM)	
Antibody	Average	SD	Average	SD	Average	SD	Average	SD
hSIRPα.50H1L1	0.883	0.212	0.864	0.109	nd	nd	1.485*	0.120
hSIRPα.50H1L2	0.781	0.104	0.816	0.161	nd	nd	1.259*	0.155
hSIRPα.50H1L3	1.094	0.112	1.107	0.238	nd	nd	2.579*	0.672
hSIRPα.50H1L4	1.488	0.259	1.621	0.320	nd	nd	7.435*	0.208
hSIRPα.50H1L5	0.962	0.235	0.848	0.239	nd	nd	1.013*	0.115
hSIRPα.50H3L1	1.097	0.286	1.056	0.303	nd	nd	1.424*	0.080

hSIRPa.50H3L2	1.055	0.347	0.999	0.450	nd	nd	1.S02*	0.305
hSIRPa.S0H3L3	1.159	0.417	1.160	0.429	nd	nd	2.471*	0.530
hSIRPa.50H3L4	1.261	0.317	1.520	0.333	nd	nd	5.175*	0.210
hSIRPa.50H3L5	0.878	0.097	0.868	0.190	nd	nd	1.199*	0.120
hSIRPa.S0H4Ll	0.683	0.027	0.681	0.156	nd	nd	0.950*	0.171
hSIRPa.50H4L2	0.737	0.110	0.651	0.147	nd	nd	0.871*	0.062
hSIRPa.S0H4L3	0.933	0.078	0.898	0.133	nd	nd	1.596*	0.144
hSIRPa.50H4L4	1.197	0.175	1.240	0.238	nd	nd	1.980*	0.681
hSIRPa.50H4L5	0.701	0.136	0.661	0.161	nd	nd	0.808*	0.038
hSIRPa.S0H5Ll	0.731	0.039	0.709	0.063	nd	nd	1.028*	0.087
hSIRPa.50H5L2	0.675	0.086	0.572	0.023	nd	nd	0.822*	0.046
hSIRPa.SOH5L3	1.029	0.084	0.796	0.004	nd	nd	1.612*	0.247
hSIRPa.50H5L4	1.169	0.197	1.115	0.060	nd	nd	4.028*	0.342
hSIRPa.50H5L5	0.681	0.066	0.611	0.030	nd	nd	0.868*	0.028
hSIRPa.50A	1.365	0.164	1.296	0.186	nd	nd	1.249*	0.179

*Note that variants with the H2 heavy chain could not be expressed in FreeStyle 293-F cells; values indicated with * were extrapolated; nd, not detected*

[00468] Binding of the parental and humanized hSIRPa antibodies to hSIRPy was further assessed using NK-92MI cells (ATCC CRL-2408), an interleukin-2 (IL-2) independent natural killer cell line derived from the NK-92 cell line. NK-92MI cells were seeded in 96-well round bottomed tissue culture plates and incubated for 30 minutes with the humanized hSIRPa.50A antibody variants (100 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1 % BSA and incubated for 30 minutes at 4°C with a FITC-labeled mouse-anti-human IgG4 (Abeam) or donkey-anti-mouse IgG (Jackson Immuno Research) detection antibody in PBS/1% BSA. After this labeling procedure, cells were washed two times, resuspended in PBS/1 % BSA and analysed by flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC).

[00469] Example 10: Blockade of hCD47 binding to hSIRPa by humanized hSIRPa.50A antibodies

[00470] hCD47 blockade was assessed by flow cytometry for the full panel of humanized hSIRPa.50A antibodies. To this end, HEK293 cells (ATCC CRL-1573) were transiently transfected using Lipofectamine 2000 (Invitrogen) with the pCI-neo vector encoding the full length open reading frame of human SIRPaV l. The transfected cells were cultured at 37°C, 5% $C0_2$ and 95% humidity in medium (DMEM-F12 (Gibco) with 10% Fetal Bovine Serum (Gibco) and Pen/Strep (Gibco)) until confluent. Subsequently, cells were dissociated and seeded in 96-

well round bottomed tissue culture plates and incubated for 30 minutes with the humanized hSIRPa.50A antibody variants (100 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1% BSA and incubated with recombinant hCD47/Fc-protein (ModiQuest; SEQ ID NO: 42) for 30 minutes at 4°C. Afterwards, cells were washed three times with PBS/1% BSA and incubated for 30 minutes at 4°C with a mouse-anti-human IgGl Hinge-FITC (Southern Biotech) detection antibody. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA and analysed by flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC) and plotted using GraphPad Prism 6 (GraphPad Software, Inc.) (Figure 8).

[00471] As depicted in Figure 8, binding of recombinant hCD47 fused to an Fc domain of human IgGl was monitored in the presence of increasing amounts of the humanized hSIRPa.50A antibody variants. All antibody variants blocked the hSIRPa/hCD47 interaction.

[00472] Example 11: Binding domain of hSIRPa.50A

[00473] To identify the binding region of hSIRPa.50A, several SIRPa exchange-mutants were designed based on the human SIRPaVl and hSIRPβ1 amino acid sequence. Based on the fold of SIRPa, the extracellular region can be subdivided into three separate domains: the Ig-like (immunoglobulin-like) V-type (IgV), Ig-like C1-type (IgCl), and Ig-like C2-type (IgC2) domain. The IgV domain is also known as the ligand-binding N-terminal domain of SIRPa (which binds to CD47). The human SIRPaVl/ β1 mutants were designed on the basis of the full length hSIRPaVl sequence (SEQ ID NO: 33) and each individual Ig-like domain was substituted for the equivalent domain of human SIRPpi (SEQ ID NO: 37). The cDNAs encoding the constructs, hSIRPa-VpClaC2a (SEQ ID NO: 55), hSIRPa-VaClpC2a (SEQ ID NO: 57), and hSIRPa-VaClaC2p (SEQ ID NO: 59) were synthesized (GeneArt) and subcloned into the pCI-neo vector. Binding of hSIRPa.50A to the exchange mutants was tested using CELISA. To this end, CHO-Kl cells were transiently transfected, using Lipofectamine 2000, with the pCI-neo vectors encoding hSIRPaVl, hSIRPaV2, hSIRPpl, hSIRPa-VpClaC2a, hSIRPa-VaCipC2a, and hSIRPa-VaClaC2p, respectively. The transfected cells were cultured at 37°C, 5% $C0_2$ and 95% humidity in medium (DMEM-F12 (Gibco) with 5% New Born Calf serum (Biowest) and Pen/Strep (Gibco)) until confluent. Subsequently, cells were trypsinized and seeded in 96-well flat-bottom tissue culture plates and cultured at 37°C, 5% $C0_2$ and 95% humidity in culture

medium until confluent. Then, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with hSIRPa.50A and anti-hSIRPa clone SE5A5 antibodies. Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with goat-anti-mouse IgG-HRP conjugate (Southern Biotech). After that, cells were washed three times with PBS-T and anti-hSIRPa immunoreactivity was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 11m.

[00474] The antibody of the present invention demonstrated loss of binding to the hSIRPa-vpClaC2a mutant, indicating that hSIRPa.50A binds to the IgV domain of hSIRPa (Figure 9; Table 14). EC50 values represent the concentration at which 50% of the total binding signal is observed (average and SD were calculated from values of two independent experiments).

[00475] Table 14:

		Antibody	
		hSIRPα.50A	anti-hSIRPα (clone SE5A5)
hSIRPαV1	EC50 (nM)	0,321	0,117
	SD	0,018	0,001
hSIRPαV2	EC50 (nM)	0,215	0,084
	SD	0,012	0,012
hSIRPβ1	EC50 (nM)	nd	0,180
	SD	nd	0,025
hSIRPα-VβC1αC2α	EC50 (nM)	nd	0,121
	SD	nd	0,003
hSIRPα-VαC1βC2α	EC50 (nM)	0,345	0,135
	SD	0,008	0,013
hSIRPα-VαC1αC2β	EC50 (nM)	0,408	0,127
	SD	0,039	0,028

[00476] To pinpoint the amino acids for interaction of hSIRPa.5()A with the IgV domain, several point mutants of hSIRPaVl were generated based on single amino acid differences between hSIRPaVl/V2 and hSIRPpi. Figure 10A shows an alignment of the hSIRPa and hSIRPpl IgV domain. Amino acids in the hSIRPa IgV domain that are altered in hSIRPβi were mutated by using the QuikChange II Site-Directed Mutagenesis Kit (Stratagene) and the full length hSIRPaVl sequence (SEQ ID NO: 33) as donor cDNA. Binding of hSIRPa.5()A to

hSIRPaVl point mutants was tested using CELISA. To this end, CHO-Kl cells were transiently transfected, using Lipofectamine 2000, with cDNA encoding the full length open reading frame of hSIRPaVl and mutants thereof, and hSIRPpi subcloned into the pCI-neo vector. Transfected cells were seeded in culture medium (DMEM-F12 (Gibco) supplemented with 5% New Born Calf Serum (BioWest) and Pen/Strep (Gibco)) in 96-well flat-bottom tissue culture plates and incubated at 37°C, 5% $C0_2$ and 95% humidity for 24 hours. Subsequently, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% $C0_2$ and 95%· humidity with purified hSIRPa antibodies (used at 10 µg/mï ~ and dilutions thereof). Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with goat-anti-mouse IgG-HRP (Southern Biotech). Subsequently, cells were washed three times with PBS-T and immunoreactivity against hSIRPaVl, hSIRPaVl mutants, and hSIRPpi was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2S0_4 and absorbances were read at 450 and 610 nm. EC50 values, the concentration at which 50% of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.) (average and SD were calculated from values of two independent experiments). As shown in Figure 10B and the following Table 15, the Proline at position 74 (P74) constitues a crucial amino acid for the specific binding of hSIRPa.50A to hSIRPaVl. Expression of hSIRPaVl(P74A) (SEQ ID NO: 61), where P74 is converted to Alanine, on CHO-Kl cells results in loss of hSIRPa.SOA antibody binding. This proline is absent in the IgV domain sequence of hSIRPp1.

[00477] Table 15:

	hSIRPαV1 binding EC50 (nM)		hSIRPβ1 binding EC50 (nM)		hSIRPαV1(P74A) binding EC50 (nM)	
Antibody	Average	SD	Average	SD	Average	SD
hSIRPα.50A	0,535	0,152	nd	nd	nd	nd
anti-hSIRPα (clone SE5A5)	0,164	0,008	0,156	0,009	0,150	0,013

[00479] Example 12: Characterization of hSIRPa.4()A and hSIRPa.50A antibodies

[00480] The binding specificity of antibodies hSIRPa.40A and hSIRPa.50A to hSIRPa were compared in a CELISA format. In short, CHO-Kl cells were transiently transfected with hSIRPaVl, hSIRPaV2, hSIRPpi, hSIRPpL, and hSIRPy cDNAs. Subsequently, hSIRPa binding was assessed by CELISA using CHO-Kl. hSIRPaVl, CHO-Kl .hSIRPaV2, CHO-Kl. hSIRPpi, CHO-Kl. hSIRPpL, and CHO-Kl .hSIRPy cells. Detection of bound antibody was done with goat-anti-mouse IgG-HRP (Southern Biotech). As shown in Figure 11 and the following Table 16, hSIRPa.40A and hSIRPa.50A antibodies bind to hSIRPaVl, hSIRPaV2, hSIRPpL, and hSIRPy, but do not display detectable hSIRPpi binding. EC50 values represent the concentration at which 50% of the total binding signal is observed (average and SD were calculated from values of two independent experiments).

[00481] Table 16:

	hSIRPαV1 binding EC50 (nM)		hSIRPαV2 binding EC50 (nM)		hSIRPβ1 binding EC50 (nM)		hSIRPγ binding EC50 (nM)		hSIRPβL binding EC50 (nM)	
Antibody	Average	SD	Average	SD	Average	SD	Average	SD	Average	SD
hSIRPα.40A	0.109	0.036	0.088	0.002	nd	nd	0.099	0.055	0.141	0.078
hSIRPα.50A	1.428	0.371	1.156	0.127	nd	nd	1.990	0.827	0.632	0.277

nd, not detected

[00482] In addition, the specificity of hSIRPa.40A for all known of hSIRPa alleles (allelic variants as described by Takenaka *et al.*, Nat Immunol. 8:1313-1323 (2007) was further investigated by CELISA using the same strategy as above. To this end, hSIRPa.40A binding was assessed using CHO-Kl cells that were transiently transfected with cDNAs encoding full length hSIRPaVl, hSIRPaV2, hSIRPaV3 (NA07()56_V3) (SEQ ID NO: 44), hSIRPaV4 (NA1 1832_V4) (SEQ ID NO: 46), hSIRPaV5 (NA1 8502_V5) (SEQ ID NO: 48), hSIRPaV6 (NA18507_V6) (SEQ ID NO: 50), hSIRPaVS (NA1857()_V8) (SEQ ID NO: 52), and hSIRPaV9 (NA18943_V9) (SEQ ID NO: 54). Figure 12 and the following Table 17 demonstrates the reactivity of antibody clone hSIRPa.4()A for each of these hSIRPa alleles. EC50 values represent the concentration at which 50% of the total binding signal is observed (average and SD were calculated from values of two independent experiments).

[00483] Table 17:

		Antibody	
		hSIRPα.40A	hSIRPα.50A
hSIRPαV1	EC50 (nM)	0.134	1.690
hSIRPαV2	EC50 (nM)	0.089	1.066
hSIRPαV3	EC50 (nM)	0.107	1.767
hSIRPαV4	EC50 (nM)	0.100	1.297
hSIRPαV5	EC50 (nM)	0.115	1.260
hSIRPαV6	EC50 (nM)	0.136	2.219
hSIRPαV8	EC50 (nM)	0.089	1.508
hSIRPαV9	EC50 (nM)	0.115	1.367

[00484] Example 13: hCD47 blocking ability of hSIRPa.40A

[00485] The hSIRPa.40A antibody was analyzed by flow cytometry for its ability to block recombinant hCD47/Fc-protein (R&D Systems, Cat.# 4670-CD-050; SEQ ID NO: 109) binding to cell surface expressed hSIRPa. For this purpose, THP-1 (ATCC TIB-202) and U-937 (ATCC CRL-1593.2) monocyte cell lines were used as the source of hSIRPa in the assay. THP-1 and U-937 cells were seeded in 96-well round bottomed tissue culture plates and incubated for 45 minutes with FcR Blocking Reagent (Miltenyi Biotec) and hSIRPa.40A antibody (100 µg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1% BSA and incubated with DyLight 488-labeled recombinant hCD47/Fc-protein for 30 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 µg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC).

[00486] As depicted in Figure 13 and the following Table 18, binding of recombinant hCD47 fused to an Fc domain of human IgG1 was monitored in the presence of increasing amounts of the hSIRPa.40A antibody. Antibody hSIRPa.40A blocked the hSIRPa/hCD47 interaction, using the flow cytometry-based method described above. IC50 values for the blockade of hCD47 were calculated from this data. IC50 values represent the concentration at which half of the inhibition is observed.

[00487] Table 18:

	THP-1	U-937
Antibody	IC50 (nM)	IC50 (nM)
hSIRPα.40A	0.646	1.344
hSIRPα.50A	7.833	19.501

[00488] Next, the binding of hSIRPa.40A to hSIRPα expressed on primary human $CD14^+$ monocytes was investigated. In addition, the ability of hSIRPa.4()A to block the interaction between hSIRPa and recombinant hCD47/Fc-protein was assessed. For this purpose, CD14+ monocytes were isolated from Ficoll-purified human peripheral blood mononuclear cells (PBMCs) using RosetteSep human monocyte enrichment cocktail (Stemcell). The percentage of monocytes present after the enrichment was determined by flow cytometry on the FACSVerse (BD Biosciences) based on CD14 staining using an APC-Cy7-conjugated mouse-anti-human CD14 detection antibody (BD Biosciences). Subsequently, CD14+ enriched PBMCs were seeded in 96-well round bottomed tissue culture plates and incubated for 40 minutes with FcR Blocking Reagent (Miltenyi Biotec) containing hSIRPa.40A antibody (20 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1% BSA and incubated with an Alexa Fluor 647-labeled goat-anti-mouse IgG (Invitrogen) detection antibody in PBS/1% BSA for 40 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 μg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC).

[00489] Figure 14A and B shows that hSIRPa.40A binds to primary human CD14+ enriched monocytes. EC50 values represent the concentration at which 50% of the total binding signal is observed. To assess the blocking ability of hSIRPa.4()A, CD14+ enriched monocytes cells were seeded in 96-well round bottomed tissue culture plates and incubated for 45 minutes with FcR Blocking Reagent (Miltenyi Biotec) and hSIRPa.40A antibody (20 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Thereafter, cells were washed three times with PBS/1% BSA and incubated with 10 μg/mL DyLight 488-labeled recombinant hCD47/Fc-protein for 45 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 μg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse

(BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC). Figure 14 C and D demonstrates the ability of antibody hSIRPa.40A to block the hSIRPa/hCD47 interaction. IC50 values for the blockade of hCD47 were calculated from this data. IC50 values represent the concentration at which half of the inhibition is observed.

[00490] Example 14: Functionality of hSIRPa.40A mAb in the human granulocyte phagocytosis assay

[00491] To confirm the functionality of hSIRPa.40A in primary immune cells, granulocytes (e.g. effector cells) were isolated from healthy human donor EDTA blood. First, the EDTA blood of each donor was pooled and centrifuged at 300 g for 6 minutes at 20°C. Next, plasma was removed by aspiration, and the remaining blood cells were gently resuspended. Cells were recovered in red blood cell (RBC) lysis buffer (155mM NH4C1; lOmM KHC03) and incubated for 10 minutes on ice. Next, cells were centrifuged at 300 g for 7 minutes. Supernatants containing lysed RBCs were removed by aspiration, and the remaining blood cells were gently resuspended in RBC lysis buffer and kept on ice for 1 minute. RBC lysis was neutralized by adding assay medium (IMDM (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco) and Pen/Strep (Gibco)). Blood cells were centrifuged at 300 g for 6 minutes and supernatants were removed by aspiration to remove remaining RBCs as much as possible. Subsequently, erythrocyte-lysed blood cells were resuspended in assay medium containing 10 ng/mL IFNγ and cells were incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity. Non-adherent blood cells containing human granulocytes were collected by mild washing of the tissue culture plate with assay medium (monocytes are depleted due to adherence to the plastic surface). The percentage of granulocytes present in the cell suspension was determined by flow cytometry on the FACSCanto II (BD Biosciences) based on high forward scatter (FSC) and side scatter (SSC). Binding of hSIRPa.40A to human granulocytes was assessed by incubating the cells for 30 minutes at 4°C with hSIRPa.4()A antibody (25 ng/mL and dilutions thereof) in PBS/1 % BSA containing 10% autologous serum (PBS/1% BSA/10% serum). Next, cells were washed three times with PBS/1% BSA/10% serum and incubated for 30 minutes at 4°C with a FITC-labeled goat-anti-mouse Ig (BD Biosciences) detection antibody. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA/10% serum and analysed by flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC). Figure 15A and the following Table 19 shows that

hSIRPa.4()A binds to primary human granulocytes. EC50 values represent the concentration at which 50% of the total binding signal is observed.

[00492] Table 19:

	Donor 1
Antibody	EC50 (nM)
hSIRPα.40A	1.227
hSIRPα.50A	4.298

[00493] Next, Ramos (ECACC 85030802) target cells were fluorescently labeled with cell proliferation dye eFluor450 (eBioscience). Labeling was performed according to manufacturer's instructions. Labeled target cells were co-cultured for 2-3 hours at 37°C, 5% $C0_2$ and 95% humidity with isolated primary human granulocytes in a 1:1 ratio ($7.5* 10^4$ cells of each target and effector per well of a 96-well round bottomed tissue culture plate) in the presence of 0.1 µg/mL rituximab (anti-hCD20). In addition, cells were co-cultured with 0.1 µg/mL rituximab in presence of 10 µg/mL hSIRPa.4()A. Phagocytosis was assayed by determining the percentage of granulocytes positive for eFluor450 using flow cytometry on the FACSCanto II (BD Biosciences). Data were processed and analysed with FlowJo V I0 software (FlowJo, LLC).

[00494] Compared to the mouse IgGl isotype control, hSIRPa.40A potently enhances tumor cell phagocytosis induced by rituximab (Figure 15B).

[00495] Example 15: Functionality of hSIRPa.4()A mAb in the human macrophage phagocytosis assay

[00496] Blockade of CD47 by hSIRPa.40A enhances the phagocytosis of human lymphoma cells tumor cells by human macrophages. Human macrophages were generated by first enriching CD14+ monocytes from Ficoll-purified human peripheral blood mononuclear cells (PBMCs) using RosetteSep human monocyte enrichment cocktail (Stemcell). Monocytes were seeded into CellCanier 96-well flat-bottom microplates (Perkin Elmer) and cultured in macrophage medium (IMDM (Gibco) supplemented with 8.5% Fetal Bovine Serum (Gibco) and Pen/Strep (Gibco)) containing 50 ng/mL human monocyte colony stimulating factor (M-CSF) for 7 days at 37°C, 5% $C0_2$ and 95% humidity to promote differentiation into macrophages. These monocyte-derived macrophages (MDMs) become adherent allowing other cells to be washed away. Human

Raji lymphoma cells were counted and labeled with cell proliferation dye eFluor450 (eBioscience) following manufacturer's instructions. After labeling, the lymphoma cells were mixed with assay medium (RPMI (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco) and Pen/Strep (Gibco)) containing 100 µg/mL anti-hSIRPa antibodies and dilutions thereof, the respective isotype control antibody, and 1 µg/mL rituximab (anti-hCD20). The lymphoma cells were then added to the individual wells containing MDMs at a ratio of 2.5:1 tumor cells per phagocyte, mixed and incubated at 37°C, 5%· CO_2 and 95%· humidity for 2 hours. After the incubation, the wells were washed with PBS to remove most of the non-phagocytosed tumor cells, and cells were fixed with 2% formaldehyde for 10 min at RT. The wells were then washed and maintained in PBS/3% BSA in dark at 4°C overnight. Lymphoma cells present in the wells were stained with biotin-conju gated anti-human CD19 clone HIB19 (eBioscience) for 1 hour at RT, and subsequently were counterstained with Alexa Fluor 488-conjugated streptavidin (Thermo Fisher Scientific) for 1 hour at RT. Next, nuclei were stained with DRAQ5 (Thermo Fisher Scientific) for 10 minutes at RT, mixture was removed, and PBS was added to each well. Cells were analysed with the Operetta automated fluorescence microscope (Perkin Elmer). Data were processed and analysed with Columbus V2.6 software.

[00497] As shown in Figure 16, hSIRPa.40A enhances rituximab-mediated phagocytosis activity. The phagocytosis of human lymphoma cells was quantified using a phagocytosis index, as follows: (number of tumor cells inside macrophages/number of macrophages) * 100; counting at least 200 macrophages per sample.

[00498] Example 16: Humanized antibody design and CDR grafting

[00499] The mouse hSIRPa.40A antibody was humanized using CDR-grafting technology (see e.g. U.S. Patent No. 5,225,539 and Williams, D.G. et al., 2010, Antibody Engineering, volume 1, Chapter 21). First, human germline sequences were identified using IgBLAST (Ye J. *et al*, Nucleic Acids Res. 41:W34-40 (2013). For the hSIRPa.40A VH human germline sequence, V-gene IGHV 1-46*01 was identified (62.2%· identity) and for the VL human germline sequence IGKV1 -39*01 was identified (68.4% identity). These two germline sequences were used as template to graft the mouse CDRs, resulting in the following two cDNA constructs: SEQ ID NO: 87 (VH) and SEQ ID NO: 99 (VL).

[00500] Next, a database was constructed containing all human sequences available in the IMGT database (Lefranc, M.-P. *et al,* Nucleic Acid Res. 27:209-212 (1999)) identifying 85,848 individual sequences. These sequences were queried using TBLASTN (2.2.31+) to identify template sequences that demonstrated the highest identify to the framework of hSIRPa.40A VH and VL sequences. Four VH and four VL sequences were identified that demonstrated a similarity score of 80% or higher and that displayed similar CDR lengths, preferably identical to those in hSIRPa.40A VH CDR1, CDR2, CDR3 and VL CDR1, CDR2 and CDR3, respectively.

[00501] For the heavy chain, the frameworks encoded by GenBank (Benson, D.A. *et al.* Nucleic Acids Res. 41(Dl):D36-42 (2013)) accession # L39130, DJ031925, DJ326840, and EF177968 were selected as templates for grafting of the hSIRPa.40A VH CDRs, resulting in the following cDNA constructs: SEQ ID NO: 77, 79, 81 and 83, respectively. For the light chain, the frameworks encoded by GenBank accession # AY731031, DQ840993, AY942002 and DQ535171 were selected as templates for straight grafting of the hSIRPa.40A VL CDRs, resulting in the following cDNA constructs: SEQ ID NO: 89, 91, 93 and 95 . Additionally, a database was constructed containing all humanized antibody sequences available in the public domain, identifying 300 sequences. These sequences were queried using BLASTP (2.2.31+) to identify template sequences that demonstrated the highest identify to the framework of hSIRPa.40A VH and VL sequences. For the heavy chain, the framework of Gemtuzumab was selected as template, for grafting of the hSIRPa.40A VH CDRs, resulting in the following cDNA construct: SEQ ID NO: 85. For the light chain, the framework of Alacizumab was selected as template, for grafting of the hSIRPa.40A VL CDRs, resulting in the following cDNA construct: SEQ ID NO: 97

[00502] Framework and CDR definition were those as described by Kabat *et al.* ("Sequences of Proteins of Immunological Interest", Kabat, E., *et al.*, US Department of Health and Human Services, (1983)).

[00503] To study the effect of humanized framework residues on the structure of the Fv, a homology model of the mouse hSIRPa.40A Fv was made using the Antibody Modeling Cascade' (default parameters) within Discovery Studio 4.5. The homology model was built on basis of PDB ID 3UMT, for the light chain, PDB ID 1EHL for the heavy chain, and PDB ID 3BGF for the Fv. The CDRs were grafted *in silica* to study residues that are close to any of the

CDRs and which might affect the loop conformation, referred to as Vernier residues. Residues that might affect the loop conformation, and which are within < 5Å to the CDR surface were identified and substituted with the mouse amino acid at this position. The resulting templates were checked for the presence of post translational modification (PTM) motifs using Discovery Studio 4.5 and where possible (i.e. non-CDR, non-Vernier residues) changed to prevent a PTM. The VH CDR2 contained a glycosylation site that was removed by an aspargine to serine mutation.

[00504] CDRs were grafted on each of the identified templates, expressed as a human IgG2 (SEQ ID NO: 68), kappa (SEQ ID NO: 64) antibody cloned in the pcDNA3.1(+) vector (Thermo Fisher Scientific) and for transient transfection in FreeStyle 293-F human embryonic kidney cells (HEK293T/17, ATCC CRL-1 1268).

[00505] Example 17: Synthesis, expression and purification of chimeric and humanized constructs

[00506] Plasmids encoding the heavy chain and light chain humanized constructs were mixed in a 1:1 ratio (30 μg in total) and transiently expressed by transfection into FreeStyle 293-F cells using 293fectin transfection reagent (Invitrogen) following the manufacturer's instructions. Supernatants (30 ml) were harvested after 7 days, filtered over a 0.22 μηι filter, and antibodies were purified using MabSelect Sure Protein A resin according to the manufacturer's instructions (GE Healthcare). Buffer was exchanged for 10 mM Histidine, 100 mM NaCl pH 5.5 buffer using Zeba desalting columns (Thermo Fisher Scientific). The concentration of purified antibodies was determined based on OD280 (Nanodrop ND-1000). Endotoxin level was determined by LAL-test according to the manufacturer's instructions (Lonza).

[00507] Example 18: Binding of humanized SIRPa antibodies

[00508] Binding of the parental and humanized antibodies to hSIRPa was assessed by flow cytometry using the CHO-K1 .hSIRPaVl stable cell line. CHO-K1 .hSIRPaVl cells were seeded in 96-well round bottomed tissue culture plates and incubated for 40 minutes with the humanized hSIRPa.4()A antibody variants (20 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1% BSA and incubated for 40 minutes at 4°C with either an Alexa Fluor 647-labeled goat-anti-mouse IgG (Invitrogen), or an Alexa Fluor 647-labeled donkey-anti-human IgG (Jackson Immuno Research) detection antibody in PBS/1%

BSA. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA, containing 0.1 µg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse (BD Biosciences). Data were processed and analysed with FlowJo VIO software (FlowJo, LLC). EC50 values, the concentration at which 50% of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.) (Figure 17 and Table 20).

[00509] Table 20:

	hSIRPαV1
Antibody	EC50 (nM)
hSIRPα.40A	0.022
hSIRPα.40H1L1	nd
hSIRPα.40H1L2	nd
hSIRPα.40H1L3	nd
hSIRPα.40H1L4	nd
hSIRPα.40H1L5	nd
hSIRPα.40H1L6	nd
hSIRPα.40H2L1	0.264
hSIRPα.40H2L2	0.298
hSIRPα.40H2L3	0.300
hSIRPα.40H2L4	0.315
hSIRPα.40H2L5	0.284
hSIRPα.40H2L6	0.251
hSIRPα.40H3L1	1.644
hSIRPα.40H3L2	1.404
hSIRPα.40H3L3	1.501
hSIRPα.40H3L4	0.693
hSIRPα.40H3L5	2.302
hSIRPα.40H3L6	0.833
hSIRPα.40H4L1	3.308
hSIRPα.40H4L2	3.360
hSIRPα.40H4L3	3.072
hSIRPα.40H4L4	3.471
hSIRPα.40H4L5	4.828
hSIRPα.40H4L6	3.028
hSIRPα.40H5L1	2.011
hSIRPα.40H5L2	1.919
hSIRPα.40H5L3	2.268
hSIRPα.40H5L4	0.869
hSIRPα.40H5L5	2.954
hSIRPα.40H5L6	2.197
hSIRPα.40H6L1	2.349

hSIRPa.4()H6L2	3.002
hSIRPa.40H6L3	3.014
hSIRPa.40H6L4	1.279
hSIRPa.4()H6L5	3.785
hSIRPa.40H6L6	2.677

nd, not delected

[005 10] Example 19: Blockade of hCD47 binding to hSIRPa by humanized hSIRPa.40A antibodies

[005 11] hCD47 blockade was assessed by flow cytometry for the full panel of humanized hSIRPa.40A antibodies. To this end, the U-937 (ATCC CRL-1593.2) monocyte cell line was used as the source of hSIRPa in the assay. U-937 cells were seeded in 96-well round bottomed tissue culture plates and incubated for 45 minutes with FcR Blocking Reagent (Miltenyi Biotec) and the parental or humanized hSIRPa.40A antibody variants (20 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1 % BSA and incubated with 10 μg/mL DyLight 488-labeled recombinant hCD47/Fc-protein for 30 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 μg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC) and plotted using GraphPad Prism 6 (GraphPad Software, Inc.).

[005 12] As depicted in Figure 18 and the following Table 21, binding of recombinant hCD47 fused to an Fc domain of human IgG1 was monitored in the presence of increasing amounts of the humanized hSIRPa.40A antibody variants. Humanized hSIRPa.40A blocked the hSIRPa/hCD47 interaction, using the flow cytometry-based method described above. IC50 values for the blockade of hCD47 were calculated from this data. IC50 values represent the concentration at which half of the inhibition is observed.

[00513] Table 21:

	U-937
Antibody	IC50 (nM)
hSIRPa.40A	1.122
hSIRPa.4()HlLl	nd
hSIRPa.40HlL2	nd
hSIRPa.4()HlL3	nd

hSIRPa.4()HlL4	nd
hSIRPa.40HlL5	nd
hSIRPa.40HlL6	nd
hSIRPa.4()H2Ll	0.638
hSIRPa.40H2L2	0.773
hSIRPa.4()H2L3	0.685
hSIRPa.40H2L4	0.718
hSIRPa.4()H2L5	0.745
hSIRPa.40H2L6	0.901
hSIRPa.40H3Ll	0.980*
hSIRPa.40H3L2	nd
hSIRPa.40H3L3	2.625*
hSIRPa.40H3L4	1.784*
hSIRPa.40H3L5	2.435*
hSIRPa.4()H3L6	97.762*
hSIRPa.40H4Ll	10.002*
hSIRPa.4()H4L2	7.579*
hSIRPa.40H4L3	75.422*
hSIRPa.4()H4L4	3.153*
hSIRPa.40H4L5	5.171*
hSIRPa.4()H4L6	3.512*
hSIRPa.40H5Ll	34.977*
hSIRPa.40H5L2	nd
hSIRPa.4()H5L3	nd
hSIRPa.40H5L4	10.772*
hSIRPa.4()H5L5	nd
hSIRPa.40H5L6	0.247*
hSIRPa.40H6Ll	2.391*
hSIRPa.40H6L2	20.427*
hSIRPa.4()H6L3	9.208*
hSIRPa.40H6L4	3.797*
hSIRPa.40H6L5	20.421*
hSIRPa.4()H6L6	9.750*

*Values indicated with * were extrapolated; nd, not detected*

[00514] Example 20: Binding domain of hSIRPa.40A

[00515] To identify the binding region of hSIRPa.40A, several SIRPβ1 exchange-mutants were designed based on the human SIRPpi and SIRPy amino acid sequences. Based on the fold of SIRPa/β1/γ, the extracellular region can be subdivided into three separate domains: the Ig-like (immunoglobulin-like) V-type (IgV), Ig-like C1-type (IgCl), and Ig-like C2-type (IgC2) domain.

The IgV domain is also known as the ligand-binding N-terminal domain of SIRPa and SIRPy (which binds to CD47). The human SIRPpi/γ mutants were designed based on the full length hSIRPpi sequence (SEQ ID NO: 38) and each individual Ig-like domain was substituted for the equivalent domain of human SIRPy (SEQ ID NO: 40). The cDNAs encoding the constructs, hSIRP-VyClpC2p (SEQ ID NO: 110), hSIRP-VpClyC2p (SEQ ID NO: 112), and hSIRP-VpClpC2y (SEQ ID NO: 114) were synthesized (GeneAit) and subcloned into the pCI-neo vector. Binding of hSIRPa.40A to the exchange mutants was tested using CELISA. To this end, CHO-K1 cells were transiently transfected, using Lipofectamine 2000, with the pCI-neo vectors encoding hSIRPaVl, hSIRPaV2, hSIRPpl, hSIRP-VYClpC2p, hSIRP~VpClyC2p, and hSIRP-VPCI pC2y, respectively. The transfected cells were cultured at 37°C, 5% $C0_2$ and 95% humidity in medium (DMEM-F12 (Gibco) with 5% New Born Calf serum (Biowest) and Pen/Strep (Gibco)) until confluent. Subsequently, cells were trypsinized and seeded in 96-well flat-bottom tissue culture plates and cultured at 37°C, 5% $C0_2$ and 95% humidity in culture medium until confluent. Then, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with hSIRPa.40A, hSIRPa.50A, and anti-hSIRPa clone SE5A5 antibodies. Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with goat-anti-mouse IgG-HRP conjugate (Southern Biotech). After that, cells were washed three times with PBS-T and anti-hSIRPa immunoreactivity was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm.

[00516] The antibody of the present invention demonstrated gain of binding to the hSIRP-VγC1pC2p mutant, indicating that hSIRPa.40A binds to the IgV domain of hSIRPa and hSIRPy (Figure 19 and Table 22). EC50 values represent the concentration at which 50% of the total binding signal is observed (average and SD were calculated from values of two independent experiments).

[00517] Table 22:

		Antibody		
		hSIRPα.40A	hSIRPα.50A	anti-hSIRPα (clone SE5A5)
hSIRPαV1	EC50 (nM)	0.133	0.968	0.350
	SD	0.065	0.432	0.136
hSIRPαV2	EC50 (nM)	0.101	0.821	0.224
	SD	0.051	0.183	0.076
hSIRPβ1	EC50 (nM)	nd	nd	0.249
	SD	nd	nd	0.091
hSIRP-VγC1βC2β	EC50 (nM)	0.123	2.524	0.287
	SD	0.040	0.609	0.026
hSIRP-VβC1γC2β	EC50 (nM)	nd	nd	0.309
	SD	nd	nd	0.140
hSIRP-VβC1βC2γ	EC50 (nM)	nd	nd	0.231
	SD	nd	nd	0.079

nd, not detected

[005 18] To pinpoint the amino acids for interaction of hSIRPa.40A with the IgV domain, several point mutants of hSIRPaVl were generated based on single amino acid differences between hSIRPaVl/V2 and hSIRPpi. The following sequence alignment shows an alignment of the hSIRPa and hSIRPpi IgV domain.

Sequence alignment of the IgV domain:

```
                                                                      P74
hSIRPaVl    EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAG    PGRELIYNQKEGHFPRV
hSIRPαV2    EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGP IQWFRGAGP¾RELIYNQKEGHFPRV
hSIRPβI     EHELQVIQPSKSVSVAAGESATLRCS  TSLIPVGPIMWFRGAGAGRELIYNQKEGHFPRV
            *:*******:*** *****:* *:*: ***** * ** ** ** *  ***************

hSIRPaVl    TTVSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSG
hSIRPaV2    TTVSESTKRENMDFSI SISNITPADAGTYYCVKFRKGSPD-TEFKSG
hSIRPβ1     TTVSELTKRNNBDFSISISNITPADAGTYYCVKFRKGSPDDVEFKSG
            ****: ***:*:**** *.********************* .*****
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[005 19] Amino acids in the hSIRPa IgV domain that are altered in hSIRPpi were mutated by using the QuikChange II Site-Directed Mutagenesis Kit (Stratagene) and the full length hSIRPaVl sequence (SEQ ID NO: 33) as donor cDNA. Binding of hSIRPa.40A to hSIRPaVl point mutants was tested using CELISA. To this end, CHO-K1 cells were transiently transfected, using Lipofectamine 2000, with cDNA encoding the full length open reading frame of

hSIRPaV1 and mutants thereof, and hSIRPpi subcloned into the pCI-neo vector. Transfected cells were seeded in culture medium (DMEM-F12 (Gibco) supplemented with 5% New Born Calf Serum (BioWest) and Pen/Strep (Gibco)) in 96-well flat-bottom tissue culture plates and incubated at 37°C, 5% $C0_2$ and 95% humidity for 24 hours. Subsequently, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% $C0_2$ and 95%· humidity with purified hSIRPa antibodies (used at 10 μg/mL and dilutions thereof). Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with goat-anti-mouse IgG-HRP (Southern Biotech). Subsequently, cells were washed three times with PBS-T and immunoreactivity against hSIRPaV1, hSIRPaV1 mutants, and hSIRPpi was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2S0_4 and absorbances were read at 450 and 610 nm. EC50 values, the concentration at which 50%· of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.) (average and SD were calculated from values of two independent experiments).

[00520] As shown in Figure 20 and the following Table 23, the Proline at position 74 (P74) constitues a crucial amino acid for the specific binding of hSIRPa.40A to hSIRPaV1. Expression of hSIRPaV1(P74A) (SEQ ID NO: 61), where P74 is converted to Alanine, on CHO-K1 cells results in loss of hSIRPa.40A antibody binding. This proline is not present in the IgV domain sequence of hSIRPpi, and could play a role in the correct conformation of the IgV domain.

[00521] Table 23:

	hSIRPαV1 binding EC50 (nM)		hSIRPβ1 binding EC50 (nM)		hSIRPαV1(P74A) binding EC50 (nM)	
Antibody	Average	SD	Average	SD	Average	SD
hSIRPα.40A	0.065	0.006	nd	nd	nd	nd
hSIRPα.50A	0.534	0.152	nd	nd	nd	nd
anti-hSIRPα (clone SE5A5)	0.163	0.008	0.156	0.009	0.149	0.013

nd, not detected

[00522] Example 21: Functionality of chimeric hSIRPa.40A mAb variants in the human macrophage phagocytosis assay

[00523] The functionality of hSIRPa.40A variable domains, grafted on different Fc constant domains, was assessed by an *in vitro* phagocytosis assay using human macrophages. Experimental conditions for the human macrophage phagocytosis assay were similar as

explained in Example 15 above. Labelled Raji lymphoma cells were mixed with assay medium containing either 10 μg/mL or 1 μg/mL chimeric hSIRPa.4()A antibody variants and 1 μg/mL rituximab and then added to MDMs at a ratio of 2.5:1 tumor cells per phagocyte. Cells were incubated at 37°C, 5% $C0_2$ and 95% humidity for 2 hours.

[00524] Analysis was performed with the Operetta automated fluorescence microscope (Perkin Elmer) and data were processed and analysed with Columbus V2.6 software. The phagocytosis of human lymphoma cells was quantified using a phagocytosis index, as follows: (number of tumor cells inside macrophages/number of macrophages) * 100; counting at least 200 macrophages per sample.

[00525] As shown in Figure 21, the wild-type (WT) chimeric liSIRPa.40A.hIgG4 antibody does not enhance rituximab-mediated phagocytosis, whereas inert chimeric hSIRPa.40A.hIgGl (SEQ ID NO: 119) antibody variants containing N297Q (SEQ ID NO: 126), L234A.L235A (LALA) (SEQ ID NO: 123), or L234A.L235A.P329G (LALAPG) (SEQ ID NO: 125) mutations enhance rituximab-mediated phagocytosis activity in a concentration-dependent manner. Likewise, hSIRPa.40A.hIgG2 and the inert chimeric hSIRPa.40A.hIgG2 antibody variant containing V234A.G237A.P238S.H268A.V309L.A330S.P331S (Sigma) (SEQ ID NO: 122) mutations enhance rituximab-mediated phagocytosis activity in a concentration-dependent manner.

[00526] Example 22: Functionality of humanized hSIRPa.40A niAb variants in the human macrophage phagocytosis assay

[00527] The functionality of a selected set of the humanized hSIRPa.40A antibody variants was assessed by an in vitro phagocytosis assay using human macrophages. Experimental conditions for the human macrophage phagocytosis assay were similar as explained in Example 6.

[00528] As shown in Figure 22, the humanized hSIRPa.4()A antibody variants enhance rituximab-mediated phagocytosis activity in a concentration-dependent manner similar to antibody KWAR23 grafted on a WgG2 Fc.

[00529] Example 23: Functionality of chimeric hSIRPa.50A niAb valiants in the human macrophage phagocytosis assay

[00530] The functionality of hSIRPa.50A variable domains, grafted on different Fc constant domains, was assessed by *in vitro* phagocytosis assays using human macrophages. As shown in Figure 23A, the chimeric hSIRPa.50A.hIgG4 antibody marginally enhances rituximab-mediated phagocytosis, whereas the chimeric hSIRPa.50A.hIgG2 antibody enhances rituximab-mediated phagocytosis activity similar to the murine hSIRPa.50A.mIgGl (SEQ ID NO: 120) antibody. Figure 23B demonstrates that the chimeric hSIRPa.50A.hIgG2 antibody potently enhances tumor cell phagocytosis induced by rituximab in a concentration-dependent manner as compared to the human IgG2 isotype control. Similarly, hSIRPa.50A.hIgG2 enhanced daratumumab-mediated phagocytosis (anti-hCD38, used at 0.05 ^ig/mL) (Figure 23C).

[00531] In addition, hSIRPa.50A.hIgG2 also enhanced rituximab-mediated phagocytosis in human granulocytes. As shown in Figure 23D, the chimeric hSIRPa.50A.hIgG2 antibody enhances phagocytosis activity induced by rituximab to a similar extend as the murine hSIRPa.50A.mIgGl antibody. Likewise, as shown in Figure 24A, the chimeric hSIRPa.50A.hIgGl.N297Q, hSIRPa.50A.hIgG4.N297Q (SEQ ID NO: 127) or hSIRPa.50A.hIgG2 antibodies enhance rituximab-mediated phagocytosis activity by human MDMs to a similar extent as the murine hSIRPa.SOA.mlgGl antibody (rituximab used at 1 pg/mL). Similar observations were made in Figure 24B when phagocytosis was induced by daratumumab (0.05 μg/mL). As shown in Figure 25, the chimeric hSIRPa.50A.hIgGl.N297Q and hSIRPa.50A hIgGl.L234A.L235A.P329G antibodies also enhance rituximab-mediated phagocytosis activity by human MDMs to a similar extent as the or hSIRPa.50A.hIgG2 antibody (rituximab used at 1 μg/mL). Chimeric variants of hSIRPa.50A mAb containing a wild-type hlgGl or hIgG4 Fc region did not enhance tumor cell phagocytosis.

[00532] Example 24: Comparison of KWAR23, clone 18D5, hSIRPa.50A, and hSIRPa.40A antibodies

[00533] A direct comparison of the specificity of monoclonal anti-hSIRPa antibodies KWAR23, clone 18D5 (SEQ ID NO: 128; SEQ ID NO: 129) from WO2017/178653, hSIRPa.50A, and hSIRPa.40A for binding to hSIRPaVl, hSIRPaVl(P74A), hSIRPaV2, and hSIRPβ1 was evaluated by CELISA. Reactivity was confirmed using CHO-K1 cells (ATCC CCL-61) expressing a cDNA encoding the full length open reading frame of hSIRPaVl, hSIRPaVl(P74A), hSIRPaV2. and hSIRPpl subcloned into the pCI-neo vector (Promega,

Madison, WI). CHO-Kl.hSIRPaVl, CHO-Kl.hSIRPaVl(P74A), CHO-Kl.hSIRPaV2, and CHO-Kl.hSIRPpi cells were seeded in culture medium (DMEM-F12 (Gibco) supplemented with 5% New Born Calf Serum (BioWest) and Pen/Strep (Gibco)) in 96-well flat-bottom tissue culture plates and incubated at 37°C, 5% CO_2 and 95% humidity for 24 hours. Subsequently, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity with purified hSIRPa antibodies (used at 10 μg/mL and dilutions thereof). Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity with goat-anti-mouse IgG-HRP (Southern Biotech). Subsequently, cells were washed three times with PBS-T and immunoreactivity against hSIRPaVl, hSIRPaVl(P74A), hSIRPaV2, and hSIRPpl was visualized with TMB Stabilized Chromogen (Invitrogen). Reactions were stopped with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm. EC50 values, the concentration at which 50% of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.).

[00534] Binding to hSIRPγ was assessed by flow cytometry using the Jurkat E6.1 T cell leukemia cell line (ECACC 88042803). Jurkat cells were seeded in 96-well round bottomed tissue culture plates and incubated for 40 minutes with the anti-hSIRPa antibodies (20 μg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1% BSA and incubated for 40 minutes at 4°C with an Alexa Fluor 647-labeled goat-anti-mouse IgG (Invitrogen) detection antibody in PBS/1% BSA. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA, containing 0.1 μg/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC). EC50 values, the concentration at which 50% of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.).

[00535] As depicted in Table 24, KWAR23 and clone 18D5 antibodies cross-react with at least hSIRPpl and the P74A variant of hSIRPaVl. The hSIRPa.50A, and hSIRPa.40A antibodies of the present invention do not bind to either hSIRPpl or the P74A variant of hSIRPaVl under the tested conditions. In this regard, the hSIRPa.50A, and hSIRPa.40A antibodies of the present invention similarly distinguish from antibody clone SIRP29 from WO2013/056352. Fig. 7A and B of WO2017/178653 compares clone SIRP29 and KWAR23 binding to SIRPpi (referred to as "sirp-b", Product No. ABIN3077231 from antibodies-

online.com), demonstrating that each of clone SIRP29 and KWAR23 has nanomolar affinity for SIRPpl.

[00536] Table 24:

Antibody	hSIRPαV1 binding EC50 (nM)	hSIRPαV1(P74A) binding EC50 (nM)	hSIRPαV2 binding EC50 (nM)	hSIRPβ1 binding EC50 (nM)	hSIRPγ binding EC50 (nM)
hSIRPα.40A	0.114	nd	0.093	nd	0.369
hSIRPα.50A	0.773	nd	0.645	nd	-
KWAR23	0.070	0.049	0.049	0.033	0.003
18D5	0.134	0.055	nd	0.055	nd

nd, not detected; -, not tested

[00537] hCD47 blockade for the KWAR23, clone 18D5, and hSIRPa.40A antibodies was assessed by flow cytometry. For this purpose, THP-1 (ATCC TIB-202) and U-937 (ATCC CRL-1593.2) monocyte cell lines were used as the source of hSIRPa in the assay. THP-1 and U-937 cells were seeded in 96-well round bottomed tissue culture plates and incubated for 45 minutes with FcR Blocking Reagent (Miltenyi Biotec) and indicated anti-hSIRPa antibodies (20 µg/mL and dilutions thereof) in PBS/1% BSA at 4°C. Next, cells were washed three times with PBS/1% BSA and incubated with 10 µg/mL DyLight 488-labeled recombinant hCD47/Fc-protein for 30 minutes at 4°C. After this labeling procedure, cells were washed two times, resuspended in PBS/1% BSA containing 0.1 ng/mL DAPI (BioLegend), and analysed by flow cytometry on the FACSVerse (BD Biosciences). Data were processed and analysed with FlowJo V10 software (FlowJo, LLC) and plotted using GraphPad Prism 6 (GraphPad Software, Inc.). Binding of recombinant hCD47 fused to an Fc domain of human IgGl was monitored in the presence of increasing amounts of the anti-hSIRPa antibodies. IC50 values for the blockade of hCD47 were calculated from this data. IC50 values represent the concentration at which half of the inhibition is observed.

[00538] As depicted in Table 18 and Table 25, hSIRPa.40A, hSIRPa.50A, and KWAR23 antibodies block rhCD47/Fc binding to both the THP-1 and U-937 monocyte cell lines which express the hSIRPaV2 and hSIRPaVl allele, respectively. Antibody clone 18D5 blocks rhCD47/Fc binding to the U-937 monocyte cell line but does not block rhCD47/Fc binding to the

THP-1 monocyte cell line, in line with the observation that 18D5 does not bind to hSIRPaV2 (Table 24). In this regard, the hSIRPa.50A, and hSIRPa.40A antibodies of the present invention similarly distinguish from antibody clone 18D5.

[00539] Table 25

	THP-1	U-937
Antibody	IC50 (nM)	IC50 (nM)
hSIRPα.40A	0.548	1.417
KWAR23	0.132	0.284
18D5	nd	1.522

nd, not detected

[00540] Example 25: Mapping the interaction interface between hSIRPa-hSrRPa.40A and hSIRPa-hSIRPa.50A

[00541] The amino acids on hSIRPα that are bound by hSIRPa.40A or hSIRPa.50A were elucidated by a procedure that involves deuterated chemical cross-linking followed by enzymatic digestion and detection using mass spectrometry. First, antibody hSIRPa.4()A and antigen rhSIRPa-HIS (SinoBiological 11612-H08H-100, SEQ ID NO: 132), or antibody hSIRPa.50A and antigen rhSIRPa-HIS were incubated to promote binding and integrity and aggregation level were verified by Ultraflex III MALDI TOF mass spectrometer (Bruker) equipped with a HM4 interaction module (CovalX). For these control experiments a dilution series of 10 µL samples of antibody or antigen (1- to 128-fold dilution, starting at 1 mg/mL) were prepared. Of each sample 9 µL was submitted to cross-linking using K200 MALDI MS analysis kit, according to the manufacturer's instructions (CovalX) and incubated for 180 minutes, while 1 µL was directly used for mass spectrometry analysis (High-Mass MALDI). The mass spectrometry analysis showed the antibody and antigen had the expected molecular weight: hSIRPa.4()A = 151.68 kDa (152.78 kDa with cross-linker), hSIRPα.5()A = 151.80 kD (153.17 kDa with cross-linker), and rhSIRPa-HIS = 46.05 kDa (48.67 kDa with cross-linker). For characterization of the antigen-antibody complex, a mixture was made with an excess of antigen (antigen:antibody ratio for rhSIRPa-HIS:hSIRPa.40A 10.8 µM:8.5 µM, and antigemantibody ratio for rhSIRPa-HIS:hSIRPa.50A 5.4 µM:2.13 µM). A 9 µL sample of the antigen-antibody mixture was submitted to cross-linking using K200 MALDI MS analysis kit, according to the manufacturer's instructions, while 1 µL was directly used for mass spectrometry analysis. The detected mass of

the antibody and antigen (hSIRPa.40A: 151.18 kDa, rhSIRPa-HIS 45.93 kDa, hSIRPa.5()A: 151.69 kDa, rhSIRPa-HIS 46.18 kDa) corresponds to the molecular weight as detected previously. The antigen-antibody complexes, after cross-linking, were detected as two non-covalent complexes with a 1:1 (195.24 kDa) and 2:1 (240.48 kDa) stoichiometry for rhSIRPa-HIS:hSIRPa.40A, and as one non-covalent complex with a 1:1 (198.24 kDa) stoichiometry for rhSIRPa-HIS:hSIRPa.50A. Antibody and antigen bound non-covalent; non-covalent aggregates or non-specific multimers were not detected.

[00542] Next, peptide mass fingerprinting of rhSIRPa-HIS was performed. Samples were submitted to ASP-N, trypsin, chymotrypsin, elastase and thermolysin (Roche Diagnostic) proteolysis, following manufacturer's instructions followed by analysis by nLC-LTQ Orbitrap MS/MS using an Ultimate 3000 (Dionex) system in line with a LTQ Orbitrap XL mass spectrometer (Thermo Scientific). This proteolysis array resulted in 98% of the sequence being covered by the identified peptides.

[00543] To determine the interacting amino acids of antibody hSIRPa.40A and hSIRPa.50A on rhSIRPa-HIS antigen with high resolution, the antigen-antibody complex (rhSIRPa-HIS:hSIRPa.40A ratio 10.8 μM:8.5 μM, rhSIRPa-HIS:hSIRPa.50A ratio 5.4 μM:2.13 μM) was incubated with deuterated cross-linkers d0/dl2 (K200 MALDI Kit) for 180 minutes and subjected to multi-enzymatic cleavage with the enzymes ASP-N, trypsin, chymotrypsin, elastase and thermolysin. After enrichment of the cross-linked peptides, the samples were analyzed by high-resolution mass spectrometry (nLC-Orbitrap MS) and the data generated were analyzed using XQuest (Jin Lee, Mol. Biosyst. 4:816-823 (2008)) and Stavrox (Gotze et al., J. Am. Soc. Mass Spectrom. 23:76-87 (2012)). The interacting amino acids of hSIRPa.40A and hSIRPa.50A to rhSIRPa-HIS were mapped onto human SIRPaVl (SEQ ID NO: 34). Cross-linked residues of hSIRPa.40A are depicted as bold, boxed, and hSIRPa.50A as bold, underlined:

MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVAAGETATLRCTATSLIPVG
PIQWFRGAGPGRELI YNQKEGHFPRVTTVSDLTKRNNMDF[S]IRIGNITPADAGTYYCVKFRKGS
PDDVEFgSGAGTELSVRAgPSAPWSGPAARATPQHTVSFTCESHGFSPRDITLKWFKNGNELS
DFQTNVDPVGESVSYSIHSTAKVVLTREDVHSQVICEVAHVTLQGDPLRGTANLSETIRVPPTL
EVTQQPVRAENQVNVTCQVRKFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNV
SAHRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSNERNIYIVVGVVCTLLV

ALLMAALYLVRIRQKKAQGSTSSTRLHEPEKNAREITQDTNDITYADLNLPKGKKPAPQAAEPN
NHTEYASIQTSPQPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK

[00544] The C-alpha distance between residue P74 and the identified cross-linked residues was measured in Discovery Studio using the crystal structure of SIRPa (PDB ID 4CMM). The cross-linked residues identified for hSIRPa.50A are within 14.0 to 21.4 angstrom C-alpha atom distance from residue P74; the cross-linked residues identified for hSIRPa.40A are within 16.2 to 33.5 angstrom C-alpha atom distance from residue P74. The C-alpha distances fit within the expected range for an epitope-paratope surface area of 700 A^2 (Rowley et al., Biotech. Ann. Rev. 10:151-188 (2004)). The identified residues and surface area are distinctly different from the binding epitope of anti-hSIRPa antibody KWAR23 (Ring et al., Proc. Natl Acad. Sci. USA 114:E10578-E10585 (2017)).

[00545] Example 26: Comparison of hSIRPa antibodies for binding to hSIRPaVl , hSIRPaVl(P74A), and hSIRPpl

[00546] The specificity of monoclonal anti-hSIRPa antibodies (e.g., including the hSIRPa antibodies known in the art, KWAR23 (U.S. Patent CA2939293 Al), 18D5 (Patent WO2017178653 A2), and various commercially available hSIRPa antibodies) for binding to hSIRPaVl, hSIRPaVl(P74A), and hSIRPpl was evaluated by CELISA. Reactivity was confirmed using CHO-K1 cells (ATCC CCL-61) expressing a cDNA encoding the full length open reading frame of hSIRPaVl , hSIRPaVl(P74A), and hSIRPpl subcloned into the pCI-neo vector (Promega, Madison, WI). CHO-Kl .hSIRPaVl , CHO-K1 .hSIRPaVl (P74A), and CHO-Kl. hSIRPβ1 cells were seeded in culture medium (DMEM-F12 (Gibco) supplemented with 5% New Born Calf Serum (BioWest) and Pen/Strep (Gibco)) in 96-well flat-bottom tissue culture plates and incubated at 37°C, 5% CO_2 and 95% humidity for 24 hours. Subsequently, culture medium was removed and cells were incubated for 1 hour at 37°C, 5% $C0_2$ and 95% humidity with purified hSIRPa antibodies (used at 10 μg/ml and dilutions thereof). Next, cells were washed with PBS-T and incubated for 1 hour at 37°C, 5% CO_2 and 95% humidity with either goat-anti-mouse IgG-HRP (Southern Biotech), goat-anti-human IgG-HRP (Jackson Immuno Research), or goat-anti-rabbit IgG-HRP (Southern Biotech). Subsequently, cells were washed three times with PBS-T and immunoreactivity against hSIRPaVl, hSIRPaVl(P74A), and hSIRPpi was visualized with TMB Stabilized Chromogen (Livitrogen). Reactions were stopped

with 0.5 M H_2SO_4 and absorbances were read at 450 and 610 nm. EC50 values, the concentration at which 50% of the total binding signal is observed, were calculated using GraphPad Prism 6 (GraphPad Software, Inc.)

[00547] As depicted in Table 26, KWAR23, clone 18D5, and all commercially available monoclonal anti-hSIRPa antibodies are able to bind to the P74A variant of hSIRPaVl whereas the hSIRPa.40A and hSIRPa.50A antibodies of the present invention do not bind to the P74A variant of hSIRPaVl under the tested conditions.

[00548] Table 26:

Antibody	hSIRPαV1 binding EC50 (nM)	hSIRPαV1(P74A) binding EC50 (nM)	hSIRPβ1 binding EC50 (nM)
hSIRPα.40A	0.053	nd	nd
hSIRPα.50A	0.307	nd	nd
KWAR23	0.135	0.077	0.065
18D5	0.128	0.073	0.064
anti-hSIRPα (clone SE5A5)	0.156	0.207	0.105
anti-hSIRPα (clone 7B3)	0.122	0.141	0.115
anti-hSIRPα (clone 1C6)	0.329	0.440	> 2.817
anti-hSIRPα (clone 27)	nd	nd	nd
anti-hSIRPα (clone SE7C2)	> 7.010	> 6.139	nd
anti-hSIRPα (clone P3C4)	0.179	0.197	0.160
anti-hSIRPα (clone 2A4A5)	nd	nd	> 6.456
anti-hSIRPα (clone 15-414)	nd	nd	nd
anti-hSIRPα (clone 1H1)	nd	nd	nd
anti-hSIRPα (clone C-7)	nd	nd	nd
anti-hSIRPα (clone 03)	> 8.247	> 8.992	> 6.092
anti-hSIRPα (clone 5E10)	nd	nd	nd
anti-hSIRPα (clone 602411)	0.047	0.076	0.051
anti-hSIRPα (clone EPR16264)	> 1.166	> 1.999	nd
anti-hSIRPα (clone D6I3M)	> 6.413	> 121.509	nd
anti-hSIRPα (clone 001)	> 0.868	> 1.192	nd
anti-hSIRPα (clone REA144)	> 3.661	> 4.793	> 3.075

nd, not detected

[00549] Example 27: Sequences refererred to in the Specification

Description	SEQ ID NO:	SEQUENCE
50A heavy chain CDR1 (amino acid sequence)	1	NYYIH
50A heavy chain CDR2 (amino acid sequence)	2	WIYPGNVNTKYNEKFKA
50A heavy chain CDR3 (amino acid sequence)	3	PTIIATDFDV
50A light chain CDR1 (amino acid sequence)	4	KASQGVGTAVG
50A light chain CDR2 (amino acid sequence)	5	WASTRHT
50A light chain CDR3 (amino acid sequence)	6	QQYSTYPFT
humanized 50 heavy chain variable region (consensus sequence)	7	EVQLX$_1$X$_2$SGX$_3$EX$_4$VKPGASVX$_5$X$_6$SCKASGFTFTNYYIHWVRQX$_7$P X$_8$QGLEWX$_9$GWIYPGNVNTKYNEKFKAX$_{10}$X$_{11}$X$_{12}$X$_{13}$TADKSTSTX$_{14}$ YMX$_{15}$LSSLX$_{16}$SX$_{17}$DX$_{18}$AVYYCARPTIIATDFDVWGQGTX$_{19}$VTVS S wherein: X$_1$ = Q, V X$_2$ = Q, E X$_3$ = A, S X$_4$ = V, L X$_5$ = K, M X$_6$ = V, I X$_7$ = A, R X$_8$ = G, E X$_9$ = I, M X$_{10}$ = R, K X$_{11}$ = V, A X$_{12}$ = T, I X$_{13}$ = I, M X$_{14}$ = A, V X$_{15}$ = D, E, Q X$_{16}$ = R, T X$_{17}$ = E, D X$_{18}$ = T, M X$_{19}$ = T, L
humanized 50 light chain variable region (consensus sequence)	8	X$_1$X$_2$X$_3$X$_4$TQSPSX$_5$LSASVGDRVTITCKASQGVGTAVGWYQX$_6$KPGK X$_7$PKLLIYWASTRHTGVPDRFSGSGSGTX$_8$FTLX$_9$IX$_{10}$X$_{11}$LQPEDX $_{12}$AX$_{13}$YYCQQYSTYPFTFGGGTKX$_{14}$EIK wherein: X$_1$ = D, E X$_2$ = I, L X$_3$ = V, Q X$_4$ = L, M X$_5$ = F, S

		X_6 = Q, K X_7 = A, s, V ¾ = E, D X_9 = T, A X.o = s, N X_{11} = s, N, G X_{12} = F, I, V X_{13} = A, D, T X.4 = L, V
hSIRPa.50AVHl (nucleotide sequence)	9	GAAGTGCAGCTGCAGCAGTCTGGCGCCGAGGTCGTGAAACCTGGCG CCTCTGTGAAGGTGTCCTGCAAGGCCTCCGGCTTCACCTTCACCAA CTACTACATCCACTGGGTGCGACAGGCCCCAGGCCAGGGACTGGAA TGGATCGGCTGGATCTACCCCGGCAACGTGAACACCAAGTACAACG AGAAGTTCAAGGCCCGCGTGACCATCACCGCCGACAAGTCTACCTC CACCGCCTACATGGACCTGTCCTCCCTGAGATCCGAGGACACCGCC GTGTACTACTGCGCCAGACCCACCATCATTGCCACCGACTTCGACG TGTGGGGCCAGGGCACAACCGTGACCGTGTCCTCT
hSlRPa.50AVHI (amino acid sequence)	10	EVQLQQSGAEVVKPGASVKVSCKASGFTFTNYYIHWVRQAPGQGLE WIGWIYPGNVNTKYNEKFKARVTITADKSTSTAYMDLSSLRSEDTA VYYCARP TII ATDFDVWGQGTTVTVS S
hSIRPa.50AVH2 (nucleotide sequence)	11	GAAGTGCAGCTGGTGGAATCCGGCTCCGAGCTCGTGAAGCCTGGCG CCTCCGTGAAGGTGTCCTGCAAGGCCTCTGGCTTCACCTTCACCAA CTAC TACATCCACTGGGTGCGACAGGCCCCAGGCCAGGGACTGGAA TGGATGGGCTGGATCTACCCCGGCAACGTGAACACCAAGTACAACG AGAAGTTCAAGGCCAAGGCCACCATCACCGCCGACAAGTCCACCTC CACCGCCTACATGGAACTGTCCTCCCTGCGGAGCGAGGACACCGCC GTGTACTACTGTGCCCGGCCTACCATCATTGCCACCGACTTCGATG TGTGGGGCCAGGGCACACTCGTGACCGTGTCCTCT
hSIRPa.50AVH2 (amino acid sequence)	12	EVQLVESGSELVKPGASVKVSCKASGFTFTNYYIHWVRQAPGQGLE WMGWIYPGNVNTKYNEKFKAKATITADKSTSTAYMELSSLRSEDTA VYYCARP TIIATDFDVWGQGTLVTVSS
hS!RPa.50AVH3 (nucleotide sequence)	13	GAAGTGCAGCTGGTGCAGTCTGGCGCCGAGGTCGTGAAACCTGGCG CCTCCGTGATGATCTCCTGCAAGGCCTCCGGCTTCACCTTCACCAA CTAC TAGATCCACTGGGTGCGACAGCGGCCAGGCCAGGGACTGGAA TGGATCGGCTGGATCTACCCCGGCAACGTGAACACCAAGTACAACG AGAAGTTCAAGGCCCGCGTGATCATGACCGCCGACAAGTCCACCTC CACCGTGTACATGCAGCTGTCCTCCCTGACCTCCGAGGACACCGCC GTGTACTACTGCGCCAGACCCACCATCATTGCCACCGACTTCGACG TGTGGGGCCAGGGCACACTCGTGACCGTGTCCTCT
hSIRPa.50AVH3 (amino acid sequence)	14	EVQLVQSGAEVVKPGASVMISCKASGFTFTNYYIHWVRQRPGQGLE WIGWIYPGNVNTKYNEKFKARVIMTADKSTSTVYMQLSSLTSEDTA VYYCARP TII ATDFDVWGQGTLVTVS S
hSIRPa.50AVH4 (nucleotide sequence)	15	GAAGTGCAGCTGCAGCAGTCTGGCGCCGAGCTCGTGAAACCTGGCG CCTCTGTGAAGGTGTCCTGCAAGGCCTCCGGCTTCACCTTCACCAA CTACTACATCCACTGGGTGCGACAGCGGCCAGGCCAGGGACTGGAA TGGATGGGCTGGATCTACCCCGGCAACGTGAACACCAAGTACAACG AGAAGTTCAAGGCCAAGGCCACCATCACCGCCGACAAGTCCACCTC CACCGCCTACATGGAACTGTCCTCCCTGACCTCCGAGGACACCGCC GTGTACTACTGCGCCAGACCCACCATCATTGCCACCGACTTCGACG TGTGGGGCCAGGGCACAACCGTGACCGTGTCCTCT
hSlRPa.50AVH4 (amino acid sequence)	16	EVQLQQSGAE LVKPGASVKVSCKASGFTFTNYYIHWVRQRPGQGLE WMGWIYPGNVNTKYNEKFKAKATITADKSTSTAYMELSSLTSEDTA VYYCARP TII ATDFDVWGQGTTVTVS S
hSIRPa.50AVH5 (nucleotide sequence)	17	GAAGTGCAGCTGGTGCAGTCTGGCGCCGAGGTCGTGAAACCTGGCG CCTCTGTGAAGGTGTCCTGCAAGGCCTCCGGCTTCACCTTCACCAA CTACTACATCCACTGGGTGCGACAGGCCCCCGAGCAGGGACTGGAA

		TGGATCGGCTGGATCTACCCCGGCAACGTGAACACCAAGTACAACG AGAAGTTCAAGGCCCGCGTGACCATGACCGCCGACAAGTCTACCTC CACCGCCTACATGGAACTGTCCTCCCTGCGGAGCGACGACATGGCC GTGTACTACTGCGCCAGACCCACCATCATTGCCACCGACTTCGACG TGTGGGGCCAGGGCACAACCGTGACCGTGTCCTCT
hSIRPa.50AVH5 (amino acid sequence)	18	EVQLVQSGAEWKPGASVKVSCKASGFTFTNYYIHWVRQAPEQGLE WIGWIYPGNVNTKYNEKFKARVTMTADKSTSTAYMELSSLRSDDMA VYYCARPTIIATDFDVWGQGTTVTVSS
hSIRPa.50AVLl (nucleotide sequence)	19	GACATCGTGCTGACCCAGTCCCCCAGCTTCCTGTCTGCCTCTGTGG GCGACAGAGTGACCATCACATGCAAGGCCTCTCAGGGCGTGGGCAC CGCTGTGGGATGGTATCAGCAGAAGCCTGGCAAGGCCCCCAAGCTG CTGATCTACTGGGCCTCTACCAGACACACCGGCGTGCCCGACAGAT TCTCCGGCTCTGGCTCTGGCACCGAGTTTACCCTGACCATCTCCAG CCTGCAGCCCGAGGATTTCGCCGCCTACTACTGCCAGCAGTACTCC ACCTACCCCTTCACCTTCGGCGGAGGCACCAAGCTGGAAATCAAG
hSIRPa.50AVLl (amino acid sequence)	20	DIVLTQSPSFLSASVGDRVTITCKASQGVGTAVGWYQQKPGKAPKL LIYWASTRHTGVPDRFSGSGSGTEFTLTISSLQPEDFAAYYCQQYS TYPFTFGGGTKLEIK
hSIRPa.50AVL2 (nucleotide sequence)	21	GACATCGTGATGACCCAGTCCCCCTCCAGCCTGTCTGCCTCTGTGG GCGACAGAGTGACCATCACATGCAAGGCCTCTCAGGGCGTGGGCAC CGCTGTGGGATGGTATCAGCAGAAGCCTGGCAAGGCCCCCAAGCTG CTGATCTACTGGGCCTCTACCAGACACACCGGCGTGCCCGACAGAT TCTCCGGCTCTGGCTCTGGCACCGACTTCACCCTGACCATCTCCAA CCTGCAGCCCGAGGACTTCGCCGACTACTACTGCCAGCAGTACTCC ACCTACCCCTTCACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG
hSIRPa.50AVL2 (amino acid sequence)	22	DIVMTQSPSSLSASVGDRVTITCKASQGVGTAVGWYQQKP GKAPKL LIYWASTRHTGVPDRFSGSGSGTDFTLTISNLQPEDFADYYCQQYS TYPFTFGGGTKVEIK
hSlRPa.50AVL3 (nucleotide sequence)	23	GAGCTCGTGATGACCCAGTCCCCTTCCAGCCTGTCTGCCTCCGTGG GCGACAGAGTGACCATCACATGCAAGGCCTCTCAGGGCGTGGGCAC CGCTGTGGGATGGTATCAGCAGAAGCCTGGCAAGGCCCCCAAGCTG CTGATCTACTGGGCCTCTACCAGACACACCGGCGTGCCCGACAGAT TCTCCGGCTCTGGCTCTGGCACCGACTTTACCCTGGCCATCTCCAG CCTGCAGCCCGAGGATATCGCCGACTAC TACTGCCAGCAGTACTCC ACCTACCCCTTCACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG
hSIRPa.50AVL3 (amino acid sequence)	24	ELVMTQSPSSLSASVGDRVTITCKASQGVGTAVGWYQQKP GKAPKL LIYWASTRHTGVPDRFSGSGSGTDFTLAISSLQPEDIADYYCQQYS TYPFTFGGGTKVEIK
hSlRPa.50AVL4 (nucleotide sequence)	25	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCCTCTGTGG GCGACAGAGTGACCATCACATGCAAGGCCTCTCAGGGCGTGGGCAC CGCTGTGGGCTGGTATCAGAAAAAGCCCGGCAAGGTGCCCAAGCTG CTGATCTACTGGGCCTCCACCAGACACACCGGCGTGCCCGATAGAT TCTCCGGCTCTGGCTCTGGCACCGACTTCACCCTGACCATCAACGG CCTGCAGCCTGAGGACGTGGCCACCTAC TACTGCCAGCAGTACTCC ACCTACCCCTTCACCTTCGGCGGAGGCACCAAGCTGGAAATCAAG
hSIRPa.50AVL4 (amino acid sequence)	26	DIQMTQSPSSLSASVGDRVTITCKASQGVGTAVGWYQKKP GKVPKL LIYWASTRHTGVPDRFSGSGSGTDFTLTTNGLQPEDVATYYCQQYS TYPFTFGGGTKLEIK
hSlRPa.50AVL5 (nucleotide sequence)	27	GACATCGTGCTGACCCAGTCCCCCAGCTTCCTGTCTGCCTCTGTGG GCGACAGAGTGACCATCACATGCAAGGCCTCTCAGGGCGTGGGCAC CGCTGTGGGATGGTATCAGCAGAAGCCCGGCAAGTCCCCCAAGCTG CTGATCTACTGGGCCTCCACCAGACACACCGGCGTGCCCGATAGAT TCTCCGGCTCTGGCTCTGGCACCGAGTTCACCCTGACCATCTCCAA CCTGCAGCCCGAGGACTTCGCCGCCTACTACTGCCAGCAGTACTCC ACCTACCCCTTCACCTTCGGCGGAGGCACCAAGCTGGAAATCAAG

hSlRPoc.50AVL5 (amino acid sequence)	28	DIVLTQSPSFLSASVGDRVTITCKASQGVGTAVGWYQQKPGKSPKL LIYWASTRHTGVPDRFSGSGSGTEFTLTISNLQPEDFAAYYCQQYS TYPFTFGGGTKLEIK
hSIRPa.50A mouse VH (nucleotide sequence)	29	CAGGTCCAGCTGCAGCAGTCTGGACCTGAACTGGTGAAGCCTGGGG CTTCAGTTAGGATATCCTGCAAGGCTTCTGGCTTCACCTTCACAAA CTACTATATACACTGGGTGAAGCAGAGGCCTGGACAGGGACTTGAG TGGATTGGATGGATTTATCCTGGAAATGTTAATACTAAGTACAATG AGAAGTTCAAGGCCAAGGCCACACTGACTGCAGACAAATCCTCCAC CACAGCCTACATGCAGCTCAGCAGCCTGGCCTCTGAGGACTCTGCG GTCTATTTCTGTGCAAGACCTACGATAATAGCTACGGACTTCGATG TCTGGGGCGCAGGGACCACGGTCACCGTCTCCTCA
hSIRPa.50A mouse VH (amino acid sequence)	30	QVQLQQSGPELVKPGASVRISCKASGFTFTNYYIHWVKQRPGQGLE WIGWIYPGNVNTKYNEKFKAKATLTADKSSTTAYMQLS SLASEDSA VYFCARPTIIATDFDVWGAGTTVTVSS
hSIRPa.50A mouse VL (nucleotide sequence)	31	GACATTGTCATGA^rr AGTCTCACAAATTCATGTCCACATCAGTAG GAGACAGGGTCAACATCACCTGCAAGGCCAGTCAGGGTGTGGGTAC TGCTGTAGGCTGGTATCAACAGAAACCAGGGCAATCTCCTAGACTA CTGATTTACTGGGCATCCACCCGGCACACTGGAGTCCCTGATCGCT TCACAGGCAGTGGATCTGGGACAGATTTCAGTCTCGCCATTAGCAA TGTGCAGTCTGAAGACCTGGCAGATTATTTCTGTCAGCAATATAGC ACCTATCCGTTCACGTTCGGAGGGGGGACCAATCTAGAAATAAAA
hSIRPa.50A mouse VL (amino acid sequence)	32	DIVMTQSHKFMSTSVGDRVNITCKASQGVGTAVGWYQQKPGQSPRL LIYWASTRHTGVPDRFTGSGSGTDFSLAISNVQSEDLADYFCQQYS TYPFTFGGGTNLEIK
human SIRPaVl (nucleotide sequence)	33	ATGGAGCCCGCCGGCCCGGCCCCCGGCCGCCTCGGGCCGCTGCTCT GCCTGCTGCTCGCCGCGTCCTGCGCCTGGTCAGGAGTGGCGGGTGA GGAGGAGCTGCAGGTGATTCAGCCTGACAAGTCCGTGTTGGTTGCA GCTGGAGAGACAGCCACTCTGCGCTGCACTGCGACCTCTCTGATCC CTGTGGGGCCCATCCAGTGGTTCAGAGGAGCTGGACCAGGCCGGGA ATTAATCTACAATCAAAAAGAAGGCCACTTCCCCCGGGTAACAACT GTTTCAGACCTCACAAAGAGAAACAACATGGACTTTTCCATCCGCA TCGGTAACATCACCCCAGCAGATGCCGGCACCTACTACTGTGTGAA GTTCCGGAAAGGGAGCCCCGATGACGTGGAGTTTAAGTCTGGAGCA GGCACTGAGCTGTCTGTGCGCGCCAAACCCTCTGCCCCCGTGGTAT CGGGCCCTGCGGCGAGGGCCACACCTCAGCACACAGTGAGCTTCAC CTGCGAGTCCCACGGCTTCTCACCCAGAGACATCACCCTGAAATGG TTCAAAAATGGGAATGAGCTCTCAGACTTCCAGACCAACGTGGACC CCGTAGGAGAGAGCGTGTCCTACAGCATCCACAGCACAGCCAAGGT GGTGCTGACCCGCGAGGACGTTCACTCTCAAGTCATCTGCGAGGTG GCCCACGTCACCTTGCAGGGGGACCCTCTTCGTGGGACTGCCAACT TGTCTGAGACCATCCGAGTTCCACCCACCTTGGAGGTTACTCAACA GCCCGTGAGGGCAGAGAACCAGGTGAATGTCACCTGCCAGGTGAGG AAGTTCTACCCCCAGAGACTACAGCTGACCTGGTTGGAGAATGGAA ACGTGTCCCGGACAGAAACGGCCTCAACCGTTACAGAGAACAAGGA TGGTACCTACAACTGGATGAGCTGGCTCCTGGTGAATGTATCTGCC CACAGGGATGATGTGAAGCTCACCTGCCAGGTGGAGCATGACGGGC AGCCAGCGGTCAGCAAAAGCCATGACCTGAAGGTCTCAGCCCACCC GAAGGAGCAGGGCTCAAATACCGCCGCTGAGAACACTGGATCTAAT GAACGGAACATCTATATTGTGGTGGGTGTGGTGTGCACCTTGCTGG TGGCCCTACTGATGGCGGCCCTCTACCTCGTCCGAATCAGACAGAA GAAAGCCCAGGGCTCCACTTCTTCTACAAGGTTGCATGAGCCCGAG AAGAATGCCAGAGAAATAACACAGGACACAAATGATATCACATATG CAGACCTGAACCTGCCCAAGGGGAAGAAGCCTGCTCCCCAGGCTGC GGAGCCCAACAACCACACGGAGTATGCCAGCATTCAGACCAGCCCG CAGCCCGCGTCGGAGGACACCCTCACCTATGCTGACCTGGACATGG TCCACCTCAACCGGACCCCCAAGCAGCCGGCCCCCAAGCCTGAGCC

		GTCCTTCTCAGAGTACGCCAGCGTCCAGGTCCCGAGGAAG
human SIRPaVl (amino acid sequence)	34	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGETATLRCTATSLIPVGPIQWFRGAGPGRELIYNQKEGHFPRVTT VSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPWSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVSYSIHSTAKVVLTREDVHSQVTCEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNIYIVVGVVCTLLVALLMAALYLVRIRQKRAQGSTSSTRLHEPE KNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRR
human SIRPaV2 (nucleotide sequence)	35	ATGGAACCTGCCGGACCTGCCCCTGGCAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGAGCGTGTCCGTGGCT GCTGGCGAGTCTGCCATCCTGCACTGTACCGTGACCAGCCTGATCC CCGTGGGCCCCATCCAGTGGTTTAGAGGCGCTGGCCCTGCCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGAGAGCACCAAGCGCGAGAACATGGACTTCAGCATCAGCA TCTCCAACATCACCCCTGCCGACGCCGGCACCTACTACTGCGTGAA GTTCAGAAAGGGCAGCCCCGACACCGAGTTCAAGAGCGGCGCTGGA ACCGAGCTGTCTGTGCGGGCTAAGCCTTCTGCCCCTGTGGTGTCTG GACCTGCCGCCAGAGCTACACCTCAGCACACCGTGTCTTTCACATG CGAGAGCCACGGCTTCAGCCCCAGAGACATCACCCTGAAGTGGTTC AAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACCCTG TGGGCGAGTCCGTGTCCTACAGCATCCACAGCACCGCCAAGGTGGT GCTGACCCGCGAGGATGTGCACAGCCAAGTGATCTGCGAGGTGGCC CACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCTAACCTGA GCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCAGCC CGTGCGGGCTGAGAACCAAGTGAACGTGACCTGCCAAGTGCGGAAG TTCTACCCTCAGAGACTGCAGCTGACCTGGCTGGAAAACGGAAACG TGTCCAGAACCGAGACAGCCAGCACCGTGACAGAGAACAAGGACGG CACATACAACTGGATGAGCTGGCTGCTCGTGAACGTGTCCGCCCAC AGAGATGACGTGAAGCTGACATGCCAGGTGGAACACGACGGCCAGC CTGCCGTGTCTAAGAGCCACGACCTGAAGGTGTCCGCTCACCCCAA AGAGCAGGGCAGCAACACCGCCGCTGAGAACACAGGCAGCAACGAG AGAAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGGTGG CTCTGCTGATGGCTGCCCTGTACCTCGTGCGGATCAGACAGAAGAA GGCCCAGGGCTCCACCTCCAGCACCAGACTGCACGAGCCTGAGAAG AACGCCCGCGAGATCACCCAGGACACCAACGACATCACCTACGCCG ACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGCCGA GCCTAACAACCACACAGAGTACGCCAGCATCCAGACCAGCCCTCAG CCTGCCAGCGAGGACACACTGACATACGCCGATCTGGACATGGTGC ACCTGAACAGAACCCCCAAGCAGCCCGCTCCCAAGCCCGAGCCTAG CTTCTCTGAGTACGCCTCCGTGCAGGTGCCCAGAAAA
human SlRPaV2 (amino acid sequence)	36	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVSVA AGESAILHCTVTSLIPVGPIQWFRGAGPARELIYNQKEGHFPRVTT VSESTKRENMDFS ISISNITPADAGTYYCVKFRKGSPDTEFKSGAG TELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDITLRWF KNGNELSDFQTNVDPVGESVSYSIHSTAKVVLTREDVHSQVICEVA HVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVRK FYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSAH RDDVKLTCQVEHDGQPAVSRSHDLKVSAHPKEQGSNTAAENTGSNE RNIYIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTS STRLHEPEK NAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTE YASIQTSPQ PASEDTLTYADLDMVHLNRTPKQPAP KPEPSFSEYASVQVPRK

human SIRPpl (nucleotide sequence)	37	ATGCCCGTGCCAGCCTCCTGGCCCCACCTTCCTAGTCCTTTCCTGC TGATGACGCTACTGCTGGGGAGACTCACAGGAGTGGCAGGTGAGGA CGAGCTACAGGTGATTCAGCCTGAAAAGTCCGTATCAGTTGCAGCT GGAGAGTCGGCCACTCTGCGCTGTGCTATGACGTCCCTGATCCCTG TGGGGCCCATCATGTGGTTTAGAGGAGCTGGAGCAGGCCGGGAATT AATCTACAATCAGAAAGAAGGCCACTTCCCACGGGTAACAACTGTT TCAGAACTCACAAAGAGAAACAACCTGGACTTTTCCATCAGCATCA GTAACATCACCCCAGCAGACGCCGGCACCTACTACTGTGTGAAGTT CCGGAAAGGGAGCCCTGACGACGTGGAGTTTAAGTCTGGAGCAGGC ACTGAGCTGTCTGTGCGCGCCAAACCCTCTGCCCCCGTGGTATCGG GCCCTGCGGTGAGGGCCACACCTGAGCACACAGTGAGCTTCACCTG CGAGTCCCATGGCTTCTCTCCCAGAGACATCACCCTGAAATGGTTC AAAAATGGGAATGAGCTCTCAGACTTCCAGACCAACGTGGACCCCG CAGGAGACAGTGTGTCCTACAGCATCCACAGCACAGCCAGGGTGGT GCTGACCCGTGGGGACGTTCACTCTCAAGTCATCTGCGAGATAGCC CACATCACCTTGCAGGGGGACCCTCTTCGTGGGACTGCCAACTTGT CTGAGGCCATCCGAGTTCCACCCACCTTGGAGGTTACTCAACAGCC CATGAGGGCAGAGAACCAGGCAAACGTCACCTGCCAGGTGAGCAAT TTCTACCCCCGGGGACTACAGCTGACCTGGTTGGAGAATGGAAATG TGTCCCGGACAGAAACAGCTTCGACCCTCATAGAGAACAAGGATGG CACCTACAACTGGATGAGCTGGCTCCTGGTGAACACCTGTGCCCAC AGGGACGATGTGGTGCTCACCTGTCAGGTGGAGCATGATGGGCAGC AAGCAGTCAGCAAAAGCTATGCCCTGGAGATCTCAGCGCACCAGAA GGAGCACGGCTCAGATATCACCCATGAAGCAGCGCTGGCTCCTACT GCTCCACTCCTCGTAGCTCTCCTCCTGGGCCCCAAGCTGCTACTGG TGGTTGGTGTCTCTGCCATCTACATCTGCTGGAAACAGAAGGCC
human SIRPβi (amino acid sequence)	38	MPVPASWPHLPSPFLLMTLLLGRLTGVAGEDELQVIQPEKSVSVAA GESATLRCAMTSLIPVGPIMWFRGAGAGRELIYNQKEGHFPRVTTV SELTKRNNLDFSISISNITPADAGTYYCVKFRKGSPDDVEFKSGAG TELSVRAKPSAPVVSGPAVRATPEHTVSFTCESHGFSPRDITLKWF KNGNELSDFQTNVDPAGDSVSYS IHSTARVVLTRGDVHSQVICEIA HITLQGDPLRGTANLSEAIRVPPTLEVTQQPMRAENQANVTCQVSN FYPRGLQLTWLENGNVSRTETASTLIENKDGTYNWMSWLLVNTCAH RDDWLTCQVEHDGQQAVSKSYALEISAHQKEHGSDITHEAALAPT APLLVALLLGPKLLLVVGVSAI YICWKQKA
human SIRPγ (nucleotide sequence)	39	ATGCCTGTCCCAGCCTCCTGGCCCCATCCTCCTGGTCCTTTCCTGC TTCTGACTCTACTGCTGGGACTTACAGAAGTGGCAGGTGAGGAGGA GCTACAGATGATTCAGCCTGAGAAGCTCCTGTTGGTCACAGTTGGA AAGACAGCCACTCTGCACTGCACTGTGACCTCCCTGCTTCCCGTGG GACCCGTCCTGTGGTTCAGAGGAGTTGGACCAGGCCGGGAATTAAT CTACAATCAAAAAGAAGGCCACTTCCCCAGGGTAACAACAGTTTCA GACCTCACAAAGAGAAACAACATGGACTTTTCCATCCGCATCAGTA GCATCACCCCAGCAGATGTCGGCACATACTACTGTGTGAAGTTTCG AAAAGGGAGCCCTGAGAACGTGGAGTTTAAGTCTGGACCAGGCACT GAGATGGCTTTGGGTGCCAAACCCTCTGCCCCCGTGGTATTGGGCC CTGCGGCGAGGACCACACCTGAGCATACAGTGAGTTTCACCTGTGA GTCCCATGGCTTCTCTCCCAGAGACATCACCCTGAAATGGTTCAAA AATGGGAATGAGCTCTCAGACTTCCAGACCAACGTGGACCCCACAG GACAGAGTGTGGCCTACAGCATCCGCAGCACAGCCAGGGTGGTACT GGACCCCTGGGACGTTCGCTCTCAGGTCATCTGCGAGGTGGCCCAT GTCACCTTGCAGGGGGACCCTCTTCGTGGGACTGCCAACTTGTCTG AGGCCATCCGAGTTCCACCCACCTTGGAGGTTACTCAACAGCCCAT GAGGGTGGGGAACCAGGTAAACGTCACCTGCCAGGTGAGGAAGTTC TACCCCCAGAGCCTACAGCTGACCTGGTCGGAGAATGGAAACGTGT GCCAGAGAGAAACAGCCTCGACCCTTACAGAGAACAAGGATGGTAC CTACAACTGGACAAGCTGGTTCCTGGTGAACATATCTGACCAAAGG GATGATGTGGTCCTCACCTGCCAGGTGAAGCATGATGGGCAGCTGG

		CGGTCAGCAAACGCCTTGCCCTAGAGGTCACAGTCCACCAGAAGGA CCAGAGCTCAGATGCTACCCCTGGCCCGGCATCATCCCTTACTGCG CTGCTCCTCATAGCTGTCCTCCTGGGCCCCATCTACGTCCCCTGGA AGCAGAAGACC
human SIRPγ (amino acid sequence)	40	MPVPASWPHPPGPFLLLTLLLGLTEVAGEEELQMIQPEKLLLVTVG KTATLHCTVTSLLPVGPVLWFRGVGPGRELIYNQKEGHFPRVTTVS DLTKRNNMDFSIRISSITPADVGTYYCVKFRKGSPENVEFKSGPGT EMALGAKPSAPVVLGPAARTTPEHTVSFTCESHGFSPRDITLKWFK NGNELSDFQTNVDPTGQSVAYS IRSTARVVLDPWDVRSQVICEVAH VTLQGDPLRGTANLSEAIRVPPTLEVTQQPMRVGNQVNVTCQVRKF YPQSLQLTWSENGNVCQRETASTLTENKDGTYNWTSWFLVNISDQR DDWLTCQVKHDGQLAVSKRLALEVTVHQKDQSSDATPGPASSLTA LLLIAVLLGP IYVPWKQKT
human CD47 (nucleotide sequence)	41	ATGTGGCCTCTGGTGGCCGCTCTGCTGCTGGGCTCTGCTTGTTGTG GATCCGCCCAGCTGCTGTTCAACAAGACCAAGTCCGTGGAGTTCAC CTTCTGCAACGATACCGTCGTGATCCCCTGCTTCGTGACCAACATG GAAGCCCAGAACACCACCGAGGTGTACGTGAAGTGGAAGTTCAAGG GCCGGGACATCTACACCTTCGACGGCGCCCTGAACAAGTCCACCGT GCCCACCGATTTCTCCAGCGCCAAGATCGAGGTGTCACAGCTGCTG AAGGGCGACGCCTCCCTGAAGATGGACAAGTCCGACGCCGTGTCCC ACACCGGCAACTACACCTGTGAAGTGACCGAGCTGACCAGAGAGGG CGAGACAATCATCGAGCTGAAGTACCGGGTGGTGTCCTGGTTCAGC CCCAACGAGAACATCCTGATCGTGATCTTCCCCATCTTCGCCATCC TGCTGTTCTGGGGCCAGTTCGGCATCAAGACCCTGAAGTACAGATC CGGCGGCATGGAC GAAAAGACAATCGCCCTGCTGGTGGCTGGCCTC GTGATCACCGTGATTGTGATCGTGGGCGCTATCCTGTTCGTGCCCG GCGAGTACAGCCTGAAGAATGCTACCGGCCTGGGCCTGATTGTGAC CTCCACCGGAATCCTGATCCTGCTGCACTACTACGTGTTCTCCACC GCTATCGGCCTGACCTCCTTCGTGATCGCCATTCTCGTGATCCAAG TGATCGCCTACATCCTGGCCGTCGTGGGCCTGTCCCTGTGTATCGC CGCCTGCATCCCTATGCACGGCCCCCTGCTGATCTCCGGCCTGTCT ATTCTGGCCCTGGCTCAGCTGCTGGGACTGGTGTACATGAAGTTCG TGGCCTCCAACCAGAAAACCATCCAGCCCCCTCGGAAGGCCGTGGA AGAACCCCTGAACGCCTTCAAAGAATCCAAGGGCATGATGAACGAC GAA
human CD47 (amino acid sequence)	42	MWPLVAALLLGSACCGSAQLLFNKTKSVEFTFCNDTVVIPCFVTNM EAQNTTEVYVKWKFKGRDI YTFDGALNKSTVPTDFSSAKIEVSQLL KGDASLKMDKSDAVSHTGNYTCEVTELTREGETI IELKYRWSWFS PNENILIVIFPIFAILLFWGQFGIKTLKYRSGGMDEKTIALLVAGL VITVIVIVGAILFVPGEYSLKNATGLGLIVTSTGILILLHYYVFST AIGLISFVIAILVIQVIAYILAWGLSLCIAACIPMHGPLLISGLS ILALAQLLGLVYMKFVASNQKTIQPPRKAVEEPLNAFKESKGMMND E
human SlRPotV3 (nucleotide sequence)	43	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGTCCGTGTCTGTGGCC GCTGGCGAGTCTGCCATCCTGCTGTGTACCGTGACCTCCCTGATCC CCGTGGGCCCCATCCAGTGGTTTAGAGGCGCTGGCCCTGCCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGAGTCCACCAAGCGCGAGAACATGGACTTCTCCATCTCCA TCAGCAACATCACCCCTGCCGACGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGACACCGAGTTCAAGTCTGGCGCTGGC ACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCTGTGGTGTCTG GACCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTACCTG CGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGGTTC AAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACCCTG

		TGGGCGAGAGCGTGTCCTACTCCATCCACTCCACCGCCAAGGTGGT GCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTGGCC CACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACCTGT CCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCAGCC AGTGCGGGCCGAGAACCAAGTGAACGTGACCTGCCAAGTGCGGAAG TTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCAATG TGTCCCGGACCGAGACAGCCAGCACCGTGACCGAGAACAAGGATGG CACCTACAATTGGATGTCTTGGCTGCTCGTGAACGTGTCCGCCCAC CGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCCAGC CTGCCGTGTCCAAGAGCCACGATCTGAAGGTGTCCGCTCATCCCAA AGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAACGAG CGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGGTGG CTCTGCTGATGGCTGCCCTGTACCTCGTGCGGATCCGGCAGAAGAA GG^PPAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCCGAGAAG AACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACGCCG ACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGCCGA GCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCTCAG CCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGGTGC ACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCCTAG CTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
human SIRPaV3 (amino acid sequence)	44	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVSVA AGESAILLCTVTSLIPVGPIQWFRGAGPARELIYNQKEGHFPRVTT VSESTKRENMDFSISISNITPADAGTYYCVKFRKGSPDTEFKSGAG TELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDITLKWF KNGNELSDFQTNVDPVGESVSYSIHSTAKWLTREDVHSQVICEVA HVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVRK FYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLWVSAH RDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSNE RNIYIWGWCTLLVALLMAALYLVRIRQKKAQGSTS STRLHEPEK NAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTE YASIQTSPQ PASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
human SIRPaV4 (nucleotide sequence)	45	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGGCCTGCAAGTGATCCAGCCCGACAAGTCCGTGTCTGTGGCC GCTGGCGAGTCTGCCATCCTGCACTGTACCGCCACCTCCCTGATCC CCGTGGGACCCATCCAGTGGTTTAGAGGCGCTGGCCCTGGCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGACCTGACCAAGCGGAACAACATGGACTTCTCCATCCGGA TCGGCAACATCACCCCTGCCGATGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGAC GACGTGGAGTTCAAATCCGGCGCT GGCACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCTGTGGTGT CTGGCCCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTAC CTGCGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGG TTCAAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACC CTGTGGGCGAGAGCGTGTCCTACTCCATCCACTCCACCGCCAAGGT GGTGCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTG GCCCACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACC TGTCCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCA GCCAGTGCGGGCCGAGAACCAAGTGAACGTGACCTGCCAAGTGCGG AAGTTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCA ATGTGTCCCGGACCGAGACAGCCTCCACCGTGACCGAGAACAAGGA TGGCACCTACAATTGGATGTCTTGGCTGCTCGTGAACGTGTCCGCC CACCGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCC AGCCTGCCGTGTCCAAGTCCCACGATCTGAAGGTGTCCGCTCATCC CAAAGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAAC GAGCGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGG TGGCTCTGCTGATGGCTGCCCTGTACCTCGTGCGGATCCGGCAGAA

		GAAGGCCCAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCCGAG AAGAACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACG CCGACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGC CGAGCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCT CAGCCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGG TGCACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCC TAGCTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
human SIRPaV4 (amino acid sequence)	46	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEGLQVIQPDKSVSVA AGE SAILHCTATSLIPVGP IQWFRGAGPGRELIYNQKEGHFPRVTT VSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVS YSIHSTAKVVLTREDVHSQVICEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNIYIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTSSTRLHEPE KNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSF.SE YASVQVPRK
human SlRPotV5 (nucleotide sequence)	47	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGTTCGTGCTGGTGGCC GCTGGCGAGACAGCCACCCTGAGATGTACCGCCACCTCCCTGATCC CCGTGGGCCCTATCCAGTGGTTTAGAGGCGCTGGCCCTGGCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGACCTGACCAAGCGGAACAACATGGACTTCTCCATCCGGA TCGGCAACATCACCCCTGCCGATGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGACGACGTGGAGTTCAAATCCGGCGCT GGCACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCTGTGGTGT CTGGCCCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTAC CTGCGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGG TTCAAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACC CTGTGGGCGAGTCCGTGTCCTACTCCATCCACTCCACCGCCAAGGT GGTGCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTG GCCCACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACC TGTCCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCA GCCAGTGCGGGCCGAGAACCAAGTGAACGTGACCTGCCAAGTGCGG AAGTTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCA ATGTGTCCCGGACCGAGACTGCCTCCACCGTGACCGAGAACAAGGA TGGCACCTACAATTGGATGTCTTGGCTGCTCGTGAACGTGTCCGCC CACCGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCC AGCCTGCCGTGTCCAAGTCCCACGATCTGAAGGTGTCCGCTCATCC CAAAGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAAC GAGC GGAACATCTACATCGTCGTGGGCGTCGTGTGCACCC TGC TGG TGGCTCTGCTGATGGCTGCCCTGTACCTCGTGCGGATCCGGCAGAA GAAGGCCCAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCCGAG AAGAACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACG CCGACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGC CGAGCCTAACAAC CACACCGAGTACGCCTCCATCCAGACCAGC CCT CAGCCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGG TGCACCTGAAC CGGAC CCCCAAGCAGC CAGC TCC TAAGC CCGAGC C TAGCTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
human SIRPaV5 (amino acid sequence)	48	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKFVLVA AGETATLRCTATSLIPVGP IQWFRGAGPGRELIYNQKEGHFPRVTT VSDLTKRNNMDFS IRIGNITPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVS YSIHSTAKVVLTREDVHSQVICEV

		AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNI YIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTSSTRLHEPE KNAREITQDTNDI TYADLNLPKGKKPAPQAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
human SlRPaV6 (nucleotide sequence)	49	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGTCCGTGCTGGTGGCT GCTGGCGAGACTGCCACCCTGAGATGTACCGCCACCTCCCTGATCC CCGTGGGCCCTATCCAGTGGTTTAGAGGCGCTGGCCCTGGCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGACCTGACCAAGCGGAACAACATGGACTTCCCCATCCGGA TCGGCAACATCACCCCTGCCGATGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGAC GACGTGGAGTTCAAATCCGGCGCT GGCACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCTGTGGTGT CTGGCCCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTAC CTGCGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGG TTCAAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACC CTGTGGGCGAGTCCGTGTCCTACTCCATCCACTCCACCGCCAAGGT GGTGCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTG GCCCACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACC TGTCCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCA GCCCGTGCGGGCTGAGAACCAAGTGAACGTGACCTGCCAAGTGCGG AAGTTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCA ATGTGTCCCGGACCGAGACAGCCTCCACCGTGACCGAGAACAAGGA TGGCACCTACAATTGGATGTCCTGGCTGCTCGTGAACGTGTCCGCC CACCGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCC AGCCTGCCGTGTCCAAGTCCCACGATCTGAAGGTGTCCGCTCATCC CAAAGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAAC GAGCGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGG TGGCACTGCTGATGGCCGCTCTGTACCTCGTGCGGATCCGGCAGAA GAAGGCCCAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCCGAG AAGAACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACG CCGACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGC CGAGCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCT CAGCCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGG TGCACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCC TAGCTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
human SlRPaV6 (amino acid sequence)	50	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGETATLRCTATSLIPVGPIQWFRGAGPGRELIYNQKEGHFPRVTT VSDLTKRNNMDFPIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVS YS IHSTAKVVLTREDVHSQVICEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNIYIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTSSTRLHEPE KNAREITQDTNDITYADLNLPKGKKPAP QAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSF.SE YASVQVPRK
human SlRPaV8 (nucleotide sequence)	51	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGTCCGTGCTGGTGGCT GCTGGCGAGACTGCCACCCTGAGATGTACCGCCACCTCCCTGATCC CCGTGGGCCCTATCCAGTGGTTTAGAGGCGCTGGCCCTGCCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC

		GTGTCCGAGTCCACCAAGCGCGAGAACATGGACTTCTCCATCTCCA TCAGCAACATCACCCCTGCCGACGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGACACCGAGTTCAAGTCTGGCGCTGGC ACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCTGTGGTGTCTG GACCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTACCTG CGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGGTTC AAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACCCTG TGGGCGAGTCCGTGTCCTACTCCATCCACTCCACCGCCAAGGTGGT GCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTGGCC CACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACCTGT CCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCAGCC CGTGCGGGCTGAGAACCAAGTGAACGTGACCTGCCAAGTGCGGAAG TTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCAATG TGTCCCGGACCGAGACAGCCAGCACCGTGACCGAGAACAAGGATGG CACCTACAATTGGATGTCCTGGCTGCTCGTGAACGTGTCCGCCCAC CGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCCAGC CTGCCGTGTCCAAGAGCCACGATCTGAAGGTGTCCGCTCATCCCAA AGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAACGAG CGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGGTGG CACTGCTGATGGCCGCTCTGTACCTCGTGCGGATCCGGCAGAAGAA GGCCCAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCCGAGAAG AACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACGCCG ACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGCCGA GCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCTCAG CCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGGTGC ACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCCTAG CTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
human SIRPaVS (amino acid sequence)	52	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGETATLRCTATSLIPVGP IQWFRGAGPARELIYNQKEGHFPRVTT VSES TKRENMDFS ISI SNI TPADAGTYYCVKFRKGSPDTEFKSGAG TELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRD ITLKWF KNGNELSDFQTNVDPVGESVSYSIHSTAKVVLTREDVHSQVICEVA HVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVRK FYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSAH RDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSNE RNIYIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTS STRLHEPEK NAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTEYASIQTSPQ PASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
human SIRPaV9 (nucleotide sequence)	53	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGTCCGTGCTGGTGGCT GCTGGCGAGACTGCCACCCTGAGATGTACCGCCACCTCCCTGATCC CCGTGGGCCCTATCCAGTGGTTTAGAGGCGCTGGCCCTGGCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGACCTGACCAAGCGGAACAACATGGACTTCTCCATCCGGA TCTCCAACATCACCCCTGCCGACGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGAC GACGTGGAGTTCAAATCCGGCGCT GGCACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCTGTGGTGT CTGGCCCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTAC CTGCGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGG TTCAAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACC CTGTGGGCGAGTCCGTGTCCTACTCCATCCACTCCACCGCCAAGGT GGTGCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTG GCCCACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACC TGTCCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCA GCCCGTGCGGGCTGAGAACCAAGTGAACGTGACCTGCCAAGTGCGG AAGTTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCA

		ATGTGTCCCGGACCGAGACAGCCTCCACCGTGACCGAGAACAAGGA TGGCACCTACAATTGGATGTCCTGGCTGCTCGTGAACGTGTCCGCC CACCGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCC AGCCTGCCGTGTCCAAGTCCCACGATCTGAAGGTGTCCGCTCATCC CAAAGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAAC GAGCGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGG TGGCACTGCTGATGGCCGCTCTGTACCTCGTGCGGATCCGGCAGAA GAAGGCCCAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCCGAG AAGAACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACG CCGACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGC CGAGCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCT CAGCCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGG TGCACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCC TAGCTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
human SIRPaV9 (amino acid sequence)	54	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGETATLRCTATSLIPVGP IQWFRGAGPGRELIYNQKEGHFPRVTT VSDLTKRNNMDFS IRI SNITPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRDTTLKW FKNGNELSDFQTNVDPVGESVSYS IHSTAKWLTREDVHSQVICEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNIYIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTSSTRLHEPE KNAREITQDTNDITYADLNLPKGKKPAP QAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
hSlRPa-VpClaC2a (nucleotide sequence)	55	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA GGACGAGCTGCAAGTGATCCAGCCCGAGAAGTCCGTGTCTGTGGCC GCTGGCGAGTCTGCCACCCTGAGATGCGCTATGACCTCCCTGATCC CCGTGGGCCCCATCATGTGGTTTAGAGGCGCTGGCGCTGGCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGAGCTGACCAAGCGGAACAACCTGGACTTCTCCATCTCCA TCAGCAACATCACCCCTGCCGACGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGACGACGTGGAGTTCAAATCCGGCGCT GGAACCGAGCTGTCCGTGCGGGCTAAACCTTCTGCCCCTGTGGTGT CTGGCCCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTAC CTGCGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGG TTCAAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACC CTGTGGGCGAGAGCGTGTCCTACTCCATCCACTCCACCGCCAAGGT GGTGCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTG GCCCACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACC TGTCCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCA GCCTGTGCGGGCCGAGAACCAAGTGAACGTGACCTGCCAAGTGCGG AAGTTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCA ATGTGTCCCGGACCGAGACAGCCAGCACCGTGACCGAGAACAAGGA TGGCACCTACAATTGGATGTCCTGGCTGCTCGTGAACGTGTCCGCC CACCGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCC AGCCTGCCGTGTCCAAGTCCCACGATCTGAAGGTGTCCGCTCATCC CAAAGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAAC GAGCGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGG TGGCTCTGCTGATGGCTGCCCTGTACCTCGTGCGGATCCGGCAGAA GAAGGCCCAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCTGAG AAGAACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACG CCGACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCCGC CGAGCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCT CAGCCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGG TGCACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCC

		TAGCTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
hSlRPα-VβC1αC2a (amino acid sequence)	56	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEDELQVIQPEKSVSVA AGESATLRCAMTSLIPVGP IMWFRGAGAGRE LI YNQKEGHFPRVTT VSEL TKRNN LDFS ISI SNI TPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPWSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVSYSIHSTAKWLTREDVHSQVICEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNIYIVVGVVCTLLVALLMAALYLVRIRQKRAQGSTSSTRLHEPE KNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
hSIRPα-VaC1βC2a (nucleotide sequence)	57	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGTCCGTGCTGGTGGCT GCTGGCGAGACTGCCACCCTGAGATGTACCGCCACCTCCCTGATCC CCGTGGGCCCTATCCAGTGGTTTAGAGGCGCTGGCCCTGGCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGACCTGACCAAGCGGAACAACATGGACTTCTCCATCCGGA TCGGCAACATCACCCCTGCCGATGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGACGACGTGGAGTTCAAATCCGGCGCT GGCACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCCGTGGTGT CTGGACCTGCCGTGCGAGCTACCCCTGAGCACACCGTGTCTTTTAC CTGCGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGG TTCAAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACC CAGCCGGCGACTCCGTGTCCTACTCCATCCACTCTACCGCCAGAGT GGTGCTGACCAGAGGCGACGTGCACTCCCAAGTGATCTGCGAGATC GCCCATATCACACTGCAGGGCGACCCCCTGAGAGGCACCGCTAACC TGTCTGAGACAATCCGGGTGCCCCCCACCCTGGAAGTGACTCAGCA GCCAGTGCGGGCCGAGAACCAAGTGAACGTGACCTGCCAAGTGCGG AAGTTCTACCCCCAGCGGCTGCAGCTGACCTGGCTGGAAAACGGCA ATGTGTCCCGGACCGAGACAGCCTCCACCGTGACCGAGAACAAGGA TGGCACCTACAATTGGATGTCTTGGCTGCTCGTGAACGTGTCCGCC CACCGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGACGGCC AGCCTGCCGTGTCCAAGTCCCACGATCTGAAGGTGTCCGCTCATCC CAAAGAGCAGGGCTCCAACACCGCCGCTGAGAACACCGGCTCTAAC GAGCGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGG TGGCACTGCTGATGGCCGCTCTGTACCTCGTGCGGATCCGGCAGAA GAAGGCCCAGGGCTCTACCTCCTCCACCAGACTGCACGAGCCCGAG AAGAACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACG CCGACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCCGC CGAGCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCT CAGCCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGG TGCACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCC TAGCTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
hSlRPa-VaCipC2a (amino acid sequence)	58	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGE TATLRCT ATSLI PVGP IQWFRGAGPGRE LI YNQKEGHFPRVTT VSDLTKRNNMDFS IRIG NI TPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPVVSGPAVRATPEHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPAGDSVS YSIHSTARVVLTRGDVHSQVICEI AHITLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNI YIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTSSTRLHEPE KNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK

hSIRP<x-VaClaC2p (nucleotide sequence)	59	ATGGAACCTGCCGGCCCTGCTCCTGGTAGACTGGGACCTCTGCTGT GTCTGCTGCTGGCCGCCTCTTGTGCTTGGAGCGGAGTGGCTGGCGA AGAGGAACTGCAAGTGATCCAGCCCGACAAGTCCGTGCTGGTGGCT GCTGGCGAGACTGCCACCCTGAGATGTACCGCCACCTCCCTGATCC CCGTGGGCCCTATCCAGTGGTTTAGAGGCGCTGGCCCTGGCAGAGA GCTGATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACC GTGTCCGACCTGACCAAGCGGAACAACATGGACTTCTCCATCCGGA TCGGCAACATCACCCCTGCCGATGCCGGCACCTACTACTGCGTGAA GTTCCGGAAGGGCTCCCCCGACGACGTGGAGTTCAAATCCGGCGCT GGCACCGAGCTGTCTGTGCGGGCTAAACCTTCTGCCCCTGTGGTGT CTGGCCCTGCCGCTAGAGCTACCCCTCAGCACACCGTGTCTTTTAC CTGCGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGG TTCAAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACC CTGTGGGCGAGTCCGTGTCCTACTCCATCCACTCCACCGCCAAGGT GGTGCTGACACGCGAGGACGTGCACTCCCAAGTGATCTGCGAGGTG GCCCACGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAACC TGTCCGAGACAATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCA GCCTATGAGAGCCGAGAACCAGGCCAACGTGACCTGCCAGGTGTCC AACTTCTACCCTCGGGGCCTGCAGCTGACCTGGCTGGAAAACGGCA ATGTGTCCCGGACCGAGACAGCCTCCACCCTGATCGAGAACAAGGA TGGCACCTACAATTGGATGTCCTGGCTGCTCGTGAACACCTGTGCC CACCGGGACGATGTGGTGCTGACCTGTCAGGTGGAACACGATGGCC AGCAGGCCGTGTCCAAGTCCTACGCTCTGGAAGTGTCCGCCCACCC CAAAGAGCAGGGCTCTAATACCGCCGCTGAGAACACCGGCTCCAAC GAGCGGAACATCTACATCGTCGTGGGCGTCGTGTGCACCCTGCTGG TGGCACTGCTGATGGCCGCTCTGTACCTCGTGCGGATCCGGCAGAA GAAGGCTCAGGGCTCCACCTCCTCCACCAGACTGCACGAGCCTGAG AAGAACGCCAGAGAGATCACCCAGGACACCAACGACATCACCTACG CCGACCTGAACCTGCCCAAGGGCAAGAAGCCTGCCCCTCAGGCTGC CGAGCCTAACAACCACACCGAGTACGCCTCCATCCAGACCAGCCCT CAGCCTGCCTCTGAGGACACCCTGACCTACGCTGATCTGGACATGG TGCACCTGAACCGGACCCCCAAGCAGCCAGCTCCTAAGCCCGAGCC TAGCTTCTCTGAGTACGCCAGCGTGCAGGTGCCCCGGAAA
hSIRPa-VaClaC2p (amino acid sequence)	60	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGETATLRCTATSLIPVGPIQWFRGAGPGRELIYNQKEGHFPRVTT VSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFRSGA GTELSVRAKPSAPWSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVSYSIHSTAKWLTREDVHSQVICEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPMRAENQANVTCQVS NFYPRGLQLTWLENGNVSRTETASTLIENKDGTYNWMSWLLVNTCA HRDDWLTCQVEHDGQQAVSKSYALEVSAHPKEQGSNTAAENTGSN ERNIYIVVGVVCTLLVALLMAALYLVRI RQKKAQGSTSSTRLHEPE KNAREITQDTNDI TYADLNLPKGKKPAPQAAEPNNHTEYAS IQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEP SFSEYASVQVPRK
human SIRPaVl(P74A) (nucleotide sequence)	61	ATGGAGCCCGCCGGCCCGGCCCCCGGCCGCCTCGGGCCGCTGCTCT GCCTGCTGCTCGCCGCGTCCTGCGCCTGGTCAGGAGTGGCGGGTGA GGAGGAGCTGCAGGTGATTCAGCCTGACAAGTCCGTGTTGGTTGCA GCTGGAGAGACAGCCACTCTGCGCTGCACTGCGACCTCTCTGATCC CTGTGGGGCCCATCCAGTGGTTCAGAGGAGCTGGAGCAGGCCGGGA ATTAATCTACAATCAAAAAGAAGGCCACTTCCCCCGGGTAACAACT GTTTCAGACCTCACAAAGAGAAACAACATGGACTTTTCCATCCGCA TCGGTAACATCACCCCAGCAGATGCCGGCACCTACTACTGTGTGAA GTTCCGGAAAGGGAGCCCCGATGACGTGGAGTTTAAGTCTGGAGCA GGCACTGAGCTGTCTGTGCGCGCCAAACCCTCTGCCCCCGTGGTAT CGGGCCCTGCGGCGAGGGCCACACCTCAGCACACAGTGAGCTTCAC CTGCGAGTCCCACGGCTTCTCACCCAGAGACATCACCCTGAAATGG TTCAAAAATGGGAATGAGCTCTCAGACTTCCAGACCAACGTGGACC

		CCGTAGGAGAGAGCGTGTCCTACAGCATCCACAGCACAGCCAAGGT GGTGCTGACCCGCGAGGACGTTCACTCTCAAGTCATCTGCGAGGTG GCCCACGTCACCTTGCAGGGGGACCCTCTTCGTGGGACTGCCAACT TGTCTGAGACCATCCGAGTTCCACCCACCTTGGAGGTTACTCAACA GCCCGTGAGGGCAGAGAACCAGGTGAATGTCACCTGCCAGGTGAGG AAGTTCTACCCCCAGAGACTACAGCTGACCTGGTTGGAGAATGGAA ACGTGTCCCGGACAGAAACGGCCTCAACCGTTACAGAGAACAAGGA TGGTACCTACAACTGGATGAGCTGGCTCCTGGTGAATGTATCTGCC CACAGGGATGATGTGAAGCTCACCTGCCAGGTGGAGCATGACGGGC AGCCAGCGGTCAGCAAAAGCCATGACCTGAAGGTCTCAGCCCACCC GAAGGAGCAGGGCTCAAATACCGCCGCTGAGAACACTGGATCTAAT GAACGGAACATCTATATTGTGGTGGGTGTGGTGTGCACCTTGCTGG TGGCCCTACTGATGGCGGCCCTCTACCTCGTCCGAATCAGACAGAA GAAAGCCCAGGGCTCCACTTCTTCTACAAGGTTGCATGAGCCCGAG AAGAATGCCAGAGAAATAACACAGGACACAAATGATATCACATATG CAGACCTGAACCTGf^AAGGGGAAGAAGCCTGCTCCCCAGGCTGC GGAGCCCAACAACCACACGGAGTATGCCAGCATTCAGACCAGCCCG CAGCCCGCGTCGGAGGACACCCTCACCTATGCTGACCTGGACATGG TCCACCTCAACCGGACCCCCAAGCAGCCGGCCCCCAAGCCTGAGCC GTCCTTCTCAGAGTACGCCAGCGTCCAGGTCCCGAGGAAG
human SIRPaVl(P74A) (amino acid sequence)	62	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGETATLRCTATSLIPVGPIQWFRGAGAGRELIYNQKEGHFPRVTT VSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPWSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVSYSIHSTAKWLTREDVHSQVICEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERNIYIVVGVVCTLLVALLMAALYLVRIRQKKAQGSTSSTRLHEPE KNAREITQDTNDITYADLNLPKGKKPAPQAAEPNNHTEYASIQTSP QPASEDTLTYADLDMVHLNRTPKQPAPKPEPSFSEYASVQVPRK
human kappa constant domain (nucleotide sequence)	63	CGGACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACG AGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAA CTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC CTGCAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCA AGGACAGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGC CGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAG GGCCTGTCTAGCCCTGTGACCAAGTCCTTCAACCGGGGCGAGTGC
human kappa constant domain (protein sequence)	64	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC
human IgG4 constant domains (including S228P) (nucleotide sequence)	65	GCTTCCACCAAGGGCCCCTCCGTGTTTCCTCTGGCCCCTTGCTCCA GATCCACCTCCGAGTCTACCGCCGCTCTGGGCTGCCTCGTGAAGGA CTACTTCCCCGAGCCTGTGACAGTGTCCTGGAACTCTGGCGCCCTG ACCTCTGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCCTCCGGCC TGTACTCCCTGTCCAGCGTCGTGACAGTGCCCTCCAGCTCTCTGGG CACCAAGACCTACACCTGTAACGTGGACCACAAGCCCTCCAACACC AAGGTGGACAAGCGGGTGGAATCTAAGTACGGCCCTCCCTGCCCTC CTTGCCCAGCCCCTGAATTTCTGGGCGGACCTTCTGTGTTTCTGTT CCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAA GTGACCTGCGTGGTGGTGGATGTGTCCCAGGAAGATCCCGAGGTGC AGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGAC CAAGCCTAGAGAGGAACAGTTCAACTCCACCTACCGGGTGGTGTCC GTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACA AGTGCAAGGTGTCCAACAAGGGCCTGCCCAGCTCCATCGAAAAGAC CATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACA

		CTGCCTCCAAGCCAGGAAGAGATGACCAAGAACCAGGTGTCCCTGA CCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATG GGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCT GTGCTGGACTCCGACGGCTCCTTCTTTCTGTACTCTCGCCTGACCG TGGACAAGTCCCGGTGGCAGGAAGGCAACGTGTTCTCCTGCAGCGT GATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCC CTGTCTCTGGGAAAA
human IgG4 constant domains (including S228P) (protein sequence)	66	AST[K]GP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQS SGLYSLSSVVTVP SSSLGTKTYTCNVDHKP SNT KVDKRVESRYGPPCPPCPAPEFLGGP SVFLFPPRPKDTLMT SRTPE VTCVWDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYT LPP SQEEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK
human lgG2 constant domains (nucleotide sequence)	67	GCTTCTACAAAGGGCCCCAGCGTGTTCCCTCTGGCTCCTTGTAGCA GAAGCACCAGCGAGTCTACAGCCGCTCTGGGCTGTCTGGTCAAGGA CTACTTTCCCGAGCCTGTGACCGTGTCCTGGAATAGCGGAGCACTG ACAAGCGGCGTGCACACCTTTCCAGCTGTGCTGCAAAGCTCCGGCC TGTACTCTCTGTCCAGCGTGGTCACAGTGCCCAGCAGCAATTTTGG CACCCAGACCTACACCTGTAATGTGGACCACAAGCCTAGCAACACC AAGGTGGACAAGACCGTGGAACGGAAGTGCTGCGTGGAATGCCCTC CTTGTCCTGCTCCTCCAGTGGCTGGCCCTTCCGTGTTTCTGTTCCC TCCAAAGCCTAAGGACACCCTGATGATCAGCAGAACCCCTGAAGTG ACCTGCGTGGTGGTGGATGTGTCCCACGAGGATCCTGAGGTGCAGT TCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAA GCCTAGAGAGGAACAGTTCAACAGCACCTTCAGAGTGGTGTCCGTG CTGACCGTGGTGCATCAGGATTGGCTGAACGGCAAAGAGTACAAGT GCAAGGTGTCCAACAAGGGCCTGCCTGCTCCTATCGAGAAAACCAT CAGCAAGACCAAAGGCCAGCCTCGCGAGCCCCAGGTTTACACACTT CCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGTCCCTGACCT GCCTCG[T]GAAGGGCTTCTACCCCAGCGAC[AT]C[X1]CCGTGGAATGGG AGAGCAATGGCCAGCCTGAGAACAACTACAAGACCACACCTCCTAT GCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTG GACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCAGCGTGA TGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCTCT GAGCCCCGGCAAA **wherein :** X_1 = G, T
human IgG2 constant domains (protein sequence)	68	ASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQS SGLYSLSSVVTVP SSNFGTQTYTCNVDHKP SNT KVDKTVERKCCVECPPCPAPPVAGP SVFLFPPKPKDTLMI SRTPEV TCWVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSV LTWHQDWLNGKEYKCKVSNKGLPAP IEKTI SKTKGQPREPQVYTL P P SREEMTKNQVSLTCLVKGFYPSD I X$_2$VEWESNGQPENNYKTTPP MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK **wherein :** X_2 = A, S
40A heavy chain CDR1 (amino acid sequence)	69	S Y[W]M[H]
40A heavy chain CDR2 (amino acid	70	AIYPVNNDTTYNQKFKG

sequence)		
40A heavy chain CDR3 (amino acid sequence)	71	SFYYSLDAAWFVY
40A light chain CDR1 (amino acid sequence)	72	RASQDIGSRLN
40A light chain CDR2 (amino acid sequence)	73	ATSSLDS
40A light chain CDR3 (amino acid sequence)	74	LQYASSPFT
humanized 40 heavy chain variable region (consensus sequence)	75	EVQX1X2QSGAX3X4X5KPGASVKXiSCKASGS TFTSYWMHWVX7QX8 **PGQGLEWX9GAiyPVNSDTTYNQKFKGXioXiiTXi2TVX 13X14SXi5S** TX16YMX17LSS LX18X19EDX20AVYYCX21RSFYYSLDAAWFVYWGQG TX22X23TVSS **wherein :** X1 = F, L X2 = Q, R, V X3 = E, V X4 = L, V X5 = A, K, V X6 = L, M, V X7 = K, R X8 = A, R, T X9 = I, M X10 = K, R X11 = A, V X12 = L, M X13 = D, V X14 = K, T X15 = A, S, T X16 = A, V X17 = E, Q X18 = R, T X19 = F, S X20 = S, T X21 = A, T X22 = L, T X23 = L, V
humanized 40 light chain variable region (consensus sequence)	76	DIQMTQSPSSLSASX1GX2RVX3ITCRASQDIGSRLNWLQQX4PGKA X5KRLIYATSSLDSGVPX6RFSGSXiSGX8XcX10X11LTISX^LQPE DFATYYCLQYASSPFTFGX13GTKX14EIX15 **wherein:** X1 = L, V X2 = D, E X3 = S, T X4 = K, T X5 = I, P X6 = K, S X7 = G, R X8 = S, T X9 = D, E X10 = F, Y X11 = S, T

		X_{12} = G, S X_{13} = G, Q X_{14} = L, V X_{15} = H, K
hSlRPa.40AVHl (nucleotide sequence)	77	GAGGTGCAGTTCTTGCAGTCTGGTGCCGTGCTGGCTAGACCTGGAA CCTCCGTGAAGATCTCCTGCAAGGCCTCCGGCTCCACCTTCACCTC TTACTGGATGCACTGGGTCAAGCAGAGGCCTGGACAGGGACTCGAA TGGATCGGCGCTCTGTACCCTGTGAACTCCGACACCACCTACAACC AGAAGTTCAAGGGCAGAGCCAAGCTGACCGTGGCCACCTCTGCTTC TATCGCCTACCTGGAATTTTCCAGCCTGACCAACGAGGACTCCGCC GTGTACTACTGCGCCCGGTCCTTCTACTACTCTCTGGACGCCGCTT GGTTTGTGTACTGGGGCCAGGGAACTCTGGTGACCGTGTCCTCT
hSIRPa.40AVHl (amino acid sequence)	78	EVQFLQSGAVLARP GTSVKISCKAS GSTFTSYWMHWVKQRPGQGLE WIGALYPVNSDTTYNQKFKGRAKLTVATSAS IAYLEF S SLTNEDSA VYYCARSFYYSLDAAWFVYWGQGTLVTVSS
hSIRPa.40AVH2 (nucleotide secjuence)	79	GAGGTGCAGCTGGTTCAGTCTGGCGCTGAGGTTGTGAAGCCTGGCG CTTCCGTGAAGCTGTCCTGCAAGGCTTCTGGCTCCACCTTCACCAG CTACTGGATGCACTGGGTCAAGCAGGCCCCTGGACAAGGCCTGGAA TGGATCGGCGCTATCTACCCCGTGAACTCCGACACCACCTACAACC AGAAGTTCAAGGGCAAAGCTACCCTGACCGTGGACAAGTCTGCCTC CACCGCCTACATGGAACTGTCCAGCCTGAGATCTGAGGACACCGCC GTGTACTACTGCACCCGGTCCTTCTACTACTCCCTGGACGCCGCTT GGTTTGTGTATTGGGGCCAGGGAACACTGGTGACCGTGTCCTCT
hSlRPa.40AVH2 (amino acid sequence)	80	EVQLVQSGAEVVKPGASVKLSCKASGSTFTSYWMHWVKQAP GQGLE WIGAIYPVNSDTTYNQKFKGKATLTVDKSAS TAYMELSSLRSEDTA VYYCTRSFYYSLDAAWFVYWGQGTLVTVSS
hSIRPa.40AVH3 (nucleotide sequence)	81	GAGGTGCAGCTGAGACAGTCTGGCGCTGTGCTTGTGAAGCCTGGCG CCTCCGTGAAGATGTCCTGCAAGGCTTCTGGCTCCACCTTCACCAG CTACTGGATGCACTGGGTCAAGCAGACCCCTGGACAGGGACTCGAG TGGATCGGCGCTATCTACCCTGTGAACTCCGACACCACCTACAACC AGAAGTTCAAGGGCAAAGCTACCCTGACCGTGGACAAGTCCTCCTC CACCGCTTACATGCAGCTGTCCAGCCTGACCTCTGAGGACTCCGCC GTGTACTACTGCGCCCGGTCCTTCTACTACTCTCTGGACGCCGCTT GGTTTGTGTACTGGGGCCAGGGCACAACCCTGACAGTGTCCTCT
hSIRPa.40AVH3 (amino acid sequence)	82	EVQLRQSGAVLVKPGASVKMSCKASGSTFTS YWMHWVKQTPGQGLE WIGAIYPVNSDTTYNQKFKGKATLTVDKSSSTAYMQLS SLTSEDSA VYYCARSFYYSLDAAWFVYWGQGTTLTVSS
hS!RPa.40AVH4 (nucleotide sequence)	83	GAGGTGCAGTTCGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCG CCTCTGTGAAGGTGTCCTGCAAGGCTTCTGGCTCCACCTTCACCAG CTACTGGATGCACTGGGTCCGACAGGCTCCAGGACAAGGCTTGGAA TGGATGGGCGCTATCTACCCCGTGAACTCCGACACCACCTACAACC AGAAATTCAAGGGCAGAGTGACCATGACCGTCGTGACCTCCACCTC CACCGTGTACATGGAACTGTCCAGCCTGAGATCCGAGGACACCGCC GTGTACTACTGCGCCCGGTCCTTCTACTACTCTCTGGACGCCGCTT GGTTTGTGTACTGGGGCCAGGGAACTCTGGTGACCGTGTCCTCT
hSIRPa.40AVH4 (amino acid sequence)	84	EVQFVQ SGAEVKKP GAS VKVS CKASGSTFTS YWMHWVRQAPGQGLE WMGAIYPVNSDTTYNQKFKGRVTMTVVTSTSTVYMELS SLRSEDTA VYYCARSFYYSLDAAWFVYWGQGTLVTVSS
hSIRPa.40AVH5 (nucleotide sequence)	85	GAGGTCCAGCTGCAACAGTCTGGTGCCGTGTTGGCTAAGCCTGGCG CCTCCGTGAAGATGTCCTGCAAGGCTTCTGGCTCCACCTTCACCAG CTACTGGATGCACTGGGTCAAGCAGAGGCCTGGACAGGGACTCGAG TGGATCGGCGCTATCTACCCTGTGAACTCCGACACCACCTACAACC AGAAGTTCAAGGGCAAAGCTACCCTGACCGTGGACAAGTCCTCCTC CACCGCTTACATGCAGCTGTCCAGCCTGACCTTCGAGGACTCCGCC GTGTACTACTGCGCCCGGTCCTTCTACTACTCTCTGGACGCCGCTT GGTTTGTGTACTGGGGCCAGGGCACAACCCTGACAGTGTCCTCT

hSlRPoc.40AVH5 (amino acid sequence)	86	EVQLQQSGAVLAKPGASVKMSCKASGSTFTSYWMHWVKQRPGQGLE WIGAIYPVNSDTTYNQKFKGKATLTVDKSSSTAYMQLSSLTFEDSA VYYCARSFYYSLDAAWFVYWGQGTTLTVSS
hSIRPa.40AVH6 (nucleotide sequence)	87	GAGGTGCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCG CCTCTGTGAAGGTGTCCTGCAAGGCTTCTGGCTCCACCTTCACCAG CTACTGGATGCACTGGGTCCGACAGGCTCCAGGACAAGGCTTGGAA TGGATGGGCGCTATCTACCCCGTGAACTCCGACACCACCTACAACC AGAAATTCAAGGGCAGAGTGACCATGACCGTGGACACCTCCACCAG CACCGTGTACATGGAACTGTCCAGCCTGAGATCCGAGGACACCGCC GTGTACTACTGCGCCCGGTCCTTCTACTACTCTCTGGACGCCGCTT GGTTTGTGTACTGGGGCCAGGGAACTCTGGTGACCGTGTCCTCT
hSIRPa.40AVH6 (amino acid sequence)	88	EVQLVQSGAEVKKPGASVKVSCKASGSTFTSYWMHWVRQAPGQGLE WMGAIYPVNSDTTYNQKFKGRVTMTVDTSTSTVYMELSSLRSEDTA VYYCARSFYYSLDAAWFVYWGQGTLVTVSS
hSlRPa.40AVLl (nucleotide sequence)	89	GACATCCAGATGA^rr AGTCTCCATCCTCTCTGTCCGCCTCTGTGG GCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGACATCGGCTC CAGACTGAACTGGCTGCAGCAGACCCCTGGCAAGGCCATCAAGAGA CTGATCTACGCCACCTCCAGCCTGGATTCTGGCGTGCCCTCTAGAT TCTCCGGCTCTAGATCTGGCACCGACTTCTCCCTGACCATCTCTGG ACTGCAGCCTGAGGACTTCGCCACCTACTACTGTCTGCAGTACGCC AGCTCTCCATTCACCTTTGGCGGAGGCACCAAGGTGGAAATCCAC
hSIRPa.40AVLl (amino acid sequence)	90	DIQMTQSPSSLSASVGDRVTITCRASQDIGSRLNWLQQTPGKAIKR LIYATSSLDSGVP SRFSGSRSGTDFSLTISGLQPEDFATYYCLQYA SSPFTFGGGTKVEIH
hSlRPa.40AVL2 (nucleotide sequence)	91	GACATCCAGATGA^rr AGTCTCCATCCTCTCTGTCCGCCTCTGTGG GCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGACATCGGCTC CAGACTGAACTGGCTGCAGCAGAAGCCTGGCAAGGCCATCAAGAGA CTGATCTACGCCACCTCCAGCCTGGATTCTGGCGTGCCCTCTAGAT TCTCCGGCTCTAGATCTGGCACCGACTTTACCCTGACAATCAGCTC CCTGCAGCCTGAGGACTTCGCCACCTACTACTGTCTGCAGTACGCC TCCTCTCCATTCACCTTTGGCCAGGGCACCAAGGTGGAAATCAAG
hSIRPa.40AVL2 (amino acid sequence)	92	DIQMTQSPSSLSASVGDRVTITCRASQDIGSRLNWLQQKPGKAIKR LIYATSSLDSGVP SRFSGSRSGTDFTLTISSLQPEDFATYYCLQYA SSPFTFGQGTKVEIK
hSlRPa.40AVL3 (nucleotide sequence)	93	GACATCCAGATGACCCAGTCTCCATCCTCTCTGTCCGCCTCTGTGG GCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGACATCGGCTC CAGACTGAACTGGCTGCAGCAGAAGCCTGGCAAGGCCATCAAGAGA CTGATCTACGCCACCTCCAGCCTGGATTCTGGCGTGCCCTCTAGAT TCTCCGGCTCTAGATCTGGCACCGACTTTACCCTGACAATCAGCTC CCTGCAGCCTGAGGACTTCGCCACCTACTACTGTCTGCAGTACGCC AGCTCTCCATTCACCTTTGGCGGAGGCACCAAGCTGGAAATCAAG
hSIRPa.40AVL3 (amino acid sequence)	94	DIQMTQSPSSLSASVGDRVTITCRASQDIGSRLNWLQQKPGKAIKR LIYATSSLDSGVP SRFSGSRSGTDFTLTISSLQPEDFATYYCLQYA SSPFTFGGGTKLEIK
hSIRPa.40AVL4 (nucleotide sequence)	95	GACATCCAGATGACCCAGTCTCCATCCTCTCTGTCCGCCTCTGTGG GCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGACATCGGCTC CAGACTGAACTGGCTGCAGCAGAAGCCTGGCAAGGCCCCTAAGAGA CTGATCTACGCCACCTCCAGCCTGGATTCTGGCGTGCCCTCTAGAT TCTCCGGCTCTGGCTCTGGCACCGAGTTTACCCTGACAATCAGCTC CCTGCAGCCTGAGGACTTCGCCACCTACTACTGTCTGCAGTACGCC AGCTCTCCATTCACCTTTGGCGGAGGCACCAAGGTGGAAATCAAG
hSIRPa.40AVL4 (amino acid sequence)	96	DIQMTQSPSSLSASVGDRVTITCRASQDIGSRLNWLQQKPGKAPKR LIYATSSLDSGVP SRFSGSGSGTEFTLTISSLQPEDFATYYCLQYA SSPFTFGGGTKVEIK
hSIRPa.40AVL5 (nucleotide secjuence)	97	GACATCCAGATGACCCAGTCTCCATCCTCTCTGTCCGCCTCTGTGG GCGACAGAGTGACCATCACCTGTAGAGCCTCTCAGGACATCGGCTC

		CAGACTGAACTGGCTGCAGCAGAAGCCTGGCAAGGCCATCAAGAGA CTGATCTACGCCACCTCCAGCCTGGATTCTGGCGTGCCCAAGAGAT TCTCCGGCTCTAGATCCGGCTCCGACTATACCCTGACAATCAGCTC CCTGCAGCCTGAGGACTTCGCCACCTACTACTGTCTGCAGTACGCC TCCTCTCCATTCACCTTTGGCCAGGGCACCAAGGTGGAAATCAAG
hSIRPa.40AVL5 (amino acid sequence)	98	DIQMTQSPSSLSASVGDRVTITCRASQDIGSRLNWLQQKPGKAIKR LIYATSSLDSGVPKRFSGSRSGSDYTLTISSLQPEDFATYYCLQYA SSPFTFGQGTKVE IK
hSIRPa.40AVL6 (nucleotide sequence)	99	GACATCCAGATGACCCAGTCTCCATCCTCTCTGTCTGCTTCCCTGG GCGAGAGAGTGTCCATCACCTGTAGAGCCTCTCAGGACATCGGCTC CAGACTGAACTGGCTGCAGCAGAAGCCTGGCAAGGCCATCAAGAGA CTGATCTACGCCACCTCCAGCCTGGATTCTGGCGTGCCCTCTAGAT TCTCCGGCTCTAGATCTGGCACCGACTTTACCCTGACAATCAGCTC CCTGCAGCCTGAGGACTTCGCCACCTACTACTGTCTGCAGTACGCC AGCTCTCCATTCACCTTTGGCGGAGGCACCAAGGTGGAAATCAAG
hSIRPa.40AVL6 (amino acid sequence)	100	DIQMTQSPSSLSASLGERVSITCRASQDIGSRLNWLQQKPGKAIKR LIYATSSLDSGVP SRFSGSRSGTDFTLTISSLQPEDFATYYCLQYA SSPFTFGGGTKVE IK
hSIRPa.40A mouse VH (nucleotide sequence)	101	GAGGTTCAGTTCCAGCAGTCTGGGACTGTGCTGGCAAGGCCAGGGA CTTCAGTGAAGATGTCCTGCAAGGCTTCTGGCTCCACCTTTACCAG CTACTGGATGCACTGGGTAAAACAGGGGCCTGGACAGGGTCTGCAA TGGATTGGCGCTATTTATCCTGTAAATAATGATACTACCTATAATC AGAAGTTCAAGGGCAAGGCCGAACTCACTGTAGTCACTTCCACCAG CACTGCCTACATGGAGGTCAGTAGTCTGACAAATGAGGACTCTGCG GTCTATTACTGTACAAGATCGTTCTACTATAGTCTCGACGCGGCCT GGTTTGTTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA
hSIRPa.40A mouse VH (amino acid sequence)	102	EVQFQQSGTVLARPGTSVKMSCKASGSTFTSYWMHWVKQGPGQGLQ WIGAIYPVNNDTTYNQKFKGKAELTVVTSTSTAYMEVSSLTNEDSA VYYCTRSFYYSLDAAWFVYWGQGTLVTVSA
hSlRPoc.40A mouse VL (nucleotide sequence)	103	GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTGCCTCTCTGG GAGAAAGAGTCAGTCTCACTTGTCGGGCAAGTCAGGACATTGGTAG TAGGTTAAACTGGCTTCAGCAGGAACCAGATGGAACTATTAAACGC CTGATCTACGCCACATCCAGTTTAGATTCTGGTGTCCCCAAAAGGT TCAGTGGCAGTAGGTCTGGGTCAGATTATTCTCTCACCATCAGCGG CCTTGAGTCTGAAGACTTTGTAGACTATTACTGTCTACAATATGCT AGTTCTCCGTTCACGTTCGGAGGGGGGACCAAGCTGGAAATAAAC
hSIRPa.40A mouse VL (amino acid sequence)	104	DIQMTQSPSSLSASLGERVSLTCRASQDIGSRLNWLQQEPDGTIKR LIYATSSLDSGVP KRFSGSRSGSDYSLTISGLESEDFVDYYCLQYA SSPFTFGGGT KLEIN
hSlRPoc.40A mouse heavy chain (amino acid sequence; constant domain underlined, signal peptide not shown)	105	EVQFQQSGTVLARPGTSVKMSCKASGSTFTSYWMHWVKQGPGQGLQ WIGAIYPVNNDTTYNQKFKGKAELTWTSTSTAYMEVSSLTNEDSA VYYCTRSFYYSLDAAWFVYWGQGTLVTVSAAKTTPPSVYPLAPGSA AQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLY TLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCI CTVPEVSSVFIFPPKPKDVLTITLTPKVTCVWDISKDDPEVQFSW FVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRV NSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMI TDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKS NWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK
hSIRPa.40A mouse light chain (amino acid sequence; constant domain underlined, signal peptide not shown)	106	DIQMTQSPSSLSASLGERVSLTCRASQDIGSRLNWLQQEPDGTIKR LIYATSSLDSGVP KRFSGSRSGSDYSLTISGLESEDFVDYYCLQYA SSPFTFGGGTKLEINRADAAPTVSIFPPSSEQLTSGGASWCFLNN FYPKDINVKWKIDGSERQNGVLNSWTDQDSKDST YSMSSTLTLTKD EYERHNSYTCEATHKTSTSPIVKSFNRNEC

rhSIRPa/Fc (amino acid sequence)	107	(GVAG) EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFR GAGPGRELI YNQKEGHFPRVTTVSDLTKRNNMDFS IRIGNITPADA GTYYCVKFRKGSPDDVEFKSGAGTELSVRAKPSAPVVSGPAARATP QHTVSFTCESHGFSPRDITLKWFKNGNELSDFQTNVDPVGESVSYS IHSTAKWLTREDVHSQVICEVAHVTLQGDPLRGTANLSETIRVPP TLEVTQQPVRAENQVNVTCQVRKFYPQRLQLTWLENGNVSRTETAS TVTENKDGTYNWMSWLLWVSAHRDDVKLTCQVEHDGQPAVSKSHD LKVSAHPKEQGSNTAAENTGSNERIEGRMDPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVWDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRWSVLTVLHQDWLNGKEYKCKVS NKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
rhSIRP7/Fc (amino acid sequence)	108	VLWFRGVGPGRELI YNQKEGHFPRVTTVSDLTKRNNMDFS IRISSI TPADVGTYYCVKFRKGSPENVEFKSGPGTEMALGAKP SAPVVLGPA ARTTPEHTVSFTCESHGFSPRD ITLKWFKNGNELSDFQTNVDPTGQ SVAYSIRSTARVVLDPWDVRSQVICEVAHVTLQGDPLRGTANLSEA IRVPPTLEVTQQPMRAGNQVNVTCQVRKFYPQSLQLTWLENGNVCQ RETASTLTENKDGTYNWTSWFLVNISDQRDDWLTCQVKHDGQLAV SKRLALEVTVHQKDQSSDATPGPAS IEGRMDPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
rhCD47/Fc (amino acid sequence)	109	QLLFNKTKSVEFTFCNDTWIPCFVTNMEAQNTTEVYVKWKFKGRD IYTFDGALNKSTVPTDFSSAKIEVSQLLKGDASLKMDKSDAVSHTG NYTCEVTELTREGETI lELKYRWSWFSPIEGRMDPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRWSVLTVLHQDWLNGKEY KCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
hSIRP-VγC1βC2β (nucleotide sequence)	110	ATGCCCGTGCCTGCCTCTTGGCCTCATCTGCCCAGCCCCTTTCTGC TGATGACCCTGCTGCTGGGCAGGCTGACAGGCGTGGCAGGCGAAGA GGAACTGCAGATGATCCAGCCCGAGAAGCTGCTGCTCGTGACCGTG GGCAAGACCGCCACCCTGCACTGCACCGTGACATCCCTGCTGCCTG TGGGACCCGTGCTGTGGTTTAGAGGCGTGGGCCCTGGCAGAGAGCT GATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACCGTG TCCGACCTGACCAAGCGGAACAACATGGACTTCTCCATCCGGATCT CCAGCATCACCCCTGCCGACGTGGGCACCTACTACTGCGTGAAGTT CCGGAAGGGCTCCCCCGAGAACGTGGAGTTCAAGTCTGGCCCAGGC ACCGAGATGGCCCTGGGCGCTAAACCTTCTGCCCCTGTGGTGTCTG GACCTGCCGTGCGGGCTACCCCTGAGCACACCGTGTCTTTTACCTG CGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGGTTC AAGAACGGCAACGAGCTGTCCGACTTCCAGACCAACGTGGACCCTG CCGGCGACTCCGTGTCCTACTCCATCCACTCTACCGCCAGAGTGGT GCTGACCAGAGGCGACGTGCACTCCCAAGTGATCTGCGAGATCGCC CATATCACACTGCAGGGCGACCCCCTGAGAGGCACCGCCAATCTGT CTGAGGCCATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCAGCC TATGAGAGCCGAGAACCAGGCCAACGTGACCTGTCAGGTGTCCAAC TTCTACCCTCGGGGCCTGCAGCTGACCTGGCTGGAAAACGGCAATG TGTCCCGGACCGAGACAGCCTCCACCCTGATCGAGAACAAGGACGG CACCTACAATTGGATGTCCTGGCTGCTCGTGAACACCTGTGCCCAC AGGGACGACGTGGTGCTGACATGCCAGGTGGAACACGATGGCCAGC AGGCCGTGTCCAAGTCCTACGCCCTGGAAATCTCCGCCCATCAGAA

		AGAGCACGGCTCCGATATCACCCACGAGGCCGCTCTGGCTCCTACC GCTCCTCTGCTGGTGGCTCTGCTGCTGGGACCTAAGCTGCTGCTGG TCGTGGGCGTGTCCGCCATCTACATCTGCTGGAAGCAGAAGGCCTG A
hSIRP-VγC1βC2β (amino acid sequence)	111	MPVPASWPHLPSPFLLMTLLLGRLTGVAGEEELQMIQPEKLLLVTV GKTATLHCTVTSLLPVGPVLWFRGVGPGRELIYNQKEGHFPRVTTV SDLTKRNNMDFSIRISSITPADVGTYYCVRFRRGSPENVEFKSGPG TEMALGAKPSAPVVSGPAVRATPEHTVSFTCESHGFSPRDITLKWF KNGNELSDFQTNVDPAGDSVSYSIHSTARVVLTRGDVHSQVICEIA HITLQGDPLRGTANLSEAIRVPPTLEVTQQPMRAENQANVTCQVSN FYPRGLQLTWLENGNVSRTETASTLIENKDGTYNWMSWLLVNTCAH RDDVVLTCQVEHDGQQAVSKSYALEISAHQKEHGSDITHEAALAPT APLLVALLLGPKLLLWGVSAI YICWKQKA
hSIRP-VβC1γC2β (nucleotide sequence)	112	ATGCCCGTGCCTGCCTCTTGGCCTCATCTGCCCAGCCCCTTTCTGC TGATGACCCTGCTGCTGGGCAGGCTGACAGGCGTGGCAGGCGAAGA TGAGCTGCAAGTGATCCAGCCCGAGAAGTCCGTGTCTGTGGCCGCT GGCGAGTCTGCCACCCTGAGATGCGCTATGACCTCCCTGATCCCCG TGGGCCCCATCATGTGGTTTAGAGGCGCTGGCGCTGGCAGAGAGCT GATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACCGTG TCCGAGCTGACCAAGCGGAACAACCTGGACTTCTCCATCTCCATCA GCAACATCACCCCTGCCGACGCCGGCACCTACTACTGCGTGAAGTT CCGGAAGGGCTCCCCCGACGACGTGGAGTTCAAATCCGGCGCTGGA ACCGAGCTGTCCGTGCGGGCTAAACCTTCTGCCCCTGTGGTGCTGG GACCTGCCGCTAGAACCACCCCTGAGCACACCGTGTCTTTTACCTG CGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGGTTC AAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACCCTA CCGGCCAGTCCGTGGCCTACTCCATCAGATCCACCGCCAGAGTGGT GCTGGACCCTTGGGATGTGCGGTCCCAAGTGATCTGCGAGGTGGCC CATGTGACACTGCAGGGCGATCCTCTGAGAGGCACCGCCAATCTGT CTGAGGCCATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCAGCC TATGAGAGCCGAGAACCAGGCCAACGTGACCTGCCAGGTGTCCAAC TTCTACCCTCGGGGCCTGCAGCTGACCTGGCTGGAAAACGGCAATG TGTCCCGGACCGAGACAGCCTCCACCCTGATCGAGAACAAGGATGG CACCTACAATTGGATGTCCTGGCTGCTCGTGAACACCTGTGCCCAC CGGGATGACGTGGTGCTGACTTGTCAGGTGGAACACGACGGCCAGC AGGCCGTGTCCAAGTCCTACGCCCTGGAAATCTCCGCCCATCAGAA AGAGCACGGCTCCGATATCACCCACGAGGCCGCTCTGGCTCCTACC GCTCCTCTGCTGGTGGCTCTGCTGCTGGGACCTAAGCTGCTGCTGG TCGTGGGCGTGTCCGCCATCTACATCTGCTGGAAGCAGAAGGCCTG A
hSIRP-VpclvC2p (amino acid sequence)	113	MPVPASWPHLPSPFLLMTLLLGRLTGVAGEDELQVIQPEKSVSVAA GESATLRCAMTSLIPVGPIMWFRGAGAGRELIYNQKEGHFPRVTTV SELTKRNNLDFSIsISNITPADAGTYYCVKFRKGSPDDVEFKSGAG TELSVRAKPSAPVVLGPAARTTPEHTVSFTCESHGFSPRDITLKWF KNGNELSDFQTNVDPTGQSVAYS IRSTARVVLDPWDVRSQVICEVA HVTLQGDPLRGTANLSEAIRVPPTLEVTQQPMRAENQANVTCQVSN FYPRGLQLTWLENGNVSRTETASTLIENKDGTYNWMSWLLVNTCAH RDDWLTCQVEHDGQQAVSKSYALEI SAHQKEHGSDITHEAALAPT APLLVALLLGPKLLLWGVSAI YICWKQKA
hSIRP-VβC1βC2γ (nucleotide sequence)	114	ATGCCCGTGCCTGCCTCTTGGCCTCATCTGCCCAGCCCCTTTCTGC TGATGACCCTGCTGCTGGGCAGGCTGACAGGCGTGGCAGGCGAAGA TGAGCTGCAAGTGATCCAGCCCGAGAAGTCCGTGTCTGTGGCCGCT GGCGAGTCTGCCACCCTGAGATGCGCTATGACCTCCCTGATCCCCG TGGGCCCCATCATGTGGTTTAGAGGCGCTGGCGCTGGCAGAGAGCT GATCTACAACCAGAAAGAGGGCCACTTCCCCAGAGTGACCACCGTG TCCGAGCTGACCAAGCGGAACAACCTGGACTTCTCCATCTCCATCA

		GCAACATCACCCCTGCCGACGCCGGCACCTACTACTGCGTGAAGTT CCGGAAGGGCTCCCCCGACGACGTGGAGTTCAAATCCGGCGCTGGA ACCGAGCTGTCCGTGCGGGCTAAACCTTCTGCCCCTGTGGTGTCTG GACCTGCTGTGCGCGCTACCCCTGAGCACACCGTGTCTTTTACCTG CGAGTCCCACGGCTTCAGCCCTCGGGACATCACCCTGAAGTGGTTC AAGAACGGCAACGAGCTGAGCGACTTCCAGACCAACGTGGACCCTG CCGGCGACTCCGTGTCCTACTCCATCCACTCTACCGCCAGAGTGGT GCTGACCAGAGGCGACGTGCACTCCCAAGTGATCTGCGAGATCGCC CATATCACACTGCAGGGCGACCCCCTGAGAGGCACCGCCAATCTGT CTGAGGCCATCAGAGTGCCCCCCACCCTGGAAGTGACCCAGCAGCC TATGAGAGTGGGCAACCAAGTGAACGTGACCTGCCAAGTGCGGAAG TTCTACCCCCAGTCCCTGCAGCTGACTTGGAGCGAGAATGGCAACG TGTGCCAGAGAGAGACAGCCTCCACCCTGACCGAGAACAAGGACGG AACCTACAACTGGACCTCCTGGTTCCTCGTGAACATCTCCGACCAG CGGGACGACGTGGTGCTGACATGCCAAGTGAAGCACGATGGACAGC TGGCCGTGTCCAAGCGGCTGGCTCTGGAAGTGACAGTGCACCAGAA AGAGCACGGCTCCGACATCACCCACGAGGCCGCTCTGGCTCCTACA GCTCCTCTGCTGGTGGCTCTGCTGCTGGGACCTAAGCTGCTGCTGG TCGTGGGCGTGTCCGCCATCTACATCTGCTGGAAGCAGAAGGCCTG A
hSIRP-VβC1βC2γ (amino acid sequence)	115	MPVPASWPHLPSPFLLMTLLLGRLTGVAGEDELQVIQPERSVSVAA GESATLRCAMTSLIPVGPIMWFRGAGAGRELIYNQKEGHFPRVTTV SELTKRNNLDFSI SISNITPADAGTYYCVKFRKGSPDDVEFKSGAG TELSVRAKPSAPVVSGPAVRATPEHTVSFTCESHGFSPRDITLKWF KNGNELSDFQTNVDPAGDSVSYSIHSTARWLTRGDVHSQVICEIA HITLQGDPLRGTANLSEAIRVPPTLEVTQQPMRVGNQVNVTCQVRK FYPQSLQLTWSENGNVCQRETASTLTENKDGTYNWTSWFLWISDQ RDDVVLTCQVKHDGQLAVSKRLALEVTVHQKEHGSDITHEAALAPT APLLVAL LLGPKLLLW GVSAIYICWKQKA
human SIRPpL (nucleotide sequence)	116	ATGCCTGTGCCTGCCTCTTGGCCTCATCTGCCCTCTCCATTTCTGC TGATGACCCTGCTGCTGGGCAGACTGACAGGTGTTGCTGGCGAAGA GGAACTGCAAGTGATCCAGCCTGACAAGAGCATCTCTGTGGCCGCT GGCGAATCTGCCACACTGCACTGTACCGTGACATCTCTGATCCCTG TGGGCCCCATCCAGTGGTTTAGAGGTGCTGGACCTGGCAGAGAGCT GATCTACAACCAGAAAGAGGGACACTTCCCCAGAGTGACCACCGTG TCCGACCTGACCAAGCGGAACAACATGGACTTCAGCATCCGGATCA GCAACATCACCCCTGCCGATGCCGGCACCTACTACTGCGTGAAGTT CAGAAAGGGCAGCCCCGACCACGTCGAGTTTAAAAGCGGAGCCGGC ACAGAGCTGAGCGTGCGGGCTAAACCTTCTGCTCCTGTGGTGTCTG GACCAGCCGCTAGAGCTACACCTCAGCACACCGTGTCTTTTACCTG CGAGAGCCACGGCTTCAGCCCCAGAGATATCACCCTGAAGTGGTTC AAGAACGGCAACGAGCTGTCCGACTTCCAGACCAATGTGGACCCAG CCGGCGATAGCGTGTCCTACAGCATTCACAGCACCGCCAAGGTGGT GCTGACCCGGGAAGATGTGCACAGCCAAGTGATTTGCGAGGTGGCC CACGTTACCCTGCAAGGCGATCCTCTGAGAGGAACCGCCAACCTGA GCGAGACAATCCGGGTGCCACCTACACTGGAAGTGACCCAGCAGCC TGTGCGGGCCGAGAATCAAGTGAACGTGACCTGCCAAGTGCGGAAG TTCTACCCTCAGAGACTGCAGCTGACCTGGCTGGAAAACGGCAATG TGTCCCGGACCGAGACAGCCAGCACACTGACCGAGAACAAGGATGG CACCTACAATTGGATGAGCTGGCTGCTGGTCAATGTGTCTGCCCAC CGGGACGATGTGAAGCTGACATGCCAGGTGGAACACGATGGCCAGC CTGCCGTGTCTAAGAGCCACGACCTGAAGGTGTCCGCTCATCCCAA AGAGCAGGGCAGCAATACTGCCCCTGGACCTGCTCTTGCTTCTGCC GCTCCTCTGCTGATCGCCTTTCTGCTGGGACCTAAGGTGCTGCTGG TTGTGGGAGTGTCCGTGATCTACGTGTACTGGAAGCAGAAGGCC
human SIRPβL (amino	117	MPVPASWPHLPSPFLLMTLLLGRLTGVAGEEELQVIQPDKSISVAA

acid sequence)		GESATLHCTVTSLIPVGP IQWFRGAGPGREL IYNQKEGHFPRVTTV SDLTKRNNMDFS IRI SNITPADAGTYYCVKFRKGSPDHVEFKSGAG TELSVRAKPSAPVVSGPAARATPQHTVSFTCESHGFSPRD ITLKWF KNGNELSDFQTNVDPAGDSVSYS I HSTAKVVLTREDVHSQVICEVA HVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVRK FYPQRLQLTWLENGNVSRTETASTLTENKDGTYNWMSWLLVNVSAH RDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAPGPALASA APLLIAFLLGPKVLLWGVSVI YVYWKQKA
human IgG 1 constant domains (nucleotide sequence)	118	GCCAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA CTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGG CACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC AAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACA CATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG ACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACC CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGG GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG GTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGG TCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGC CGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCA AGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA
human IgG 1 constant domains (amino acid sequence)	119	ASTKGPSVFPLAP SSKSTSGGTAALGCLVRD YFPEPVTVSWNSGAL TSGVHTFPAVLQS SGLYSLSSWTVP SSSLGTQTYICNVNHKP SNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVWDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR WSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQ VYTLPP SRDELTKNQVSLTCLVKGFYP SDI AVEWE SNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
mouse IgG1 constant domains (amino acid sequence)	120	AKTTPPSVYP LAPGCGDTTGSSVTLGCLVKGYFPESVTVTWNSGSL SSSVHTFPALLQSGLYTMSSSVTVP SSTWPSQTVTCSVAHPASSTT VDKKLEP SGP IST INPCPPCKECHKCPAPNLEGGP SVF IFPPN IKD VLMI SLTPKVTCVWDVSEDDPDVQI SWFVNNVEVHTAQTQTHRED YNST IRWSTLP IQHQDWMSGKEFKCKVNNKDLP SP IERTI SKIKG LVRAPQVYILPPPAEQLSRKDVSLTCLWGFNPGDISVEWTSNGHT EENYKDTAPVLDSDGS YFIYSKLNMKTSKWEKTDSFSCNVRHEGLK NYYLKKTISRSPGR
mouse kappa constant domain (amino acid sequence)	121	RADAAPTVSIFPP SSEQLTSGGASVVCFLNNFYPKD INVKWKIDGS ERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHK TSTSP IVKSFNRNEC
human lgG2 constant domains, V234A-G237A-P238S-H268A-V309L-A330S-P33 IS (Sigma) mutant (amino acid	122	ASTKGPSVFPLAPCSRSTSESTAALGCLVKD YFPEPVTVSWNSGAL TSGVHTFPAVLQS SGLYSLSSVVTVP SSNFGTQTYTCNVDHKP SNT KVDKTVERKCCVECPPCPAPPAAASSVFLFPPKPKDTLMI SRTPEV TCVWDVSAEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKTKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSD IX1VEWESNGQPENNYKTTPP MLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS

sequence)		LSPGK **wherein :** X_1 = A, S
human IgG1 constant domains, L234A-L235A mutant (amino acid sequence)	123	ASTKGPSVFPLAP SSKSTSGGT AALGCLVKDYFPEPVTVSWNS GAL TSGVHTFPAVLQS SGLYSLSSVVTVP SSSLGTQTYICNVNHKP SNT KVDKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMT SR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYR VVSVLTVLHQDWLNGKEYRCKVSNKALPAP IEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
human IgGl constant domains, L234A-L235A-P329G mutant (nucleotide sequence)	124	GCTAGCACAAAGGGCCCTAGTGTGTTTCCTCTGGCTCCCTCTTCCA AATCCACTTCTGGTGGCACTGCTGCTCTGGGATGCCTGGTGAAGGA TTACTTTCCTGAACCTGTGACTGTCTCATGGAACTCTGGTGCTCTG ACTTCTGGTGTCCACACTTTCCCTGCTGTGCTGCAGTCTAGTGGAC TGTACTCTCTGTCATCTGTGGTCACTGTGCCCTCTTCATCTCTGGG AACCCAGACCTACATTTGTAATGTGAACCACAAACCATCCAACACT AAAGTGGACAAAAAAGTGGAACCCAAATCCTGTGACAAAACCCACA CCTGCCCACCTTGTCCGGCGCCTGAAGCGGCGGGAGGACCTTCTGT GTTTCTGTTCCCCCCCAAACCAAAGGATACCCTGATGATCTCGCGA ACCCCTGAGGTGACATGTGTGGTGGTGGATGTGTCTCATGAGGACC CCGAAGTCAAATTTAATTGGTATGTCGACGGCGTCGAGGTGCATAA TGCCAAAACCAAGCCTAGAGAGGAACAGTACAATTCAACCTACAGA GTCGTCAGTGTGCTGACTGTGCTGCATCAGGATTGGCTGAATGGCA AGGAATACAAGTGTAAAGTCTCAAACAAGGCCCTGGGAGCTCCAAT TGAGAAAACAATCTCAAAGGCCAAAGGACAGCCTAGGGAACCCCAG GTCTACACCCTGCCACCTTCGAGAGACGAACTGACCAAAAACCAGG TGTCCCTGACATGCCTGGTCAAAGGCTTCTACCCTTCTGACATTGC TGTGGAGTGGGAGTCAAATGGACAGCCTGAGAACAACTACAAAACA ACCCCCCCCTGTGCTGGATTCTGATGGCTCTTTCTTTCTGTACTCCA AACTGACTGTGGACAAGTCTAGATGGCAGCAGGGGAATGTCTTTTC TTGCTCTGTCATGCATGAGGCTCTGCATAACCAC TACACTCAGAAA TCCCTGTCTCTGTCTCCCGGGAAA
human IgG1 constant domains, L234A-L235A-P329G mutant (amino acid sequence)	125	ASTKGPSVFP LAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQS SGLYSLSSVVTVP SSSLGTQT YICNVNHKP SNT KVDKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMI SR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYR WSVLTVLHQDWLNGKEYKCKVSNKALGAP IEKT ISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
human IgG1 constant domains, N297Q mutant (amino acid sequence)	126	ASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQS SGLYSLSSVVTVP SSSLGTQT YICNVNHKP SNT KVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMT SR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQS TYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAP TEKT ISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK S LSLSPGK
human IgG4 constant domains, S228P-N297Q mutant (amino acid sequence)	127	ASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQS SGLYSLSSVVTVP SSSLGTKTYTCNVDHKP SNT KVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMT SRTPE VTCVWDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRWS VLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYT LPP SQEEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPP

		VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK
18D5 VH (amino acid sequence)	128	QVQLQQPGAELVRPGSSVKLSCKASGYTFTS YWVHWVKQRPIQGLE WIGNIDPSDSDTHYNQKFKDKASLTVDKSSSTAYMQLSSLTFEDSA VYYCVRGGTGTMAWFAYWGQGTLVTVSA
18D5 VL (amino acid sequence)	129	DVVMTQTPLSLPVSLGDQASISCRS SQSLVHSYGNTYLYWYLQKPG QSPKLLI YRVSNRFSGVPDRFSGSGSGTDFTLKI SRVEAEDLGVYF CFQGTHVPYTFGSGTKLEIK
KWAR23 VH (amino acid sequence)	130	EVQLQQSGAELVKPGASVKLSCTASGFNIKDYYIHWVQQRTEQGLE WIGRIDPEDGETKYAPKFQDKATITADTSSNTAYLHLSSLTSEDTA VYYCARWGAYWGQGTLVTVSS
KWAR23 VL (amino acid sequence)	131	QIVLTQSPAIMSASPGEKVTLTCSASSSVSSSYLYWYQQKPGSSPK LWIYSTSNLASGVPARFSGSGSGTS YSLTISSMEAEDAASYFCHQW SSYPRTFGAGTKLELK
rhSIRPa-HIS (amino acid sequence)	132	MEPAGPAPGRLGPLLCLLLAASCAWSGVAGEEELQVIQPDKSVLVA AGETATLRCTATSLIPVGP IQWFRGAGPGRELIYNQKEGHFPRVTT VSDLTKRNNMDFS IRIGNITPADAGTYYCVKFRKGSPDDVEFKSGA GTELSVRAKPSAPWSGPAARATPQHTVSFTCESHGFSPRDITLKW FKNGNELSDFQTNVDPVGESVSYS IHSTAKWLTREDVHSQVICEV AHVTLQGDPLRGTANLSETIRVPPTLEVTQQPVRAENQVNVTCQVR KFYPQRLQLTWLENGNVSRTETASTVTENKDGTYNWMSWLLVNVSA HRDDVKLTCQVEHDGQPAVSKSHDLKVSAHPKEQGSNTAAENTGSN ERHHHHHH

[00418] All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry *(e.g.* Genbank sequences or GenelD entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. This statement of incorporation by reference is intended by Applicants, pursuant to 37 C.F.R. §1.57(b)(1), to relate to each and every individual publication, database entry *(e.g.* Genbank sequences or GenelD entries), patent application, or patent, each of which is clearly identified in compliance with 37 C.F.R. §1.57(b)(2), even if such citation is not immediately adjacent to a dedicated statement of incorporation by reference. The inclusion of dedicated statements of incorporation by reference, if any, within the specification does not in any way weaken this general statement of incorporation by reference. Citation of the references herein is not intended as an admission that the reference is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents. To the extent that the references provide a definition for a claimed term that conflicts with the definitions provided in the instant specification, the definitions provided in the instant specification shall be used to interpret the claimed invention.

[00419] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described

herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00420] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

CLAIMS

1. An antibody or antigen binding fragment thereof that binds to human SIRPa, wherein the antibody or antigen binding fragment comprises one or more, and optionally each, of:

m. a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:69 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, or 3 conservative substitutions,

n. a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:70 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, or 3 conservative substitutions,

o. a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:71 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, or 3 conservative substitutions,

p. a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:72 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, or 3 conservative substitutions,

q. a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:73 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, or 3 conservative substitutions, and

r. a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:74 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, or 3 conservative substitutions.

or wherein the antibody or antigen binding fragment comprises one or more, and optionally each, of:

s. a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:1 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, or 3 conservative substitutions,

t. a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:2 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, or 3 conservative substitutions,

u. a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:3 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, or 3 conservative substitutions,

v. a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:4 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, or 3 conservative substitutions,

w. a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:5 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, or 3 conservative substitutions, and

x. a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:6 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, or 3 conservative substitutions.

2. The antibody or antigen binding fragment of claim 1,

wherein the antibody or antigen binding fragment comprises

each of a heavy chain sequence comprising the amino acid sequence of SEQ ID NO:69 or an amino acid sequence differing from SEQ ID NO: 69 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO:70 or an amino acid sequence differing from SEQ ID NO: 70 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO: 71 or an amino acid sequence differing from SEQ ID NO: 71 by 1, 2, or 3 conservative substitutions;

and/or

each of a light chain sequence comprising the amino acid sequence of SEQ ID NO: 72 or an amino acid sequence differing from SEQ ID NO: 72 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO: 73 or an amino acid sequence differing from SEQ ID NO: 73 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence differing from SEQ ID NO: 74 by 1, 2, or 3 conservative substitutions;

or wherein the antibody or antigen binding fragment comprises

each of a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence differing from SEQ ID NO: 1 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO:2 or an amino acid sequence differing from SEQ ID NO: 2 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO:3 or an amino acid sequence differing from SEQ ID NO: 3 by 1, 2, or 3 conservative substitutions;

and/or

each of a light chain sequence comprising the amino acid sequence of SEQ ID NO:4 or an amino acid sequence differing from SEQ ID NO: 4 by 1, 2, or 3 conservative substitutions; the amino acid sequence of SEQ ID NO:5 or an amino acid sequence differing from SEQ ID NO: 5 by 1, 2, or 3 conservative substitutions; and the amino acid sequence of SEQ ID NO:6 or an amino acid sequence differing from SEQ ID NO: 6 by 1, 2, or 3 conservative substitutions.

3. The antibody or antigen binding fragment of claim 2,

wherein the antibody or antigen binding fragment comprises one or both of:

a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 75 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 78 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 80 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 82 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 84 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 86 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 88 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 102 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto;

and

a light chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 76 or an amino acid sequence at least 90%, 95%, 97%, 98%. or 99% identical thereto,

SEQ ID NO: 90 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 92 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 94 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 96 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 98 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 100 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 104 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto;

or wherein the antibody or antigen binding fragment comprises one or both of:

a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 7 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 10 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 12 or an amino acid sequence at least 90%, 95%, 97%, 98%. or 99% identical thereto,

SEQ ID NO: 14 or an amino acid sequence at least 90%, 95%, 97%, 98%. or 99% identical thereto,

SEQ ID NO: 16 or an amino acid sequence at least 90%, 95%, 97%, 98%. or 99% identical thereto,

SEQ ID NO: 18 or an amino acid sequence at least 90%, 95%, 97%, 98%. or 99% identical thereto, and

SEQ ID NO: 30 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto;

and

a light chain variable region comprising an amino acid sequence selected from the group consisting of:

SEQ ID NO: 8 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 20 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 22 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 24 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

SEQ ID NO: 26 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 28 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and

SEQ ID NO: 32 or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

4. The antibody or antigen binding fragment of claim 3, wherein the antibody or fragment thereof has the following characteristics:

binds to a cell expressing human SIRPaVl protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 **11M**, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about ().3nM or less;

binds to a cell expressing human SIRPαV2 protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about ().3nM or less;

does not appreciably bind to SIRPpi protein at an antibody concentration of 50 nM, preferably 67 nM, and more preferably 100 nM; or alternatively at a concentration that is 10-fold greater, preferably 50-fold greater, more preferably 100-fold greater, and still more preferably 200-fold greater than the antibody's $EC5_0$ for SIRPaVl or SIRPaV2;

inhibits binding between human SIRPa and CD47 with an IC_{50} < 10.0 nM, more preferably < 5.0 nM, still more preferably < 2.5 nM, and most preferably about 1.0 nM or less; and

exhibits a T20 "humanness" score of at least 79, and more preferably 85.

5. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment thereof comprises one of the following combinations of heavy chain sequence / light chain sequence:

SEQ ID NO: 78 / SEQ ID NO: 90,

SEQ ID NO: 78 / SEQ ID NO: 92,

SEQ ID NO: 78 / SEQ ID NO: 94,

SEQ ID NO: 78 / SEQ ID NO: 96,

SEQ ID NO: 78 / SEQ ID NO: 98,

SEQ ID NO: 78 / SEQ ID NO: 100,

SEQ ID NO: 80 / SEQ ID NO: 90,

SEQ ID NO: 80 / SEQ ID NO: 92,

SEQ ID NO: 80 / SEQ ID NO: 94,

SEQ ID NO: 80 / SEQ ID NO: 96,

SEQ ID NO: 80 / SEQ ID NO: 98,

SEQ ID NO: 80 / SEQ ID NO: 100,

SEQ ID NO: 82 / SEQ ID NO: 90,

SEQ ID NO: 82 / SEQ ID NO: 92,

SEQ ID NO: 82 / SEQ ID NO: 94,

SEQ ID NO: 82 / SEQ ID NO: 96,

SEQ ID NO: 82 / SEQ ID NO: 98,

SEQ ID NO: 82 / SEQ ID NO: 100,

SEQ ID NO: 84 / SEQ ID NO: 90,

SEQ ID NO: 84 / SEQ ID NO: 92,

SEQ ID NO: 84 / SEQ ID NO: 94,

SEQ ID NO: 84 / SEQ ID NO: 96,

SEQ ID NO: 84 / SEQ ID NO: 98,

SEQ ID NO: 84 / SEQ ID NO: 100,

SEQ ID NO: 86 / SEQ ID NO: 90,

SEQ ID NO: 86 / SEQ ID NO: 92,

SEQ ID NO: 86 / SEQ ID NO: 94,

SEQ ID NO: 86 / SEQ ID NO: 96,

SEQ ID NO: 86 / SEQ ID NO: 98,

SEQ ID NO: 86 / SEQ ID NO: 100,

SEQ ID NO: 88 / SEQ ID NO: 90,

SEQ ID NO: 88 / SEQ ID NO: 92,

SEQ ID NO: 88 / SEQ ID NO: 94,

SEQ ID NO: 88 / SEQ ID NO: 96,

SEQ ID NO: 88 / SEQ ID NO: 98,

SEQ ID NO: 88 / SEQ ID NO: 100,

SEQ ID NO: 10 / SEQ ID NO: 20,

SEQ ID NO: 10 / SEQ ID NO: 22,

SEQ ID NO: 10 / SEQ ID NO: 24,

SEQ ID NO: 10 / SEQ ID NO: 26,

SEQ ID NO: 10 / SEQ ID NO: 28,

SEQ ID NO: 12 / SEQ ID NO: 20,

SEQ ID NO: 12 / SEQ ID NO: 22,

SEQ ID NO: 12 / SEQ ID NO: 24,

SEQ ID NO: 12 / SEQ ID NO: 26,

SEQ ID NO: 12 / SEQ ID NO: 28,

SEQ ID NO: 14 / SEQ ID NO: 20,

SEQ ID NO: 14 / SEQ ID NO: 22,

SEQ ID NO: 14 / SEQ ID NO: 24,

SEQ ID NO: 14 / SEQ ID NO: 26,

SEQ ID NO: 14 / SEQ ID NO: 28,

SEQ ID NO: 16 / SEQ ID NO: 20,

SEQ ID NO: 16 / SEQ ID NO: 22,

SEQ ID NO: 16 / SEQ ID NO: 24,

SEQ ID NO: 16 / SEQ ID NO: 26,

SEQ ID NO: 16 / SEQ ID NO: 28,

SEQ ID NO: 18 / SEQ ID NO: 20,

SEQ ID NO: 18 / SEQ ID NO: 22,

SEQ ID NO: 18 / SEQ ID NO: 24,

SEQ ID NO: 18 / SEQ ID NO: 26,

SEQ ID NO: 18 / SEQ ID NO: 28,

or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID.

6. The antibody or antigen binding fragment of one of claims 1-5, wherein the antibody is an intact IgG.

7. The antibody or antigen binding fragment of one of claims 1-6, wherein the antibody comprises a wild-type or mutated IgG2 Fc region.

8. The antibody or antigen binding fragment of one of claims 1-6, wherein the antibody comprises a mutated IgGl Fc region.

9. The antibody or antigen binding fragment of one of claims 1-6, wherein the antibody comprises a mutated IgG4 Fc region.

10. An antibody or antigen binding fragment thereof that binds to the same epitope of human SIRPα as an antibody as an antibody according to claim 5.

11. The antibody or antigen binding fragment of any of claims 1-10, wherein the antibody or antigen binding fragment is humanized.

12. The antibody or antigen binding fragment of any of claims 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 10 and each light chain comprises SEQ ID NO: 20.

13. The antibody or antigen binding fragment of any of claims 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 16 and each light chain comprises SEQ ID NO: 28.

14. The antibody or antigen binding fragment of any of claims 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 18 and each light chain comprises SEQ ID NO: 20.

15. The antibody or antigen binding fragment of any of claims 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 90.

16. The antibody or antigen binding fragment of any of claims 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 92.

17. The antibody or antigen binding fragment of any of claims 1-11 that is a humanized antibody that comprises two heavy chains and two light chains, wherein each heavy chain comprises SEQ ID NO: 80 and each light chain comprises SEQ ID NO: 95.

18. The antibody or antigen binding fragment of any one of claims 1-17 that comprises a glycosylation pattern characteristic of expression by a mammalian cell, and optionally is glycosylated by expression from a CHO cell.

19. An isolated polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 75, 78, 80, 82, 84, 86, 88, 76, 90, 92, 94, 96, 98, 100, 102, 104, 7, 10, 12, 14, 16, 18, 30, 8, 20, 22, 24, 26, 28, and 32, or an amino acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

20. An isolated nucleic acid encoding any one of the antibodies or antigen binding fragments of claims 1-18, or any one of the polypeptides of claim 19.

21. An isolated nucleic acid of claim 20 comprising:

a nucleic acid sequence of SEQ ID NO: 77 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 79 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 81 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 83 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 85 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 87 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 101 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 89 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 91 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 93 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 95 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 97 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 99 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 103 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 9 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 11 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 13 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 15 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 17 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 29 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 19 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 21 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 23 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 25 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto,

a nucleic acid sequence of SEQ ID NO: 27 or a nucleic acid sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto, and/or

a nucleic acid sequence of SEQ ID NO: 31 or a nucleic acid sequence at least 90%, 95%, 97%, 98%. or 99% identical thereto.

22. An expression vector comprising the isolated nucleic acid of claim 20 or 21.

23. An expression vector of claim 22, encoding both a heavy chain sequence and a light chain sequence of an anti-SIRPa antibody, the expression vectors comprising the following a first nucleic acid sequence / second nucleic acid sequence selected from the group consisting of:

SEQ ID NO: 77 / SEQ ID NO: 89,

SEQ ID NO: 77 / SEQ ID NO: 91,

SEQ ID NO: 77 / SEQ ID NO: 93,

SEQ ID NO: 77 / SEQ ID NO: 95,

SEQ ID NO: 77 / SEQ ID NO: 97,

SEQ ID NO: 77 / SEQ ID NO: 99,

SEQ ID NO: 79 / SEQ ID NO: 89,

SEQ ID NO: 79 / SEQ ID NO: 91,

SEQ ID NO: 79 / SEQ ID NO: 93,

SEQ ID NO: 79 / SEQ ID NO: 95,

SEQ ID NO: 79 / SEQ ID NO: 97,

SEQ ID NO: 79 / SEQ ID NO: 99,

SEQ ID NO: 81 / SEQ ID NO: 89,

SEQ ID NO: 81 / SEQ ID NO: 91,

SEQ ID NO: 81 / SEQ ID NO: 93,

SEQ ID NO: 81 / SEQ ID NO: 95,

SEQ ID NO: 81 / SEQ ID NO: 97,

SEQ ID NO: 81 / SEQ ID NO: 99,

SEQ ID NO: 83 / SEQ ID NO: 89,

SEQ ID NO: 83 / SEQ ID NO: 91,

SEQ ID NO: 83 / SEQ ID NO: 93,

SEQ ID NO: 83 / SEQ ID NO: 95,

SEQ ID NO: 83 / SEQ ID NO: 97,

SEQ ID NO: 83 / SEQ ID NO: 99,

SEQ ID NO: 85 / SEQ ID NO: 89,

SEQ ID NO: 85 / SEQ ID NO: 91,

SEQ ID NO: 85 / SEQ ID NO: 93,

SEQ ID NO: 85 / SEQ ID NO: 95,

SEQ ID NO: 85 / SEQ ID NO: 97,

SEQ ID NO: 85 / SEQ ID NO: 99,

SEQ ID NO: 87 / SEQ ID NO: 89,

SEQ ID NO: 87 / SEQ ID NO: 91,

SEQ ID NO: 87 / SEQ ID NO: 93,

SEQ ID NO: 87 / SEQ ID NO: 95,

SEQ ID NO: 87 / SEQ ID NO: 97,

SEQ ID NO: 87 / SEQ ID NO: 99,

SEQ ID NO: *9 1* SEQ ID NO: 19,

SEQ ID NO: *9 1* SEQ ID NO: 21,

SEQ ID NO: *9 1* SEQ ID NO: 23,

SEQ ID NO: 9 *1* SEQ ID NO: 25,

SEQ ID NO: *9 1* SEQ ID NO: 27,

SEQ ID NO: 11 / SEQ ID NO: 19,

SEQ ID NO: 11 / SEQ ID NO: 21,

SEQ ID NO: 11 / SEQ ID NO: 23,

SEQ ID NO: 11 / SEQ ID NO: 25,

SEQ ID NO: 11 / SEQ ID NO: 27,

SEQ ID NO: 13 / SEQ ID NO: 19,

SEQ ID NO: 13 / SEQ ID NO: 21,

SEQ ID NO: 13 / SEQ ID NO: 23,

SEQ ID NO: 13 / SEQ ID NO: 25,

SEQ ID NO: 13 / SEQ ID NO: 27,

SEQ ID NO: 15 / SEQ ID NO: 19,

SEQ ID NO: 15 / SEQ ID NO: 21,

SEQ ID NO: 15 / SEQ ID NO: 23,

SEQ ID NO: 15 / SEQ ID NO: 25,

SEQ ID NO: 15 / SEQ ID NO: 27,

SEQ ID NO: 17 / SEQ ID NO: 19,

SEQ ID NO: 17 / SEQ ID NO: 21,

SEQ ID NO: 17 / SEQ ID NO: 23,

SEQ ID NO: 17 / SEQ ID NO: 25, and

SEQ ID NO: 17 / SEQ ID NO: 27,

or, in each case, at least 90%, 95%, 97%, 98%, or 99% identical to a respective SEQ ID NO.

24. A host cell comprising expression vector of claim 22 or 23.

25. A host cell of claim 24 which produces a full length anti-SIRPa antibody.

26. The host cell of one of claims 24 or 25, which is a bacterial cell, a human cell, a mammalian cell, a *Pichia* cell, a plant cell, an HEK293 cell, or a Chinese hamster ovary cell.

27. A composition comprising the antibody or antigen binding fragment of any one of claims 1-18 and a pharmaceutically acceptable carrier or diluent.

28. The composition of claim 27, further comprising a second antibody or antigen binding fragment thereof that induces ADCC and/or ADCP, wherein said antibody or antigen binding

fragment of the invention enhances the antibody-mediated destruction of cells by the second antibody.

29. The composition according to claim 28, wherein the second antibody or antigen binding fragment thereof binds to an antigen selected from the group consisting of AMHR2, AXL, BCMA, CA IX, CD4, CD16, CD19, CD20, CD22, CD30, CD37, CD38, CD40, CD52, CD98, CSFIR, GD2, CCR4, CS1, EpCam, EGFR, EGFRvIII, Endoglin, EPHA2, EphA3, FGFR2b, folate receptor alpha, fucosyl-GMl, HER2, HER3, IL1RAP, kappa myeloma antigen, MS4A1, prolactin receptor, TA-MUC1, and PSMA.

30. The composition according to claim 29, wherein the second antibody or antigen binding fragment thereof is selected from the group consisting of Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinutuzumab, ADCT-502, Hul4.18K322A, Hu3F8, Diiiituximab, Trastuzumab, Cetuximab, Rituximab-RLI, c.60C3-RLI, Hul4.18-IL2, KM2812, AFM13, (CD20)2xCD16, erlotinib (Tarceva), daratumumab, alemtuzumab, pertuzumab, brentuximab, elotuzumab, ibritumomab, ifabotuzumab, farletuzumab, otlertuzumab, caroluximab, epratuzumab, inebilizumab, lumretuzumab, 4G7SDIE, AFM21, AFM22, LY-3022855, SNDX-6352, AFM-13, BI-836826, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, leukoluximab, isatuximab, DS-8895, FPA144, GM102, GSK-2857916, IGN523, IT1208, ADC-1013, CAN-04, XOMA-213, PankoMab-GEX, chKM-4927, IGN003, IGN004, IGN005, MDX-1097, MOR202, MOR-208, oportuzumab, ensituximab, vedotin (Adcetris), ibritumomab tiuxetan, ABBV-838, HuMax-AXL-ADC, and ado-lrastuzumab emtansine (Kadcyla).

31. The composition according to claim 28, wherein the second antibody or antigen binding fragment thereof induces ADCP.

32. The composition according to claim 31, wherein the second antibody or antigen binding fragment thereof is selected from the group consisting of Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinutuzumab, Trastuzumab, Cetuximab, alemtuzumab, ibritumomab, farletuzumab, inebilizumab, lumretuzumab, 4G7SDIE, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, GM102, GSK-2857916, PankoMab-GEX, chKM-4927, MDX-1097, MOR202, and MOR-208.

33. The composition of claim 27, further comprising one or more agents selected from the group consisting of anti-CD27 antibody, anti-CD47 antibody, anti-APRIL antibody, anli-PD-1

antibody, anti-PD-Ll antibody, anti-TIGIT antibody, anti-CTLA4 antibody, anti-CSl antibody, anti-KIR2DL 1/2/3 antibody, anti-CD137 antibody, anti-GITR antibody, anti-PD-L2 antibody, anti-ILTl antibody, anti-ILT2 antibody, anti-ILT3 antibody, anti-ILT4 antibody, anti-ILT5 antibody, anti-ILT6 antibody, anti-ILT7 antibody, anti-ILT8 antibody, anti-CD40 antibody, anti-OX40 antibody, anti-ICOS, anti-KIR2DLl antibody, anti-KIR2DL2/3 antibody, anti-KIR2DL4 antibody, anti-KIR2DL5A antibody, anti-KIR2DL5B antibody, anti-KIR3DLl antibody, anti-KIR3DL2 antibody, anti-KIR3DL3 antibody, anti-NKG2A antibody, anti-NKG2C antibody, anti-NKG2E antibody, anti-4-lBB antibody, anti-TSLP antibody, anti-IL-10 antibody, IL-10 PEGylated IL-10, an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecules (SLAM proteins), an activating NK cell receptor, a Toll like receptor, OX40, CD2, CD7, CD27, CD28, CD30. CD40, ICAM-1, LFA-1 (CD1 la/CD18), 4-1BB (CD137), B7-H3, ICOS (CD278), GITR. BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRFl), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4. VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6. CD49f, ITGAD, CD1 Id, ITGAE, CD103, ITGAL, ITGAM, CD1 lb. ITGAX. CD1 lc, ITGB1, CD29, ITGB2, CD18. ITGB7, NKG2D. NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMFl, CD150, IPO-3), SLAM7, BLAME (SLAMF8), SELPLG (CD162). LTBR, LAT. GADS, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, inhibitor of CD47, an inhibitor of PD-1, an an inhibitor of PD-Ll, an inhibitor of PD-L2, an inhibitor of CTLA4, an inhibitor of TIM3, an inhibitor of LAG3, an inhibitor of CEACAM (e.g., CEACAM-1, -3 and/or -5), an inhibitor of VISTA, an inhibitor of BTLA, an inhibitor of TIGIT, an inhibitor of LAIR1, an inhibitor of IDO, an inhibitor of TDO, an inhibitor of CD160 an inhibitor of TGFR beta, and a cyclic dinculeotide or other STING pathway agonist.

34. A method of producing an antibody or antigen binding fragment comprising:

culturing a host cell comprising a polynucleotide encoding the heavy chain and/or the light chain of any one of the antibodies or antigen binding fragments of claims 1-18 under conditions favorable to expression of the polynucleotide; and optionally,

recovering the antibody or antigen binding fragment from the host cell and/or culture medium.

35. A method for detecting the presence of a SIRPa peptide or a fragment thereof in a sample comprising contacting the sample with an antibody or fragment of any of claims 1-18 and detecting the presence of a complex between the antibody or fragment and the peptide; wherein detection of the complex indicates the presence of the SIRPa peptide.

36. An antibody or antigen binding fragment according to any one of claims 1-18 or a composition according to any one of claims 27-33, for the treatment of cancer or an infectious disease.

37. An antibody or antigen binding fragment of claims 1-18 or a composition according to any one of claims 27-33 for decreasing SIRPa/CD47 signalling in a human subject.

38. A method of treating cancer in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment of any one of claims 1-18, or an expression vector according to one of claims 22 or 23, or a host cell according to one of claims 24-26, or a composition according one of claims 27-33, optionally in association with a further therapeutic agent or therapeutic procedure.

39. A method of treating cancer in a human subject, comprising:

administering to the subject an effective amount of

(i) an antibody or antigen binding fragment thereof that induces ADCC and/or ADCP; and

(ii) an antibody or antigen binding fragment of any one of claims 1-18, or an expression vector according to one of claims 22 or 23, or a host cell according to one of claims 24-26, or a composition according one of claims 27-33, optionally in association with a further therapeutic agent or therapeutic procedure,

wherein the administration of (ii) enhances the antibody-mediated destruction of cells by the antibody or antigen binding fragment thereof that induces ADCC and/or ADCP.

40. The method according to claim 39, wherein the antibody or antigen binding fragment thereof that induces ADCC and/or ADCP binds to an antigen selected from the group consisting of AMHR2, AXL, BCMA, CA IX, CD4, CD16, CD19, CD20, CD22, CD30, CD37, CD38,

CD40, CD52, CD98, CSF1R, GD2, CCR4, CS1, EpCam, EGFR, EGFRvIII, Endoglin, EPHA2, EphA3, FGFR2b, folate receptor alpha, fucosyl-GMl, HER2, HER3, ILIRAP, kappa myeloma antigen, MS4A1, prolactin receptor, TA-MUCl, and PSMA.

41. The method according to claim 40, wherein the antibody or antigen binding fragment thereof that induces ADCC and/or ADCP is selected from the group consisting of Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinuluzumab, ADCT-502, Hul4.18K322A, Hu3F8, Dinituximab, Trastuzumab, Cetuximab, Rituximab-RLI, $_{C}$.60C3-RLI, Hul4.18~IL2, KM2812, AFM13, (CD20)2xCD16, erlotinib (Tarceva), daratumumab, alemtuzumab, pertuzumab, brenluximab, elotuzumab, ibritumomab, ifabotuzumab, farletuzumab, otlertuzumab, caroluximab, epratuzumab, inebilizumab, lumretuzumab, 4G7SDIE, AFM21, AFM22, LY-3022855, SNDX-6352, AFM-13, BI-836826, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, leukotuximab, isatuximab, DS-8895, FPA144, GM102, GSK-2857916, IGN523, IT1208, ADC-1013, CAN-04, XOMA-213, PankoMab-GEX, chKM-4927, IGN003. IGN004, IGN005, MDX-1097, MOR202, MOR-208, oportuzumab, ensituximab, vedotin (Adcetris), ibritumomab tiuxetan, ABBV-838, HuMax-AXL-ADC, and ado-trastuzumab emtansine (Kadcyla).

42. The method according to claim 39 or 40, wherein the second antibody or antigen binding fragment thereof induces ADCP.

43. The method according to claim 42, wherein the second antibody or antigen binding fragment thereof is selected from the group consisting of Rituximab, ublituximab, margetuximab, IMGN-529, SCT400, veltuzumab, Obinuluzumab, Trastuzumab, Cetuximab, alemtuzumab, ibritumomab, farletuzumab, inebilizumab, lumretuzumab, 4G7SDIE, BMS-986012, BVX-20, mogamulizumab, ChiLob-7/4, GM102, GSK-2857916, PankoMab-GEX, chKM-4927, MDX-1097, MOR202, and MOR-208.

44. A method of treating an infection or infectious disease in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment of any one of claims 1-18, or an expression vector according to one of claims 22 or 23, or a host cell according to one of claims 24-26, or a composition according one of claims 27-33, optionally in association with a further therapeutic agent or therapeutic procedure.

45. An antibody having one or more of the following characteristics:

binds human SIRPaV1 protein having the sequence of SEQ ID NO: 34 with an EC_{50} < 1 nM; exhibits at least a 100-fold higher EC_{50} for SIRPaV1 (P74A) having the sequence of SEQ ID NO: 62; and exhibits at least a 100-fold higher EC_{50} for human SIRPpl protein having the sequence of SEQ ID NO: 38, preferably when measured by cellular ELISA;

binds to a cell expressing human SIRPaV1 protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about 0.3 nM or less;

binds to a cell expressing human SIRPaV2 protein with an EC_{50} < 10 nM, preferably < 5 nM, more preferably < 1.5 nM, still more preferably < 1.0 nM, even more preferably < 0.5 nM, and most preferably about ().3nM or less;

does not appreciably bind to SIRPpi protein at an antibody concentration of 50 nM, preferably 67 nM, and more preferably 100 nM; or alternatively at a concentration that is 10-fold greater, preferably 50-fold greater, more preferably 100-fold greater, and still more preferably 200-fold greater than the antibody's EC_{50} for SIRPaV1 or SIRPaV2;

inhibits binding between human SIRPa and CD47 with an IC_{50} < 10.0 nM, more preferably < 5.0 nM, still more preferably < 2.5 nM, and most preferably about 1.0 nM or less; and

exhibits a T20 "humanness" score of at least 79, and more preferably 85.

46. The antibody or antigen binding fragment of claim 45 that binds human SIRPaV1 protein having the sequence of SEQ ID NO: 34 with an EC_{50} < 1 nM; exhibits at least a 100-fold higher EC_{50} for SIRPaV1 (P74A) having the sequence of SEQ ID NO: 62; and exhibits at least a 100-fold higher EC_{50} for human SIRPβ1 protein having the sequence of SEQ ID NO: 38.

47. The antibody or antigen binding fragment of claim 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 20 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 10 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

48. The antibody or antigen binding fragment of claim 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 28 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 16 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

49. The antibody or antigen binding fragment of claim 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 20 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and and one or two heavy chains comprising SEQ ID NO: 18 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

50. The antibody or antigen binding fragment of claim 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 90 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 80 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

51. The antibody or antigen binding fragment of claim 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 92 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and one or two heavy chains comprising SEQ ID NO: 80 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

52. The antibody or antigen binding fragment of claim 45 or 46 that comprises one or two light chains comprising SEQ ID NO: 96 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto and and one or two heavy chains comprising SEQ ID NO: 80 or a sequence at least 90%, 95%, 97%, 98%, or 99% identical thereto.

53. The antibody or antigen binding fragment of one of claims 45-52, wherein the antibody is an intact IgG.

54. The antibody or antigen binding fragment of one of claims 45-52, wherein the antibody comprises a wild-type or mutated IgG2 Fc region.

55. The antibody or antigen binding fragment of one of claims 45-52, wherein the antibody comprises a mutated IgG1 Fc region.

56. The antibody or antigen binding fragment of one of claims 45-52, wherein the antibody comprises a mutated IgG4 Fc region.

57. An antibody or antigen binding fragment thereof that binds to the same epitope of human SIRPa as an antibody as an antibody according to one of claims 45-52.

58. The antibody or antigen binding fragment of any of claims 45-52, wherein the antibody or antigen binding fragment is humanized.

59. A composition comprising the antibody or antigen binding fragment of any one of claims 45-52 and a pharmaceutically acceptable carrier or diluent.

60. An antibody or antigen binding fragment according to any one of claims 45-52 or a composition according to claim 59, for the treatment of cancer or an infectious disease.

61. An antibody or antigen binding fragment according to any one of claims 45-52 or a composition according to claim 59 for decreasing SIRPa/CD47 signalling in a human subject.

62. A method of treating cancer in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment according to any one of claims 45-52 or a composition according to claim 59, optionally in association with a further therapeutic agent or therapeutic procedure.

63. A method of treating an infection or infectious disease in a human subject, comprising administering to the subject an effective amount of an antibody or antigen binding fragment according to any one of claims 45-52 or a composition according to claim 59, optionally in association with a further therapeutic agent or therapeutic procedure.

FIG. 1

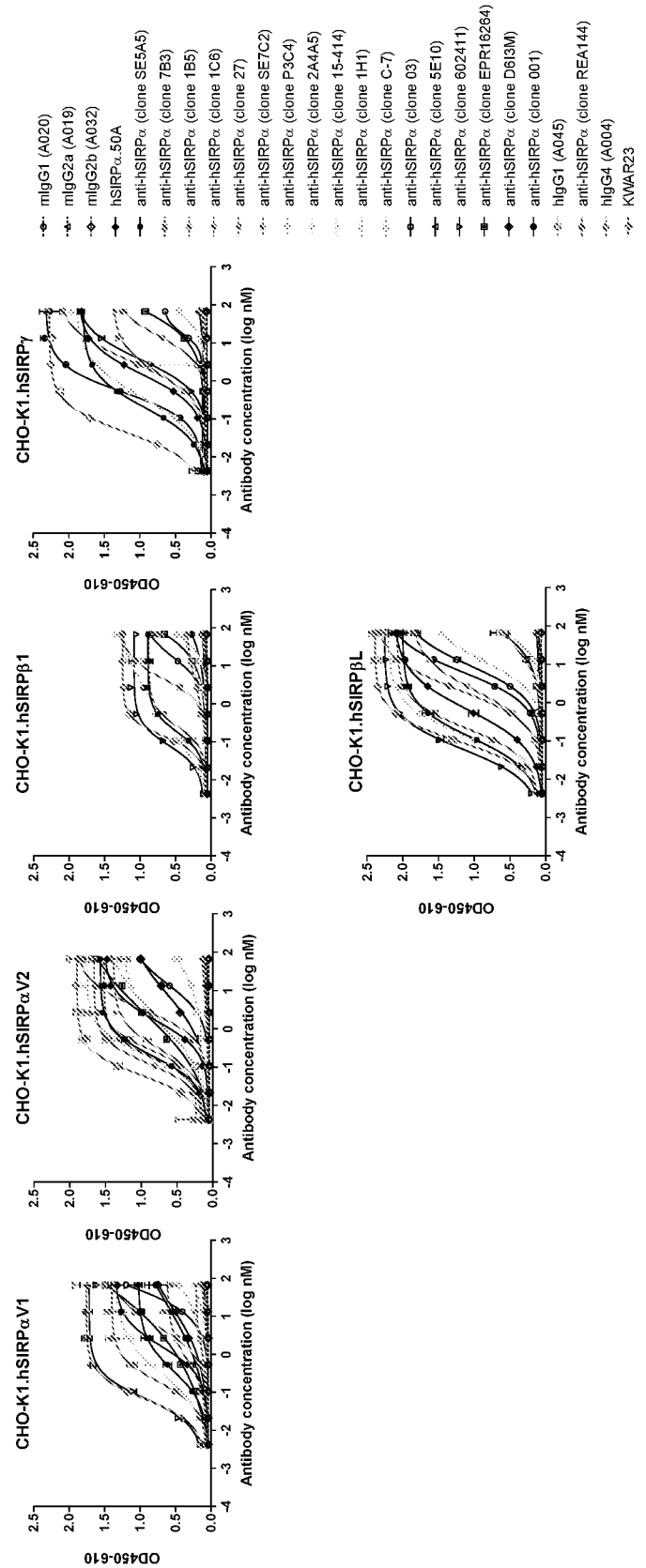

CHO-K1.hSIRPγ
CHO-K1.hSIRPβ1
CHO-K1.hSIRPβL
CHO-K1.hSIRPαV2
CHO-K1.hSIRPαV1
OD450-610
Antibody concentration (log nM)
mIgG1 (A020)
mIgG2a (A019)
mIgG2b (A032)
hSIRPα.50A
anti-hSIRPα (clone SE5A5)
anti-hSIRPα (clone 7B3)
anti-hSIRPα (clone 1B5)
anti-hSIRPα (clone 1C6)
anti-hSIRPα (clone 27)
anti-hSIRPα (clone SE7C2)
anti-hSIRPα (clone P3C4)
anti-hSIRPα (clone 2A4A5)
anti-hSIRPα (clone 15-414)
anti-hSIRPα (clone 1H1)
anti-hSIRPα (clone C-7)
anti-hSIRPα (clone 03)
anti-hSIRPα (clone 5E10)
anti-hSIRPα (clone 602411)
anti-hSIRPα (clone EPR16264)
anti-hSIRPα (clone D6I3M)
anti-hSIRPα (clone 001)
hIgG1 (A045)
anti-hSIRPα (clone REA144)
hIgG4 (A004)
KWAR23

FIG. 2

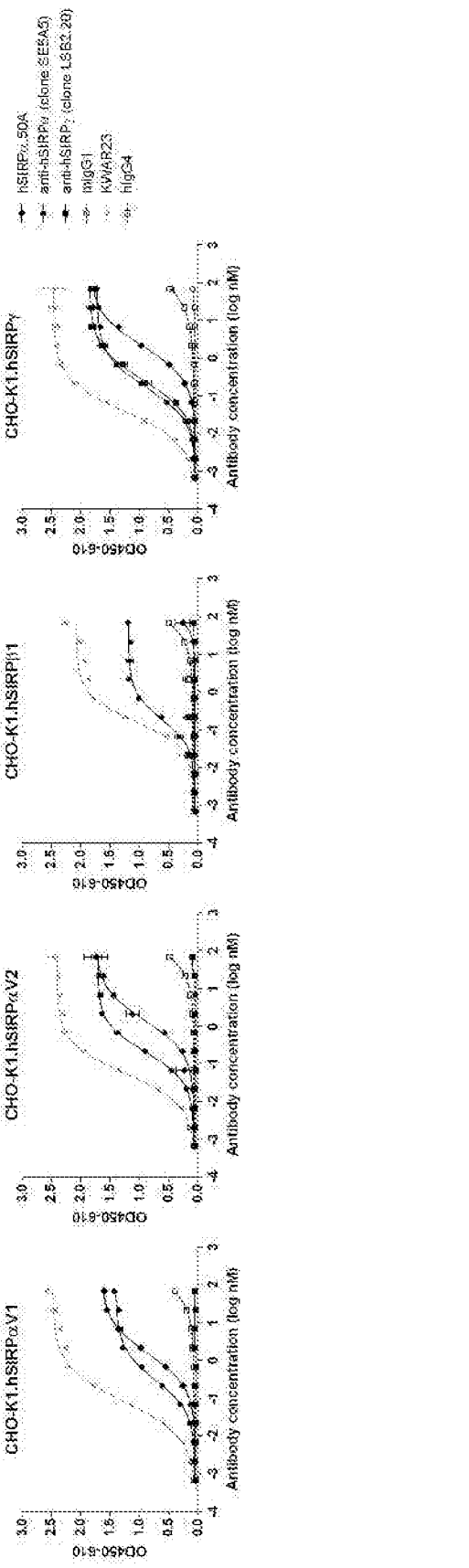
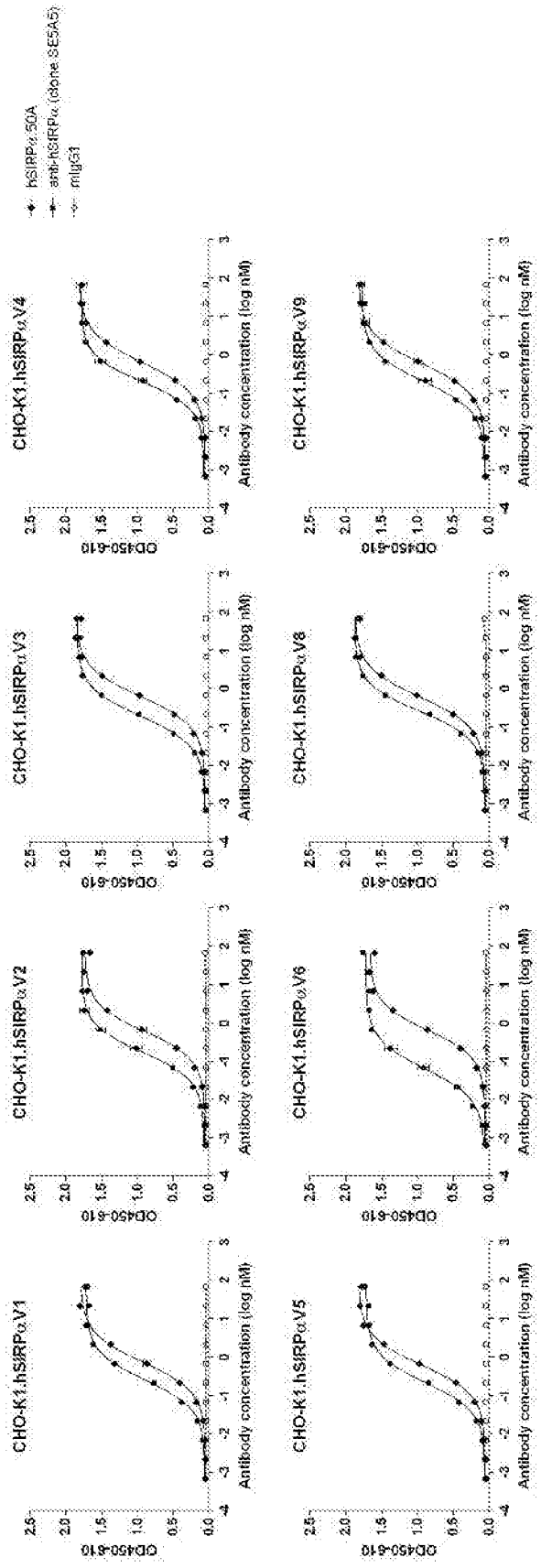

CHO-K1.hSIRPαV1
CHO-K1.hSIRPαV2
CHO-K1.hSIRPβ1
CHO-K1.hSIRPγ
OD450-610
Antibody concentration (log nM)
hSIRPα.SDA
anti-hSIRPα (clone.SE5A5)
anti-hSIRPγ (clone.LSB2.20)
mIgG1
KWAR23
hIgG4

FIG. 3


hSIRPα.50A
anti-hSIRPα (clone SE5A5)
mIgG1
CHO-K1.hSIRPαV1
CHO-K1.hSIRPαV2
CHO-K1.hSIRPαV3
CHO-K1.hSIRPαV4
CHO-K1.hSIRPαV5
CHO-K1.hSIRPαV6
CHO-K1.hSIRPαV8
CHO-K1.hSIRPαV9
OD450-610
Antibody concentration (log nM)

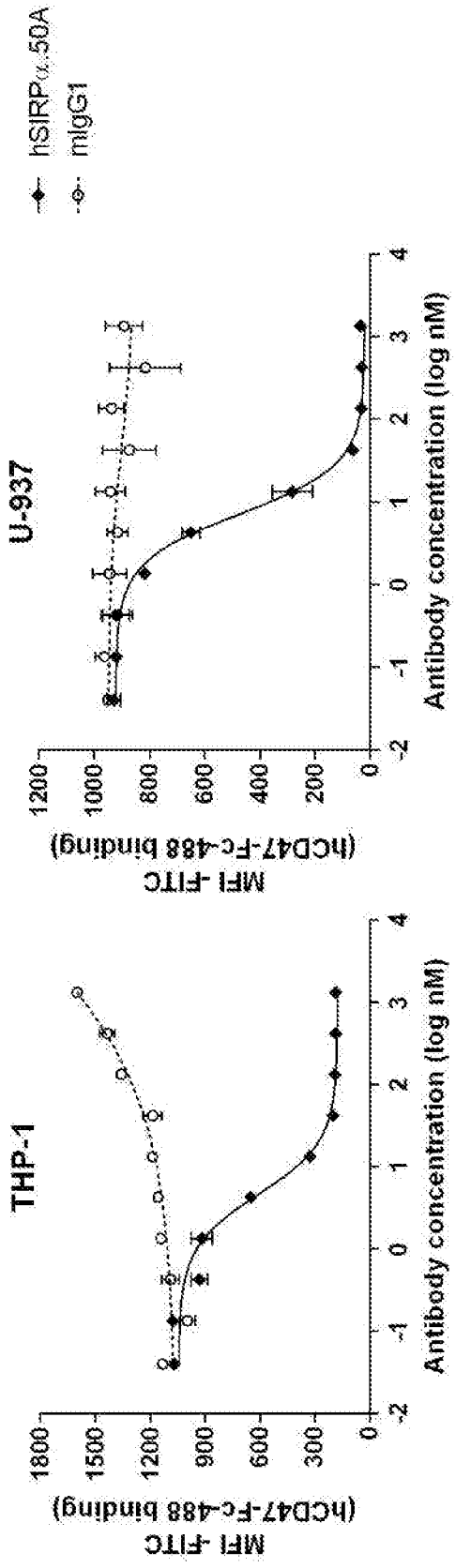
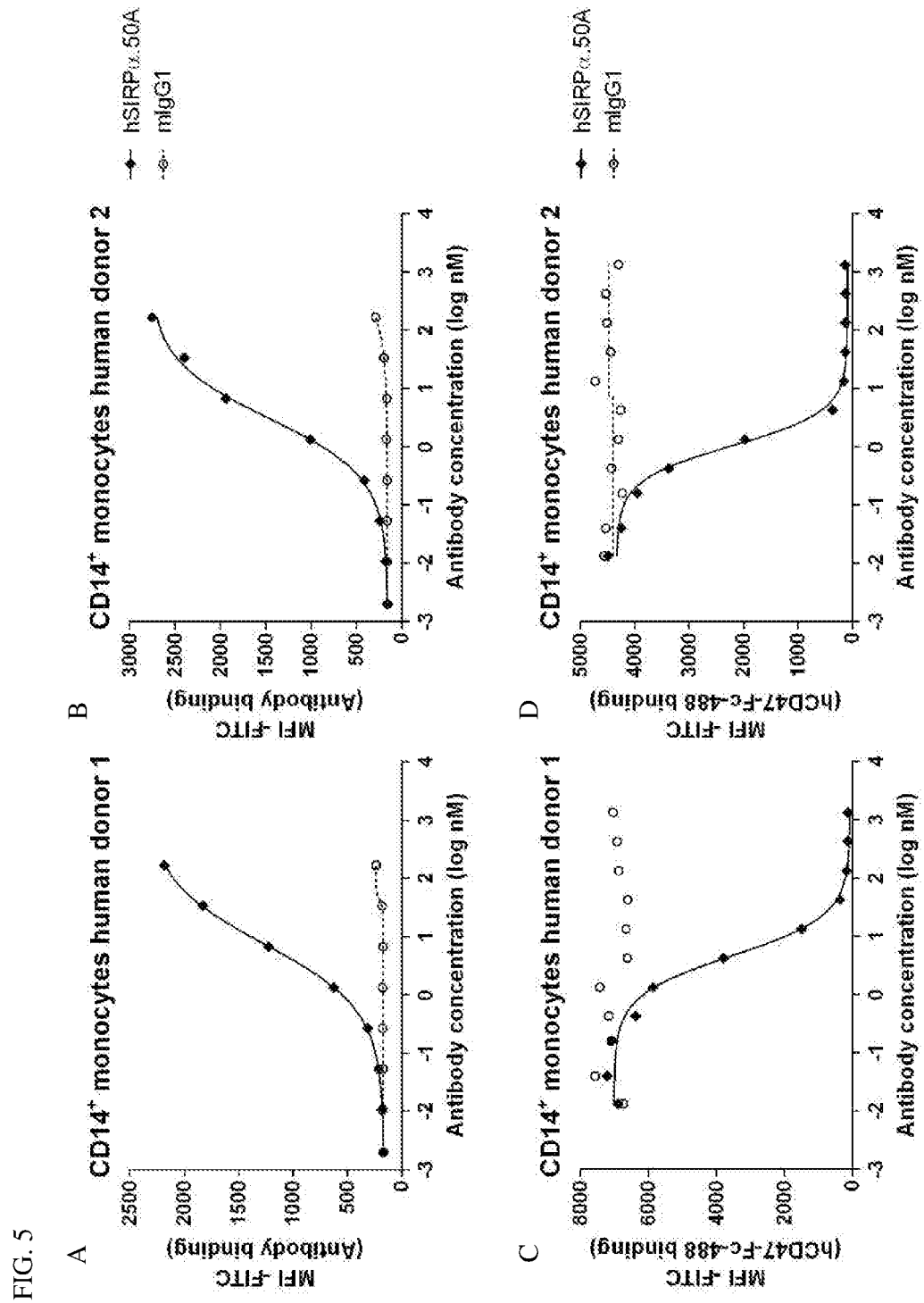

hSIRPα.50A
mIgG1
U-937
THP-1
MFI -FITC
(hCD47-Fc-488 binding)
Antibody concentration (log nM)
0
200
400
600
800
1000
1200
300
900
1500
1800
-2
-1
0
1
2
3
4

FIG. 4

FIG. 5


A
CD14+ monocytes human donor 1
MFI -FITC (Antibody binding)
Antibody concentration (log nM)
B
CD14+ monocytes human donor 2
hSIRPα.50A
mIgG1
MFI -FITC (Antibody binding)
Antibody concentration (log nM)
C
CD14+ monocytes human donor 1
MFI -FITC (hCD47-Fc-488 binding)
Antibody concentration (log nM)
D
CD14+ monocytes human donor 2
hSIRPα.50A
mIgG1
MFI -FITC (hCD47-Fc-488 binding)
Antibody concentration (log nM)

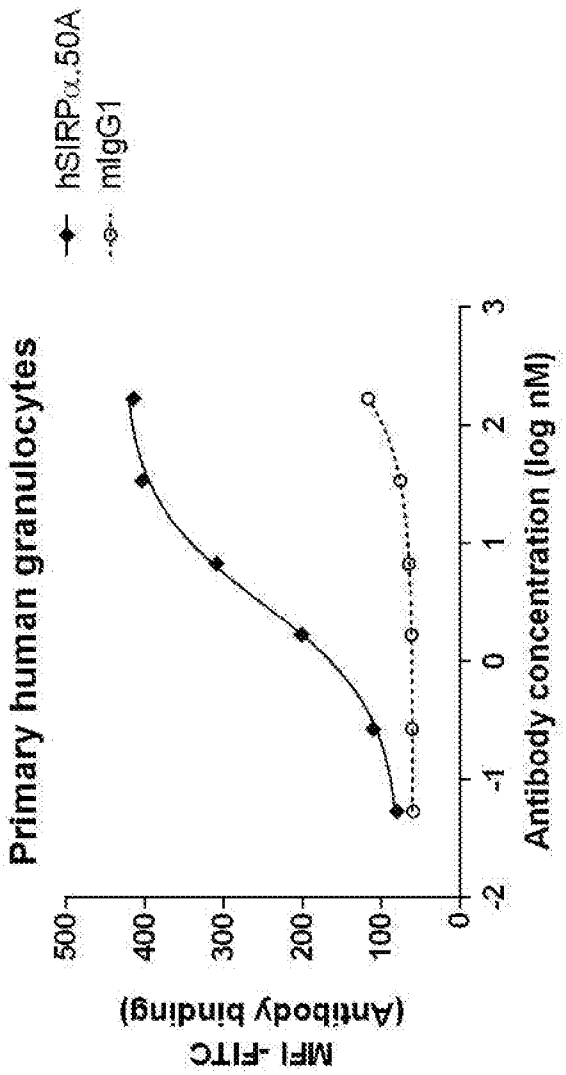

Primary human granulocytes
hSIRPα.50A
mIgG1
MFI -FITC
(Antibody binding)
500
400
300
200
100
0
-2
-1
0
1
2
3
Antibody concentration (log nM)

FIG. 6A

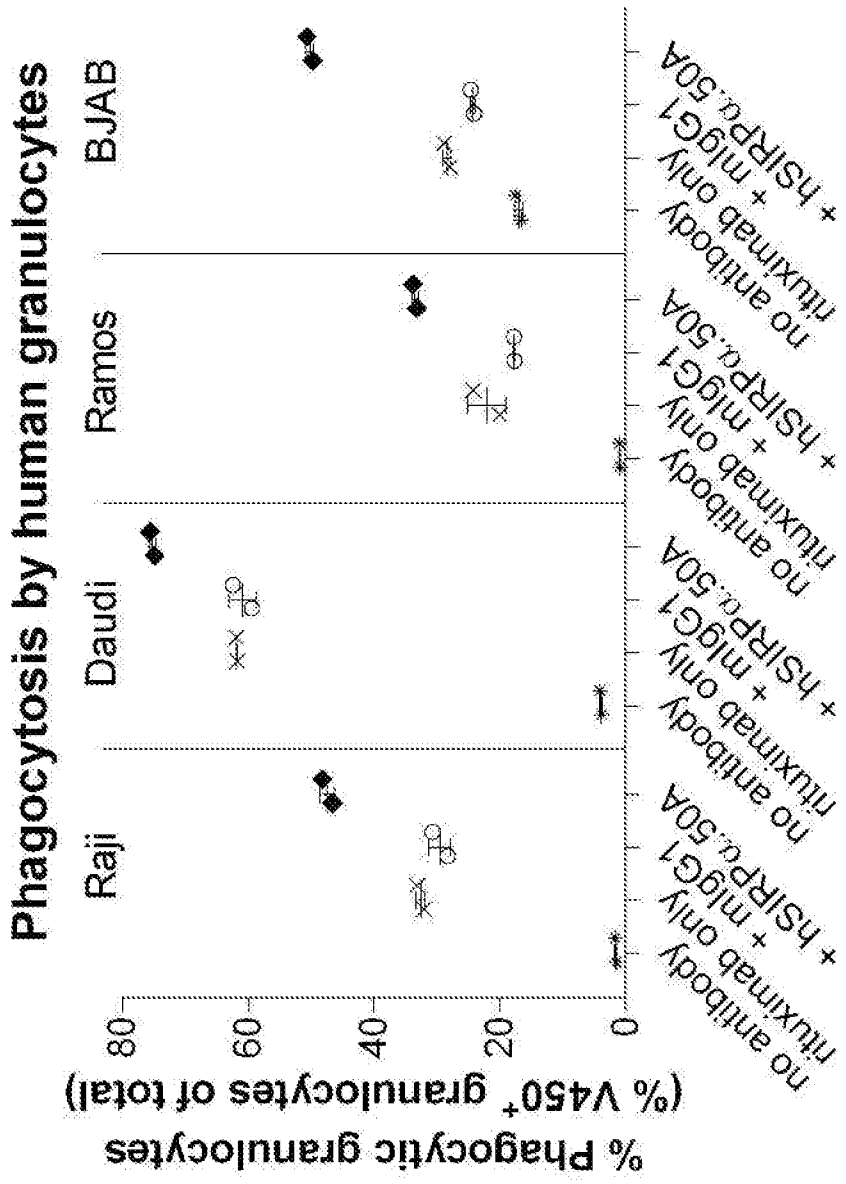

Phagocytosis by human granulocytes
Raji
Daudi
Ramos
BJAB
% Phagocytic granulocytes
(% V450+ granulocytes of total)
0
20
40
60
80
no antibody
rituximab only
mIgG1 + hSIRPα.50A
rituximab + mIgG1 + hSIRPα.50A

FIG. 6B

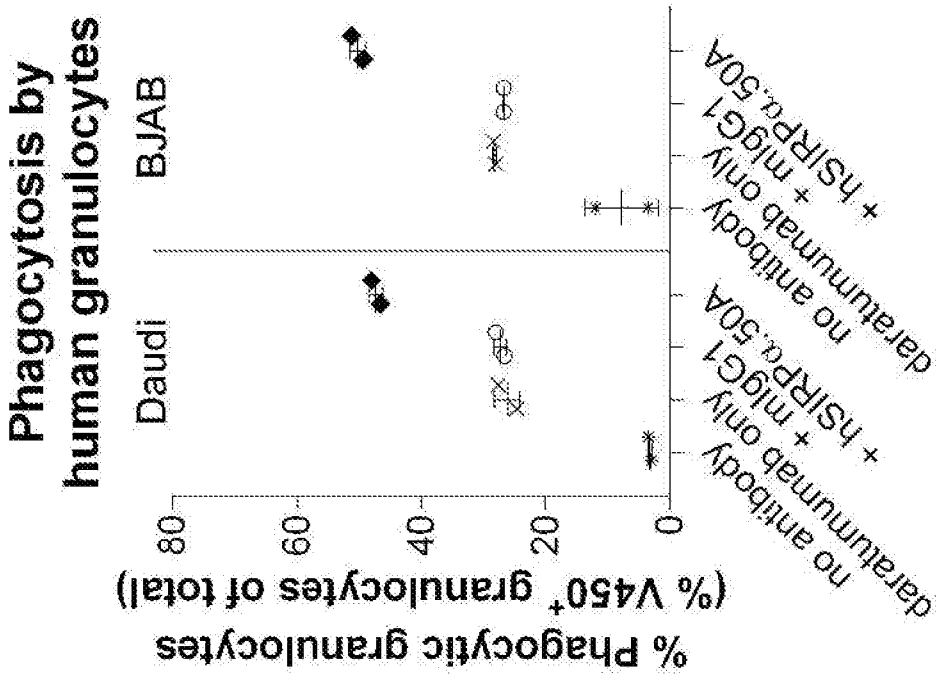

Phagocytosis by human granulocytes
Daudi
BJAB
% Phagocytic granulocytes (% V450+ granulocytes of total)
0
20
40
60
80
daratumumab
no antibody
daratumumab + mIgG1
no antibody + mIgG1
daratumumab + hSIRPα.50A
no antibody + hSIRPα.50A

FIG. 6C

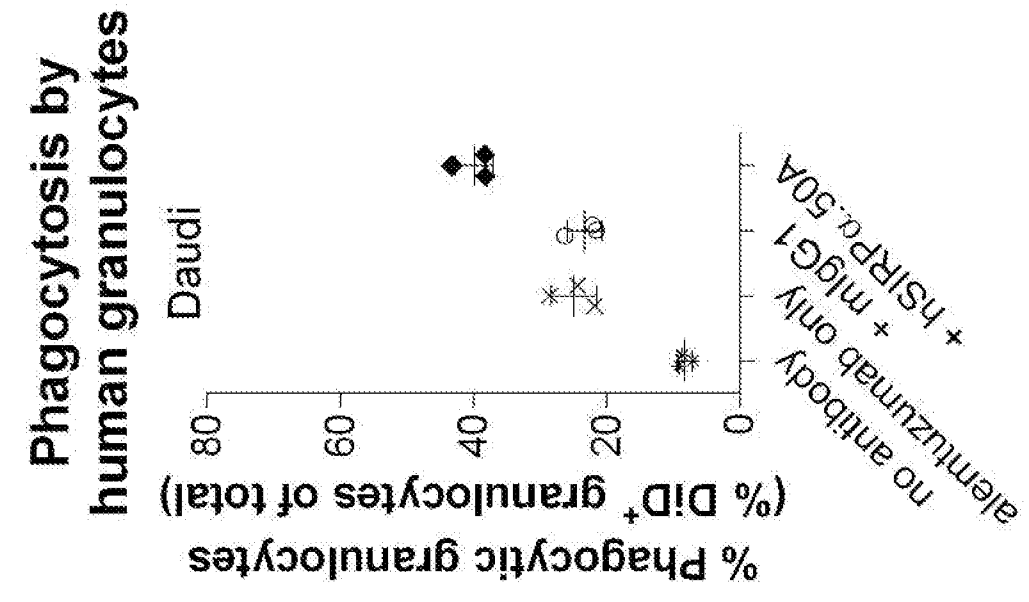

Phagocytosis by
human granulocytes
Daudi
% Phagocytic granulocytes
(% DiD+ granulocytes of total)
80
60
40
20
0
no antibody
alemtuzumab only
+ migG1
+ hSIRPα_50A

FIG. 6D

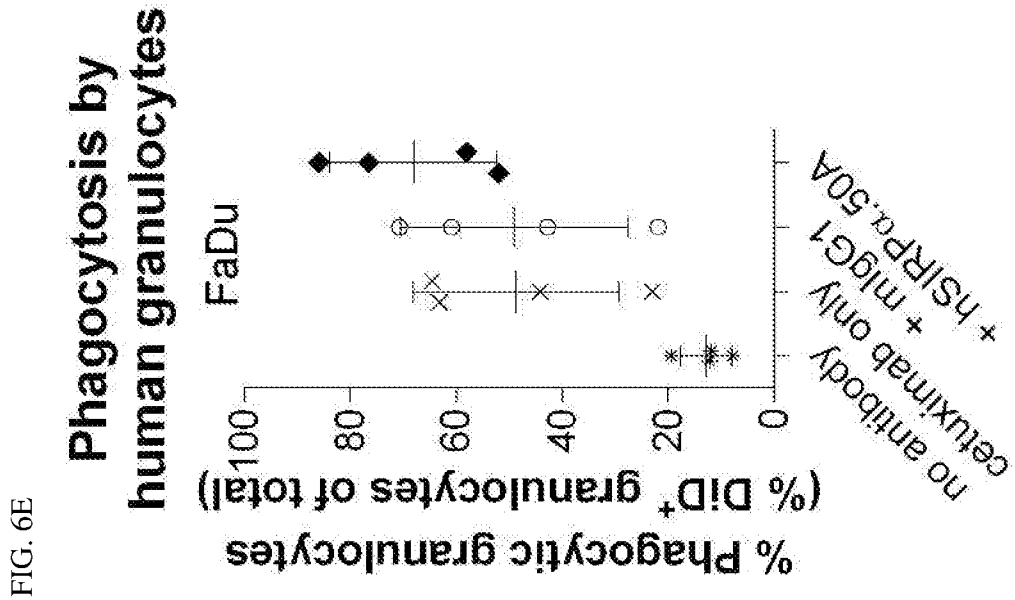

Phagocytosis by human granulocytes
FaDu
% Phagocytic granulocytes (% DiD+ granulocytes of total)
100
80
60
40
20
0
no antibody
cetuximab only
+ mIgG1
+ hSIRPα.50A

FIG. 6E

FIG. 7

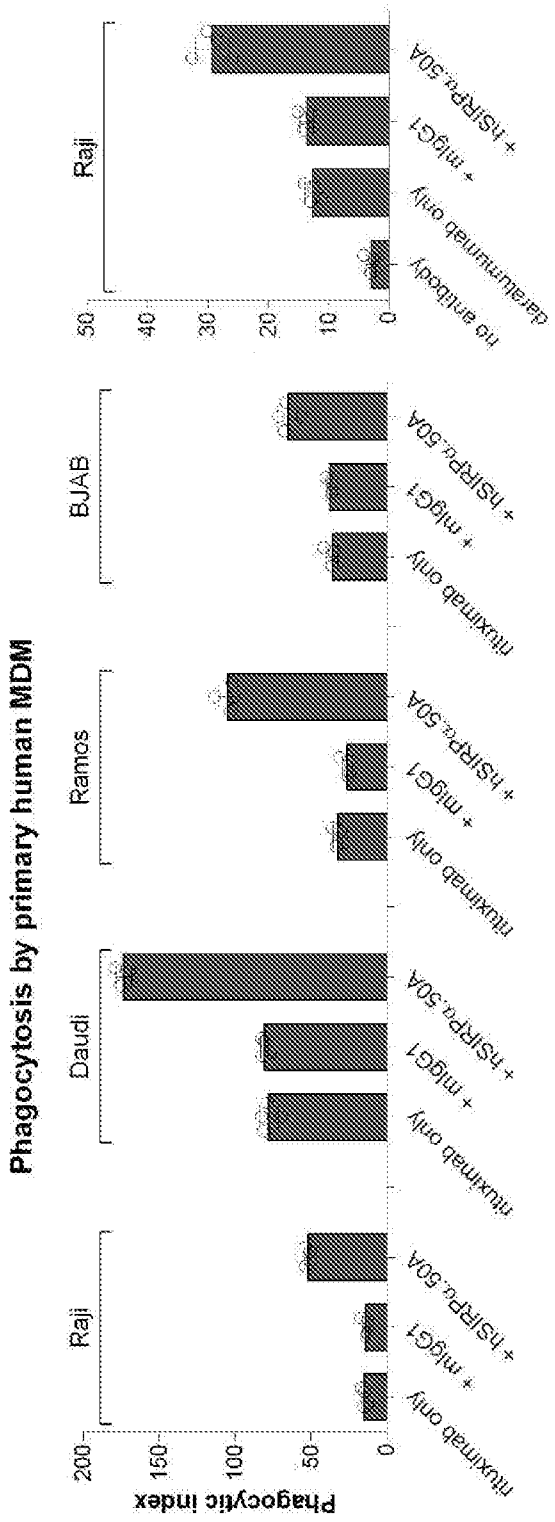

Phagocytosis by primary human MDM
Phagocytic index
200
150
100
50
0
Raji
Daudi
Ramos
BJAB
Raji
50
40
30
20
10
0
rituximab only
+ mIgG1
+ hSIRPα.50A
no antibody
daratumumab only
+ mIgG1
+ hSIRPα.50A

FIG. 8

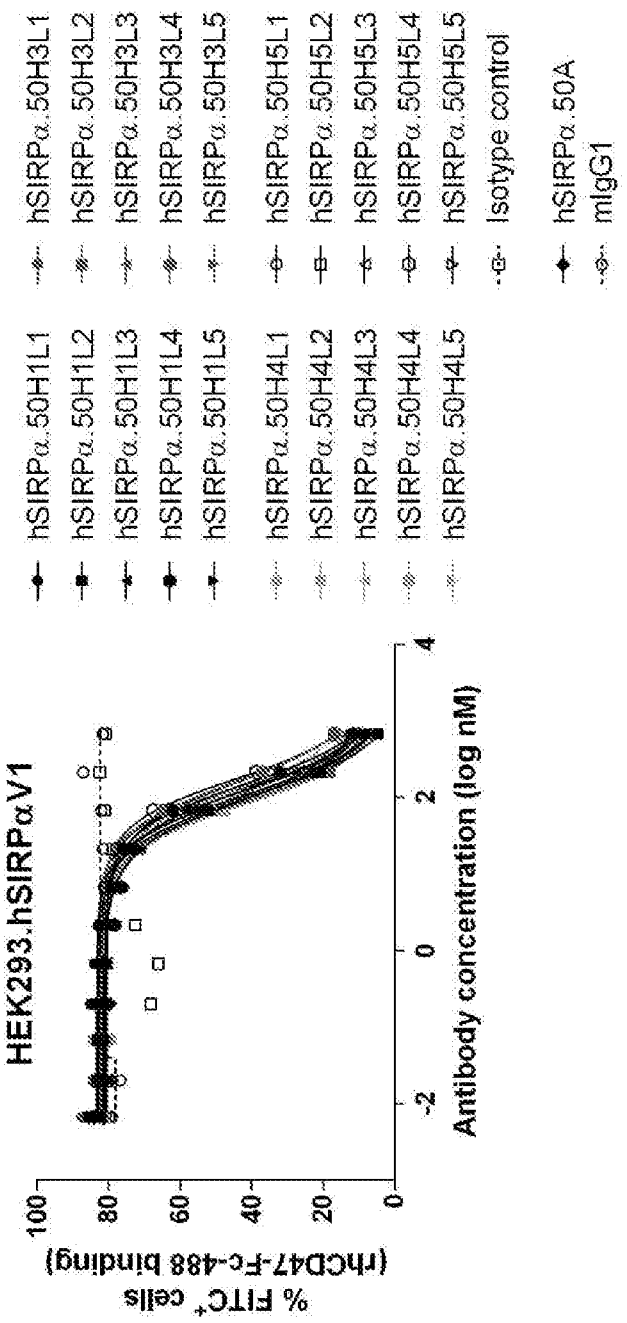

HEK293.hSIRPαV1
% FITC+ cells
(rhCD47-Fc-488 binding)
100
80
60
40
20
0
-2
0
2
4
Antibody concentration (log nM)
hSIRPα.50H1L1
hSIRPα.50H1L2
hSIRPα.50H1L3
hSIRPα.50H1L4
hSIRPα.50H1L5
hSIRPα.50H4L1
hSIRPα.50H4L2
hSIRPα.50H4L3
hSIRPα.50H4L4
hSIRPα.50H4L5
hSIRPα.50H3L1
hSIRPα.50H3L2
hSIRPα.50H3L3
hSIRPα.50H3L4
hSIRPα.50H3L5
hSIRPα.50H5L1
hSIRPα.50H5L2
hSIRPα.50H5L3
hSIRPα.50H5L4
hSIRPα.50H5L5
Isotype control
hSIRPα.50A
mIgG1

FIG. 9

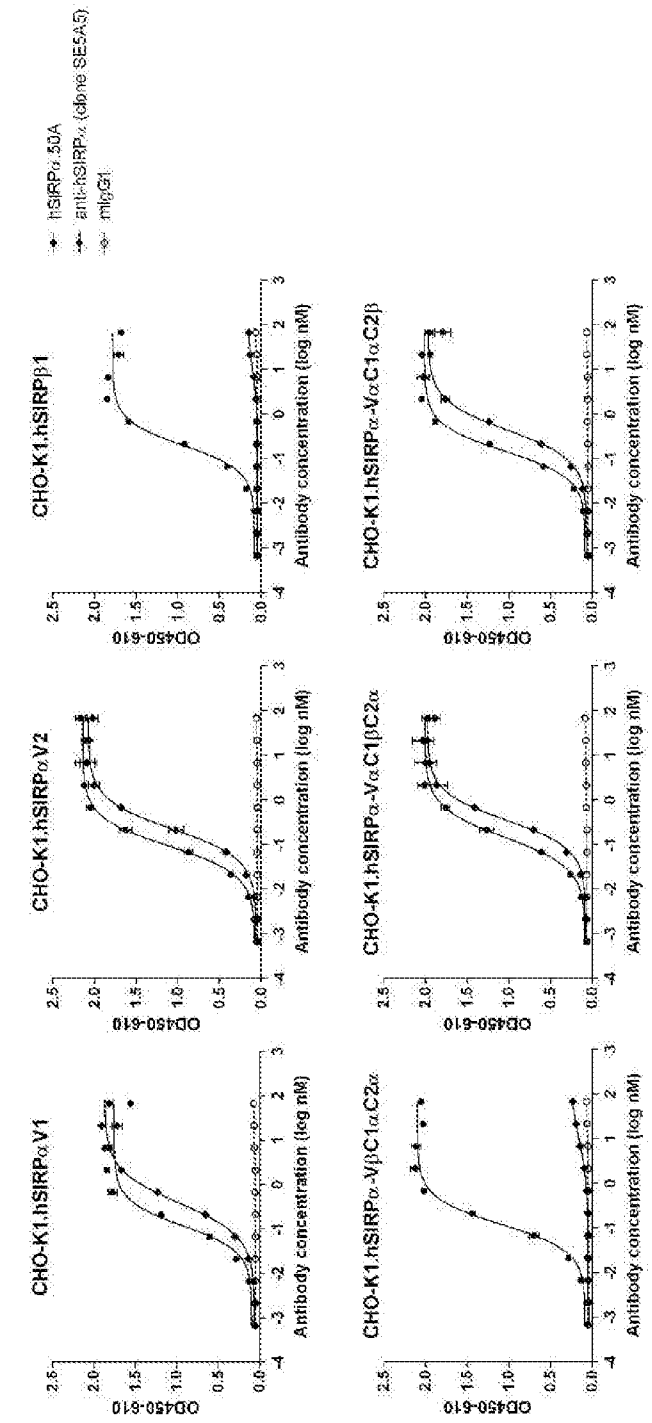

hSIRPα 50A
anti-hSIRPα (clone SE5A5)
mIgG1
CHO-K1.hSIRPα V1
CHO-K1.hSIRPα V2
CHO-K1.hSIRPβ1
CHO-K1.hSIRPα-VβC1αC2α
CHO-K1.hSIRPα-VαC1βC2α
CHO-K1.hSIRPα-VαC1αC2β
OD450-610
Antibody concentration (log nM)

FIG. 10A

```
hSIRPαV1    EEELQVIQPDKSVLVAAGETATLRCTATSLIPVGPIQWFRGAGPGRELIYNQKEGHFPRV
hSIRPαV2    EEELQVIQPDKSVSVAAGESAILHCTVTSLIPVGPIQWFRGAGPARELIYNQKEGHFPRV
hSIRPβ1     EDELQVIQPEKSVSVAAGESATLRCAMTSLIPVGPIMWFRGAGAGRELIYNQKEGHFPRV
            *:*******:*** ******:* *:*: ********* ****** .***************

hSIRPαV1    TTVSDLTKRNNMDFSIRIGNITPADAGTYYCVKFRKGSPDDVEFKSG
hSIRPαV2    TTVSESTKRENMDFSISISNITPADAGTYYCVKFRKGSPD-TEFKSG
hSIRPβ1     TTVSELTKRNNLDFSISISNITPADAGTYYCVKFRKGSPDDVEFKSG
            ****: ***:*:**** *.********************** .*****
```

FIG. 10B

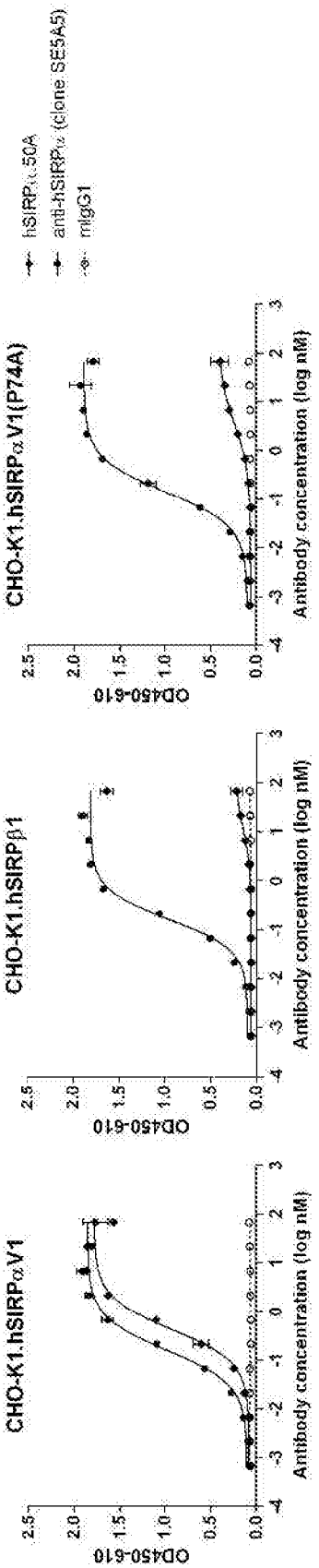

CHO-K1.hSIRPαV1
CHO-K1.hSIRPβ1
CHO-K1.hSIRPαV1(P74A)
hSIRPα.50A
anti-hSIRPα (clone SE5A5)
mIgG1
OD450-610
Antibody concentration (log nM)

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FIG. 11

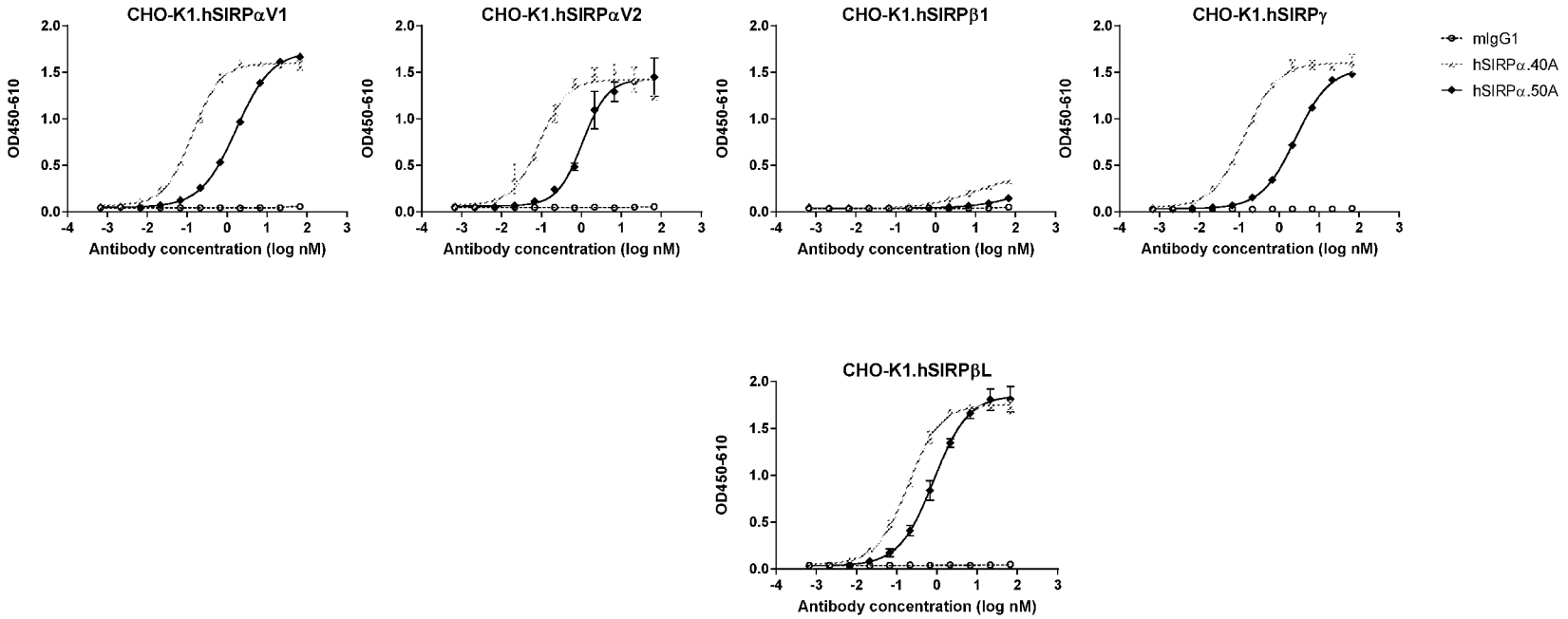

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FIG. 12

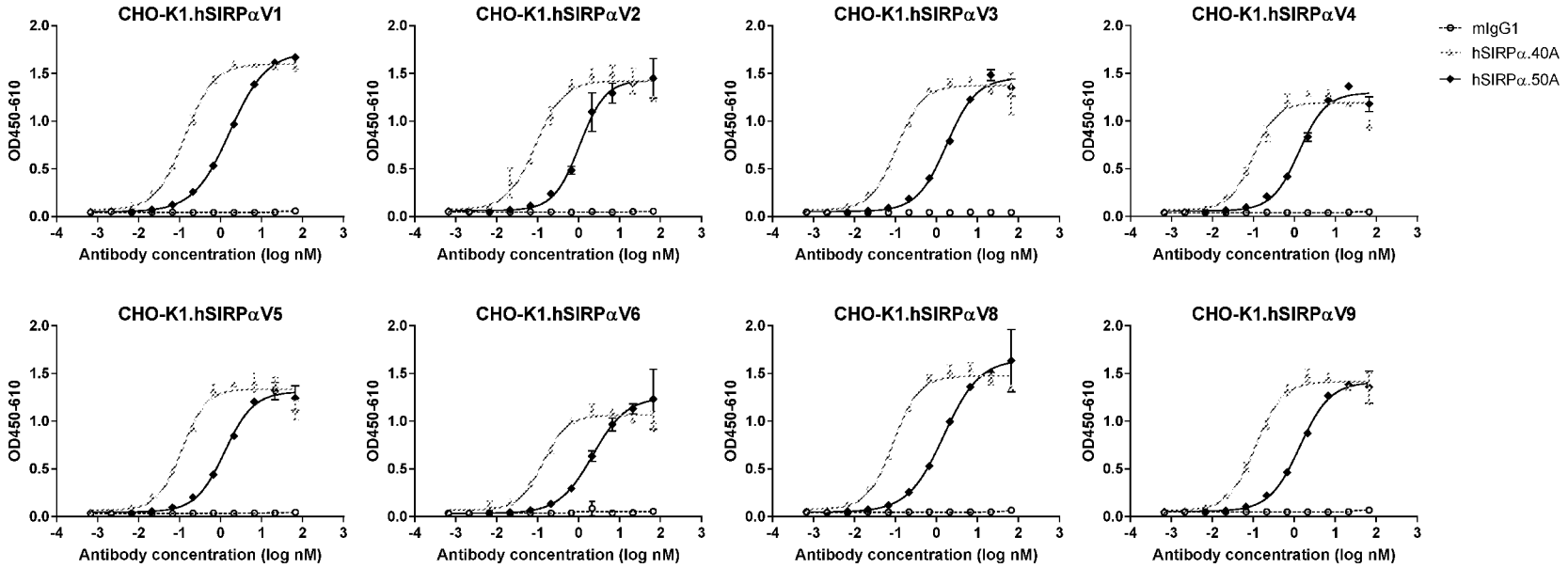

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FIG. 13

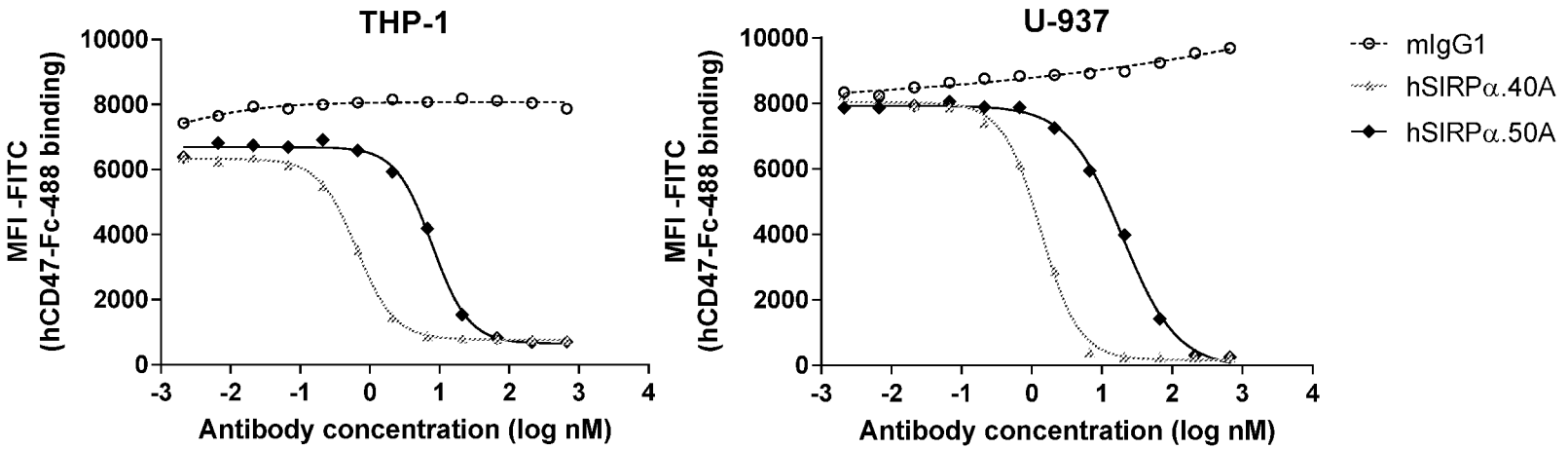


FIG. 14

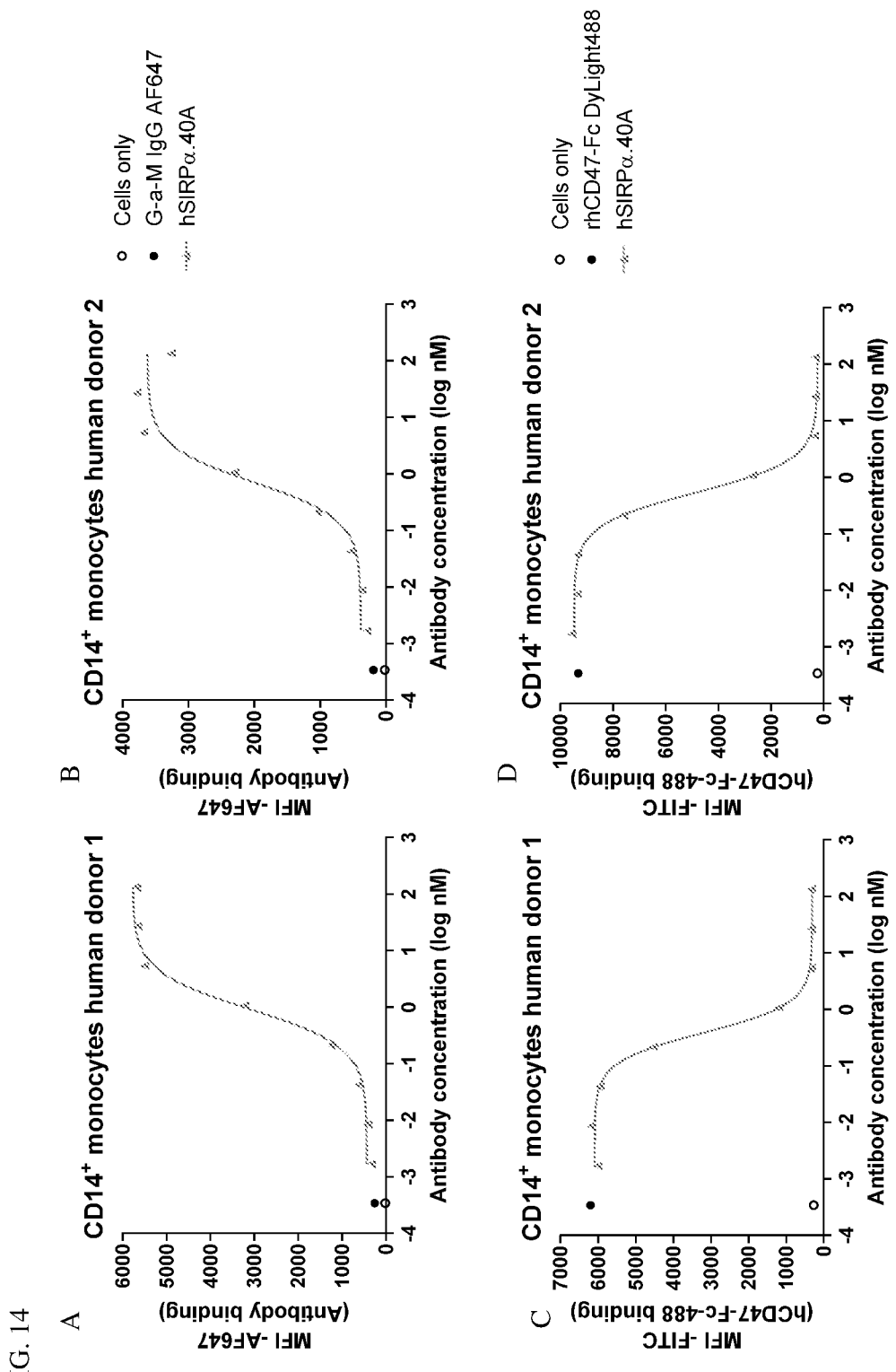
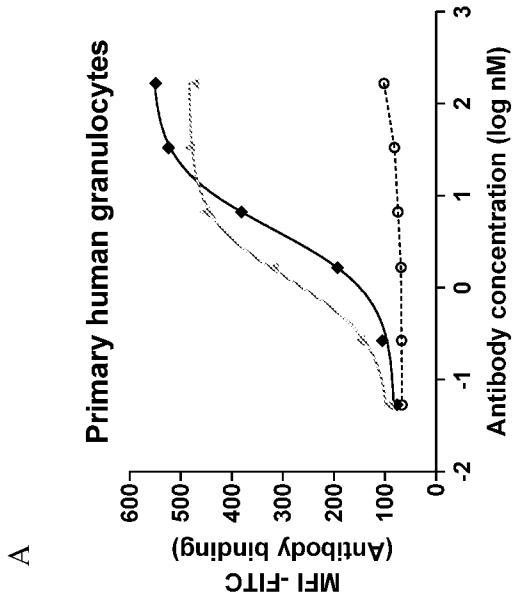
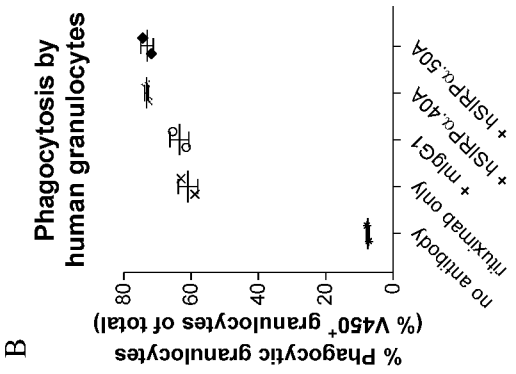

A
CD14+ monocytes human donor 1
MFI -AF647 (Antibody binding)
Antibody concentration (log nM)
B
CD14+ monocytes human donor 2
Cells only
G-a-M IgG AF647
hSIRPα.40A
C
CD14+ monocytes human donor 1
MFI -FITC (hCD47-Fc-488 binding)
D
CD14+ monocytes human donor 2
rhCD47-Fc DyLight488

FIG. 15


A
Primary human granulocytes
MFI -FITC
(Antibody binding)
600
500
400
300
200
100
0
-2
-1
0
1
2
3
Antibody concentration (log nM)
mIgG1
hSIRPα.40A
hSIRPα.50A


B
Phagocytosis by
human granulocytes
% Phagocytic granulocytes
(% V450+ granulocytes of total)
80
60
40
20
0
no antibody
rituximab only
+ mIgG1
+ hSIRPα.40A
+ hSIRPα.50A

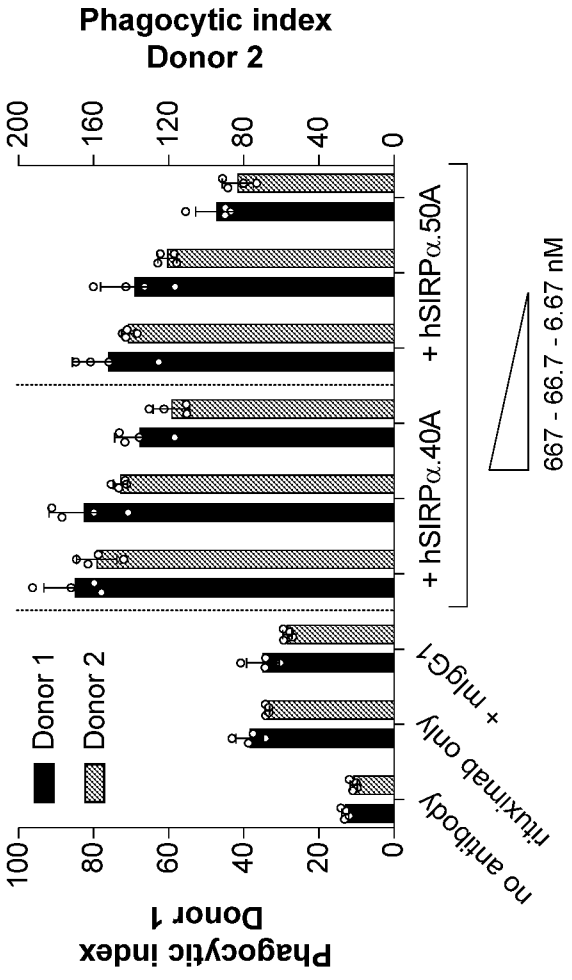

Phagocytic index
Donor 2
Phagocytic index
Donor 1
Donor 1
Donor 2
no antibody
rituximab only
+ migG1
+ hSIRPα.40A
+ hSIRPα.50A
667 - 66.7 - 6.67 nM

FIG. 16

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FIG. 17

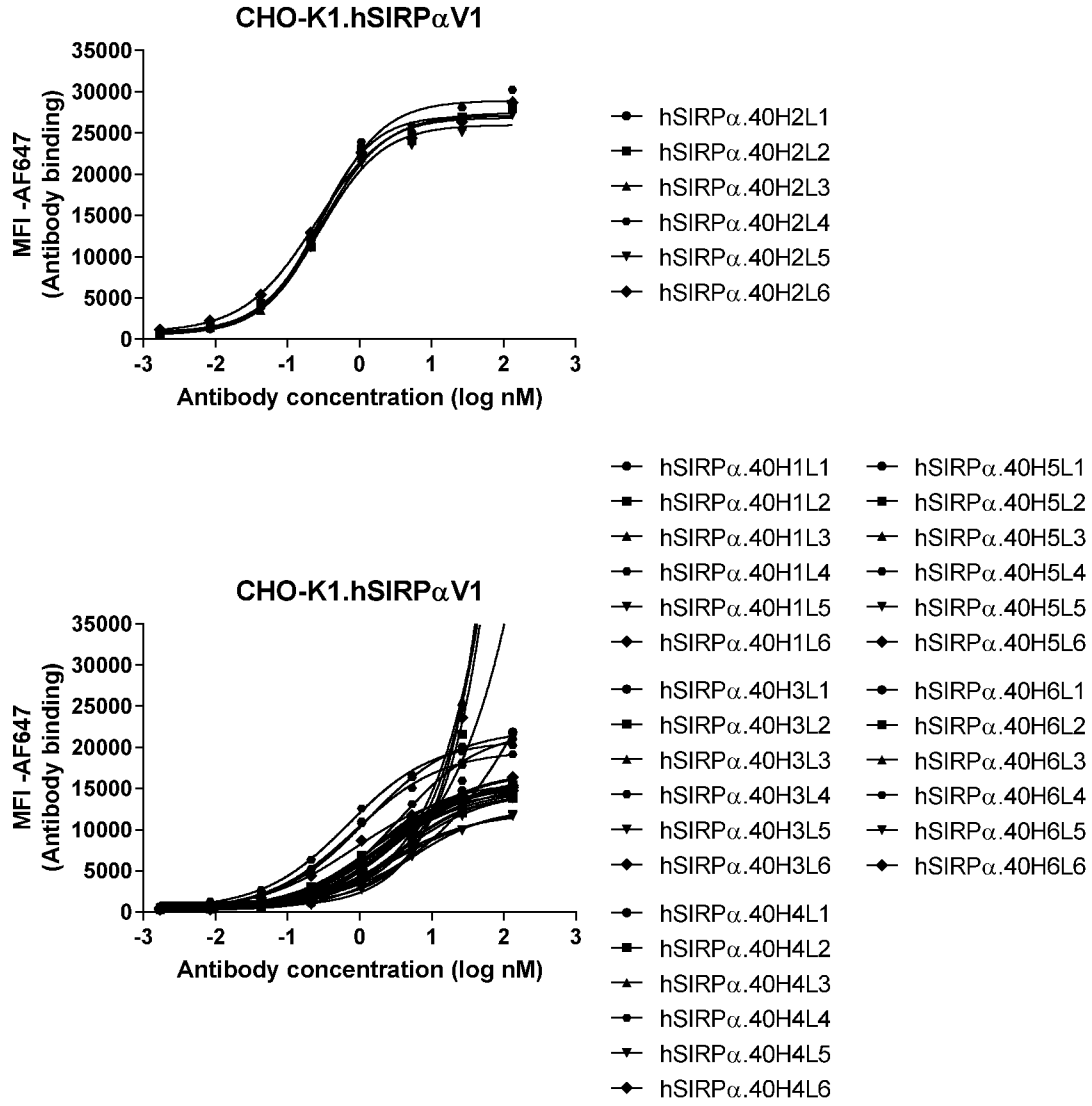

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FIG. 18

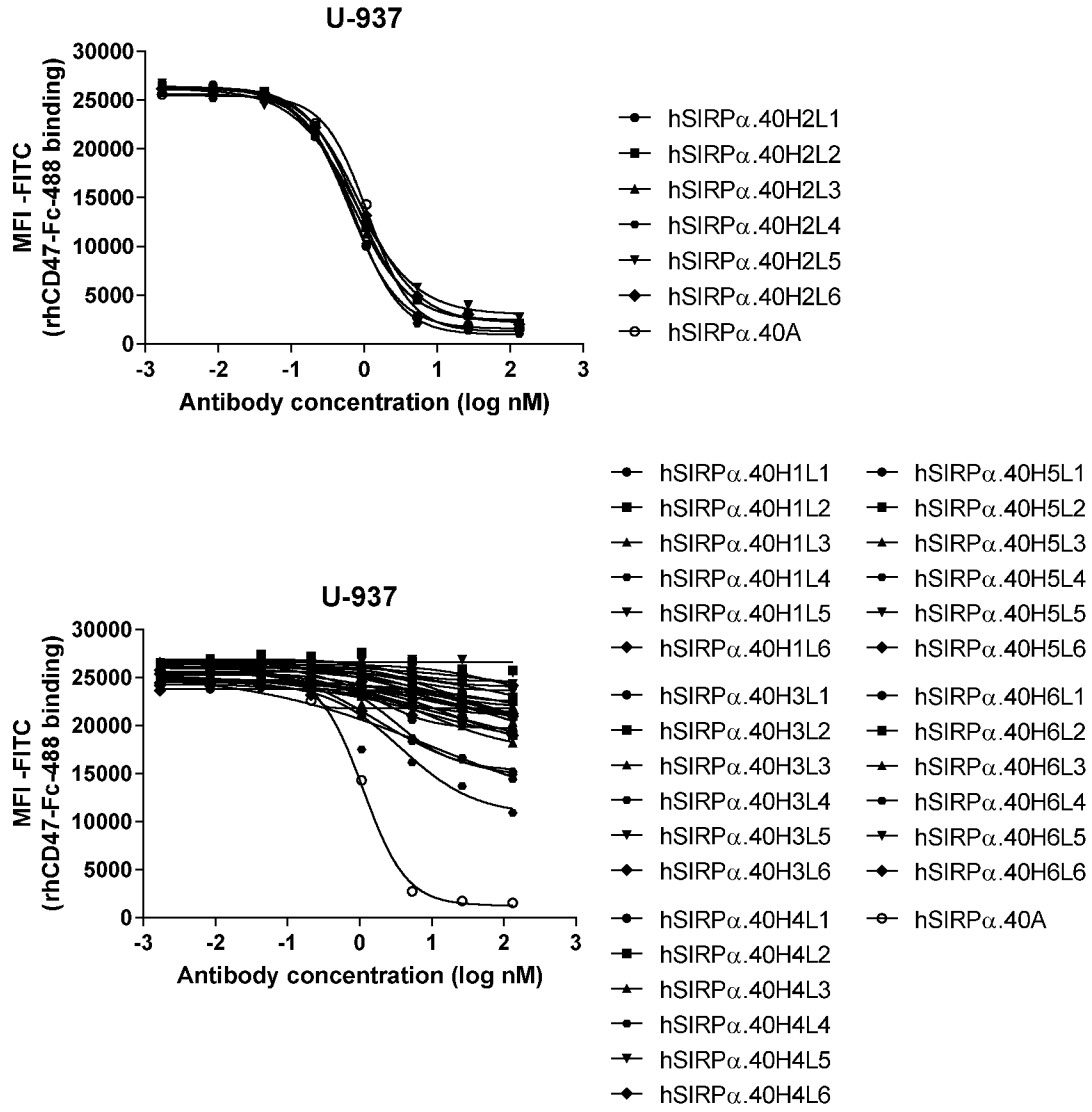


FIG. 19

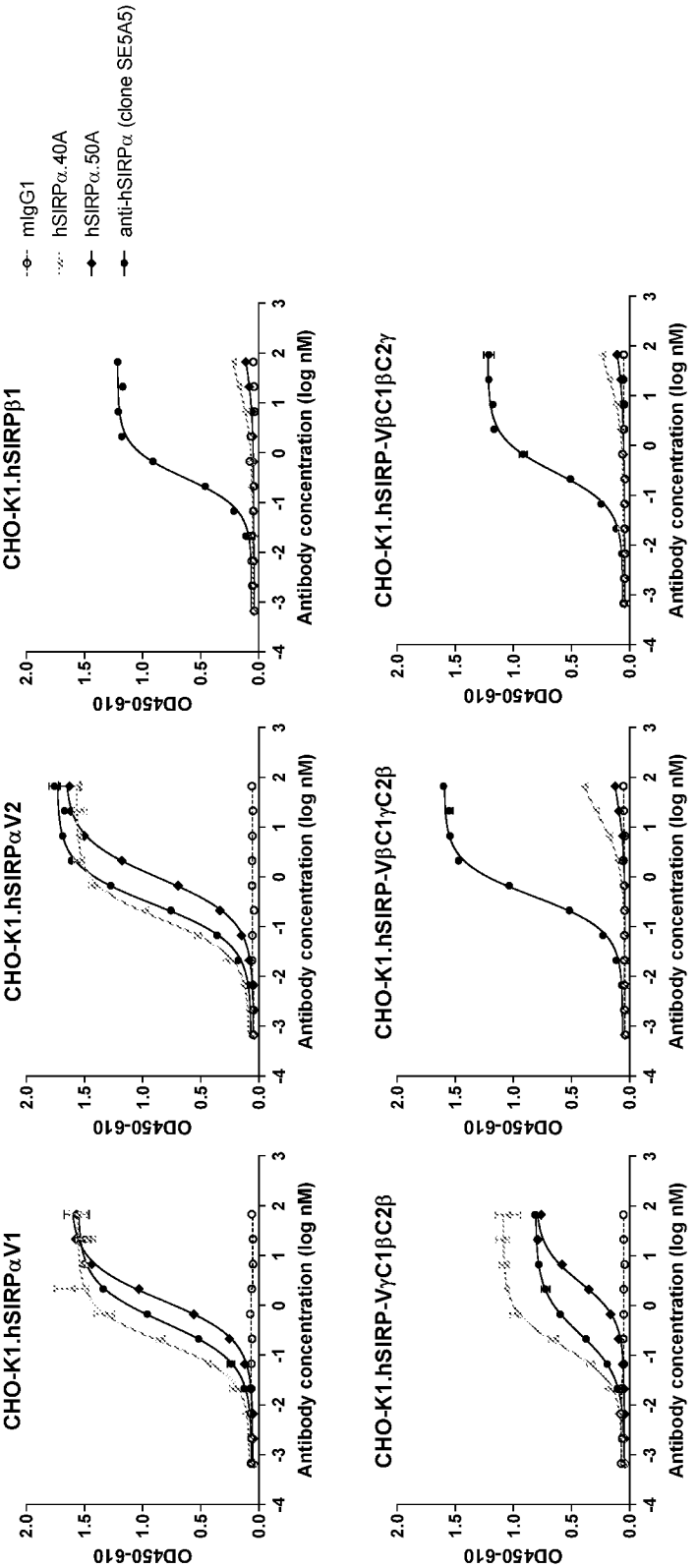
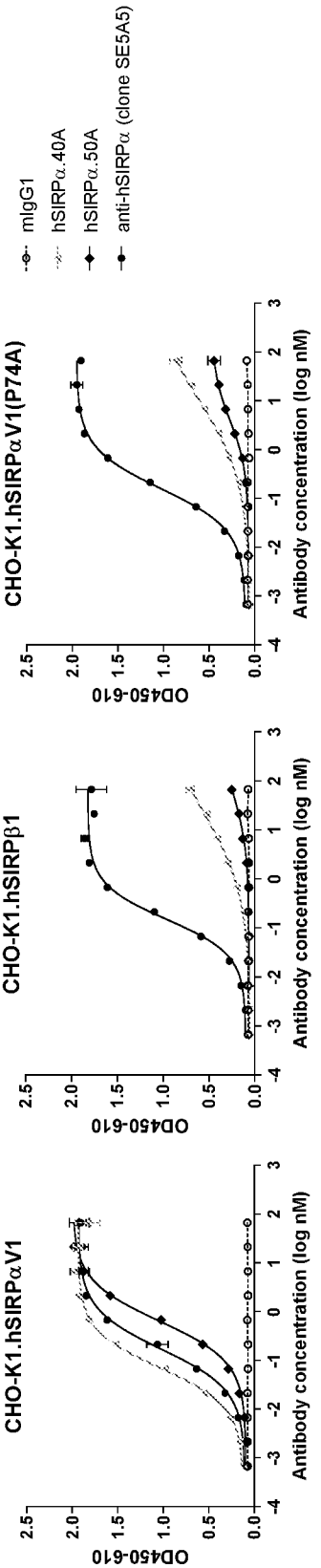

mIgG1
hSIRPα.40A
hSIRPα.50A
anti-hSIRPα (clone SE5A5)
CHO-K1.hSIRPβ1
CHO-K1.hSIRPαV2
CHO-K1.hSIRP-VβC1βC2γ
CHO-K1.hSIRPαV1
CHO-K1.hSIRP-VβC1γC2β
CHO-K1.hSIRP-VγC1βC2β
OD450-610
Antibody concentration (log nM)

FIG. 20


CHO-K1.hSIRPαV1
CHO-K1.hSIRPβ1
CHO-K1.hSIRPαV1(P74A)
OD450-610
Antibody concentration (log nM)
mIgG1
hSIRPα.40A
hSIRPα.50A
anti-hSIRPα (clone SE5A5)

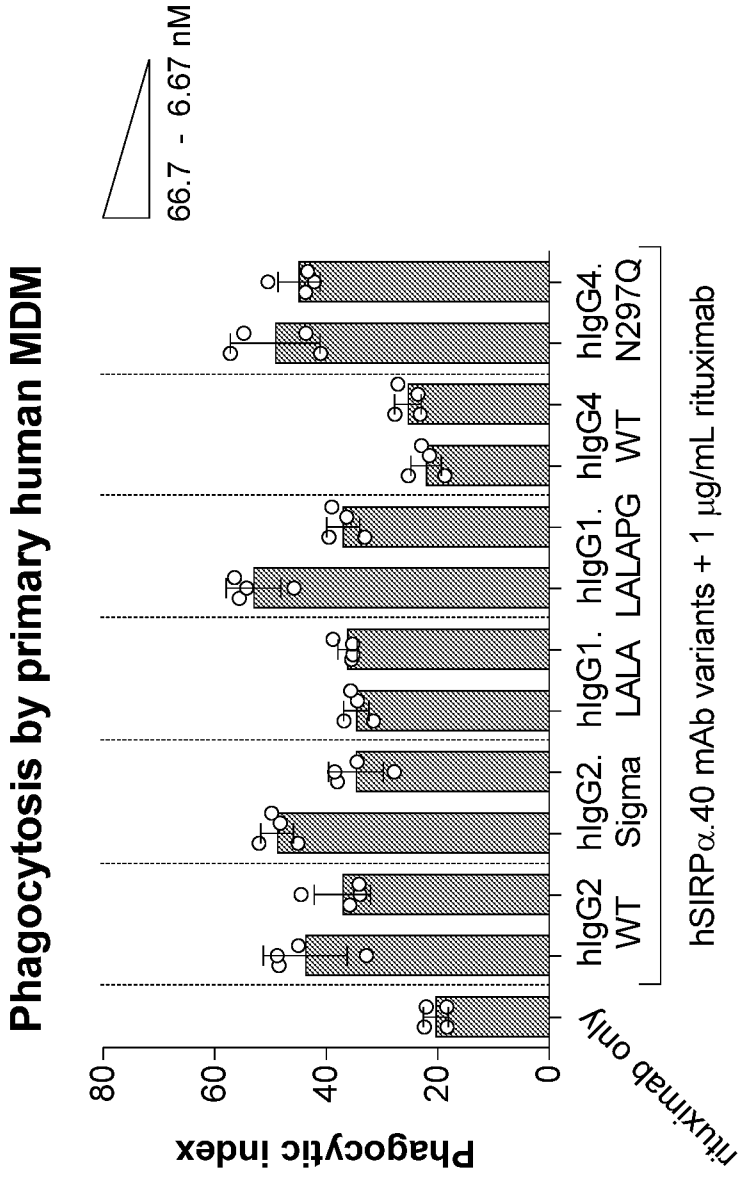

Phagocytosis by primary human MDM
66.7 - 6.67 nM
Phagocytic index
0
20
40
60
80
rituximab only
hIgG2 WT
hIgG2 Sigma
hIgG1. LALA
hIgG1. LALAPG
hIgG4 WT
hIgG4. N297Q
hSIRPα.40 mAb variants + 1 μg/mL rituximab

FIG. 21

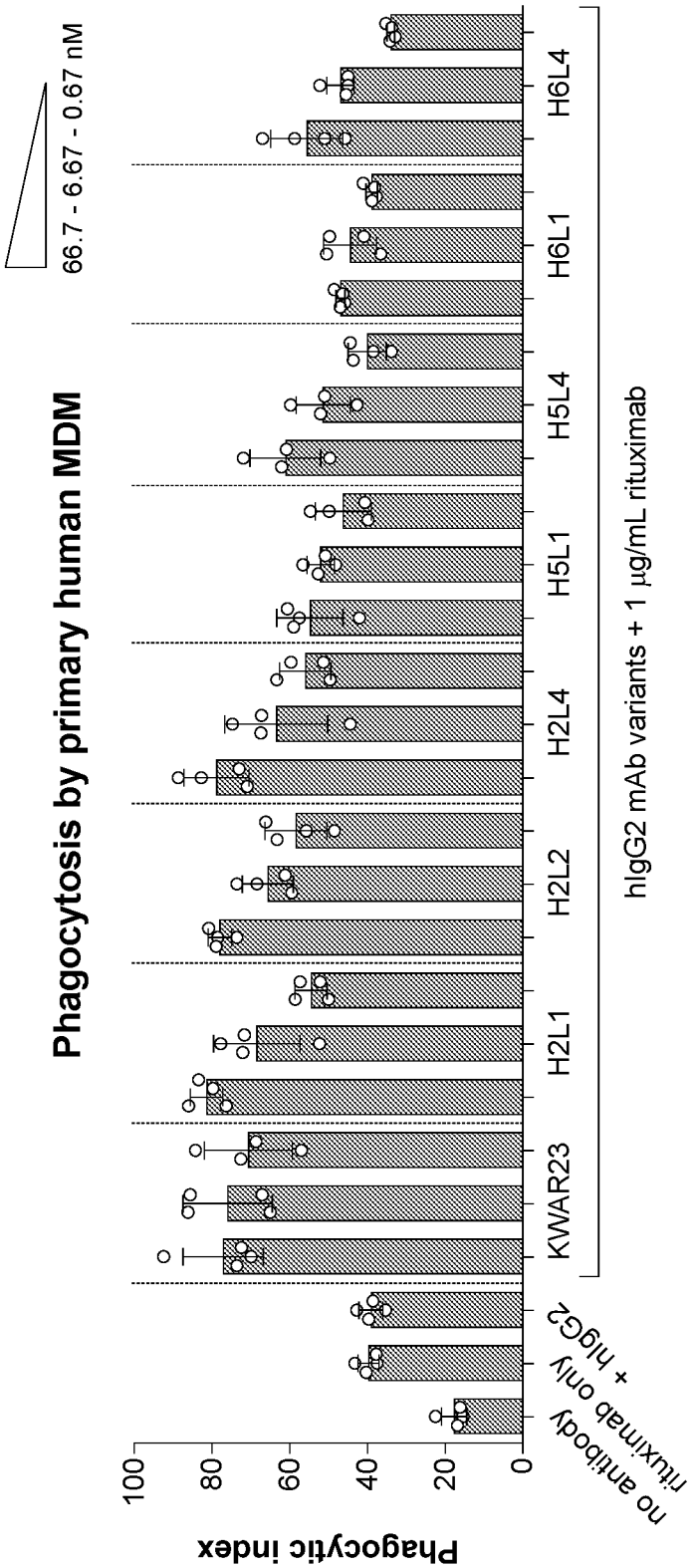

Phagocytosis by primary human MDM
66.7 - 6.67 - 0.67 nM
Phagocytic index
100
80
60
40
20
0
no antibody
rituximab only
+ hIgG2
KWAR23
H2L1
H2L2
H2L4
H5L1
H5L4
H6L1
H6L4
hIgG2 mAb variants + 1 µg/mL rituximab

FIG. 22

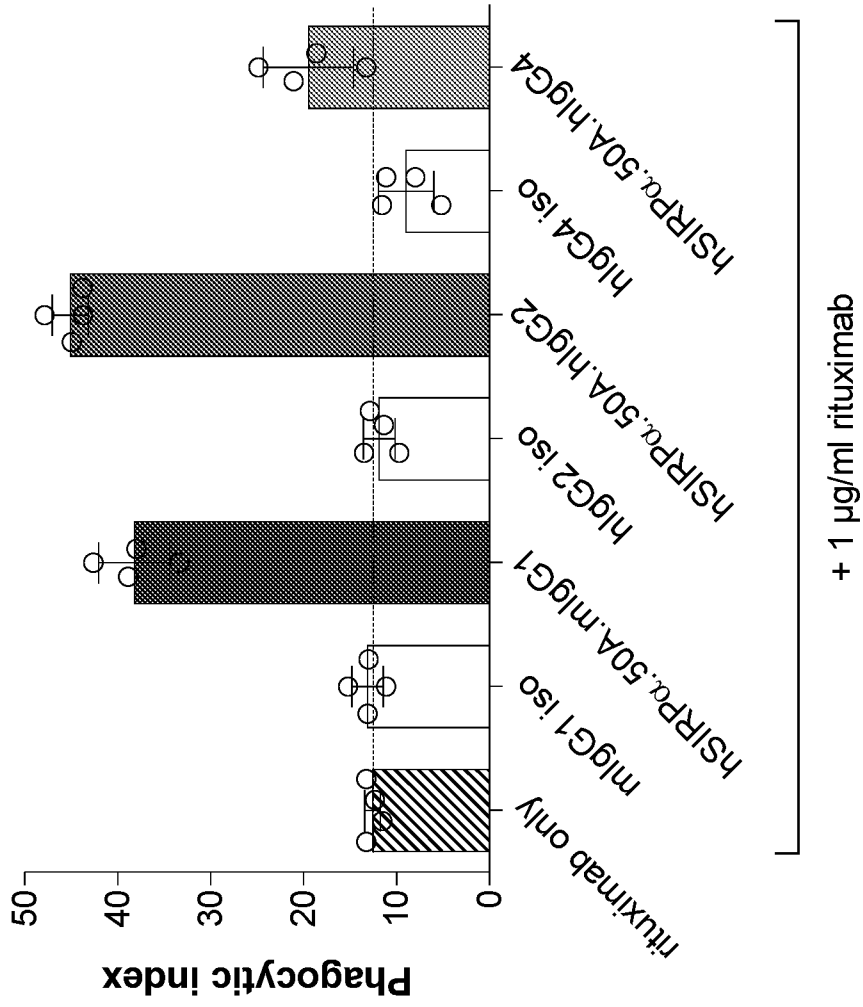

Phagocytosis by primary human MDM
Phagocytic index
0
10
20
30
40
50
rituximab only
mIgG1 iso
hSIRPα..50A.mIgG1
hIgG2 iso
hSIRPα..50A.hIgG2
hIgG4 iso
hSIRPα..50A.hIgG4
+ 1 µg/ml rituximab

FIG. 23A

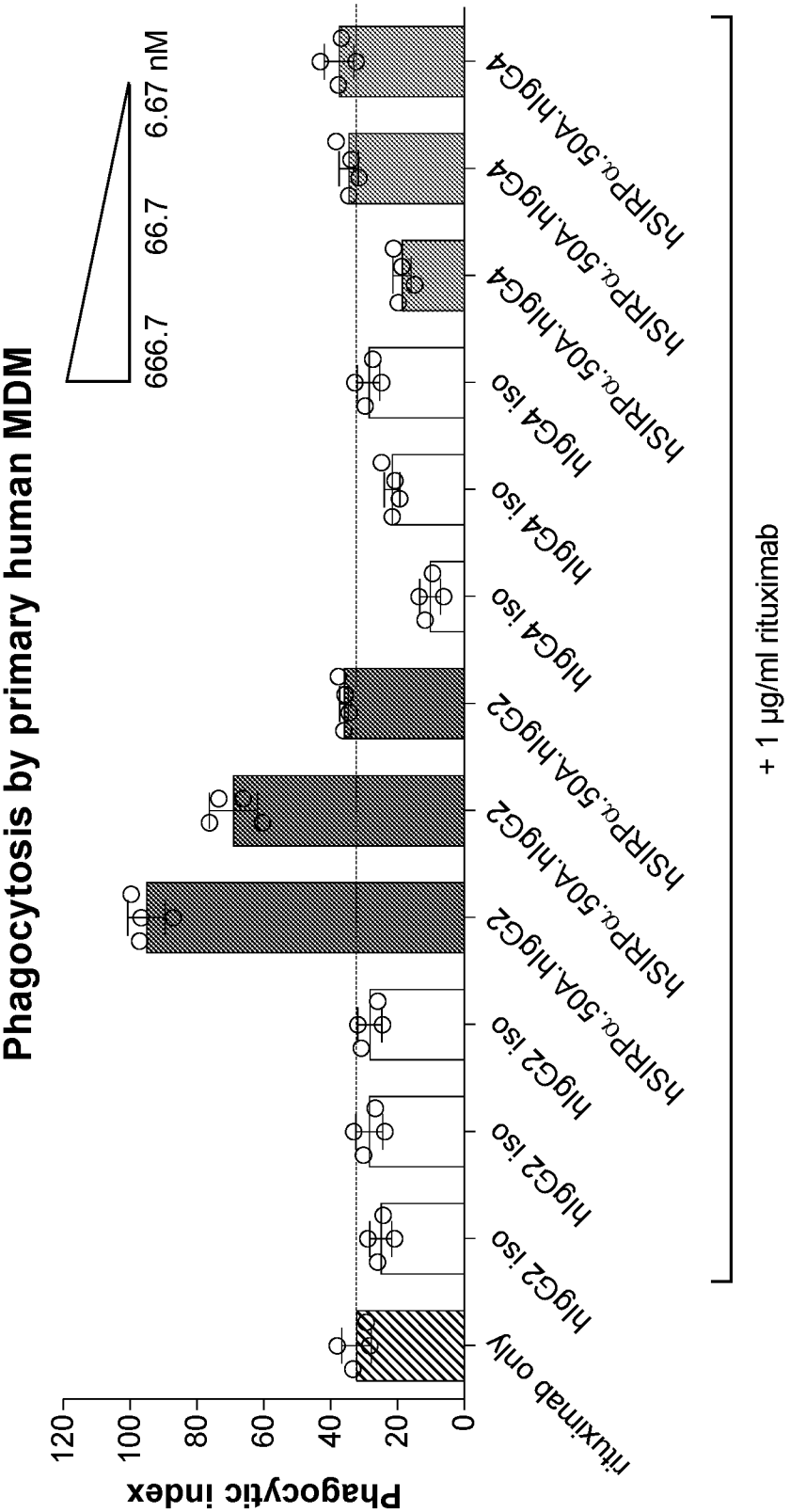

Phagocytosis by primary human MDM
Phagocytic index
120
100
80
60
40
20
0
666.7
66.7
6.67 nM
rituximab only
hIgG2 iso
hIgG2 iso
hIgG2 iso
hIgG2 iso
hSIRPα..50A.hIgG2
hSIRPα..50A.hIgG2
hSIRPα..50A.hIgG2
hSIRPα..50A.hIgG2
hIgG4 iso
hIgG4 iso
hIgG4 iso
hIgG4 iso
hSIRPα..50A.hIgG4
hSIRPα..50A.hIgG4
hSIRPα..50A.hIgG4
hSIRPα..50A.hIgG4
+ 1 µg/ml rituximab

FIG. 23B

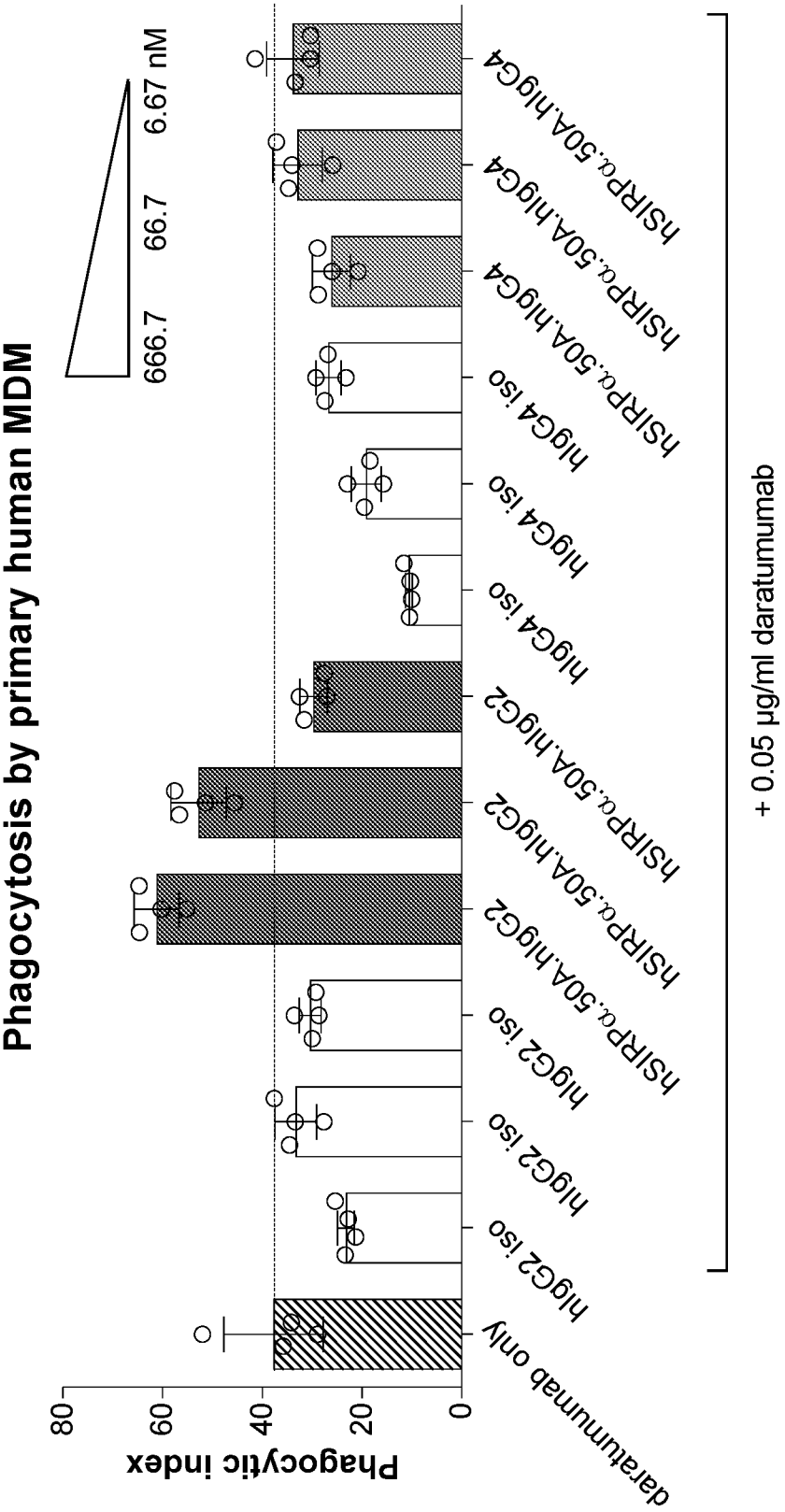

Phagocytosis by primary human MDM
Phagocytic index
0
20
40
60
80
666.7
66.7
6.67 nM
daratumumab only
hIgG2 iso
hIgG2 iso
hIgG2 iso
hIgG2 iso
hSIRPα.50A.hIgG2
hSIRPα.50A.hIgG2
hSIRPα.50A.hIgG2
hSIRPα.50A.hIgG2
hIgG4 iso
hIgG4 iso
hIgG4 iso
hIgG4 iso
hSIRPα.50A.hIgG4
hSIRPα.50A.hIgG4
hSIRPα.50A.hIgG4
hSIRPα.50A.hIgG4
+ 0.05 µg/ml daratumumab

FIG. 23C

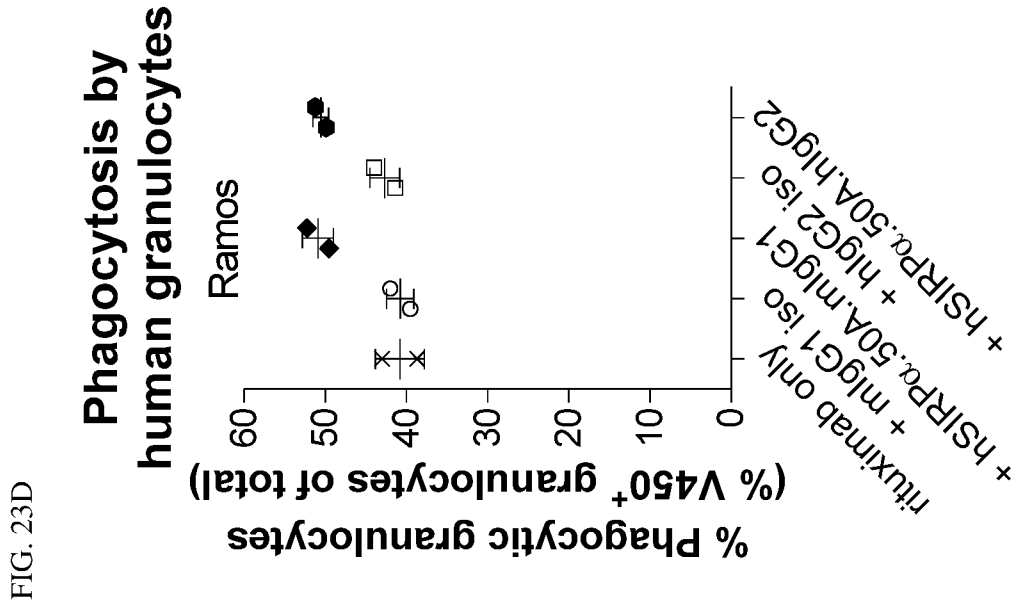

Phagocytosis by human granulocytes
Ramos
% Phagocytic granulocytes (% V450+ granulocytes of total)
0
10
20
30
40
50
60
rituximab only
+ mIgG1 iso
+ hSIRPα.50A.mIgG1
+ hIgG2 iso
+ hSIRPα.50A.hIgG2

FIG. 23D

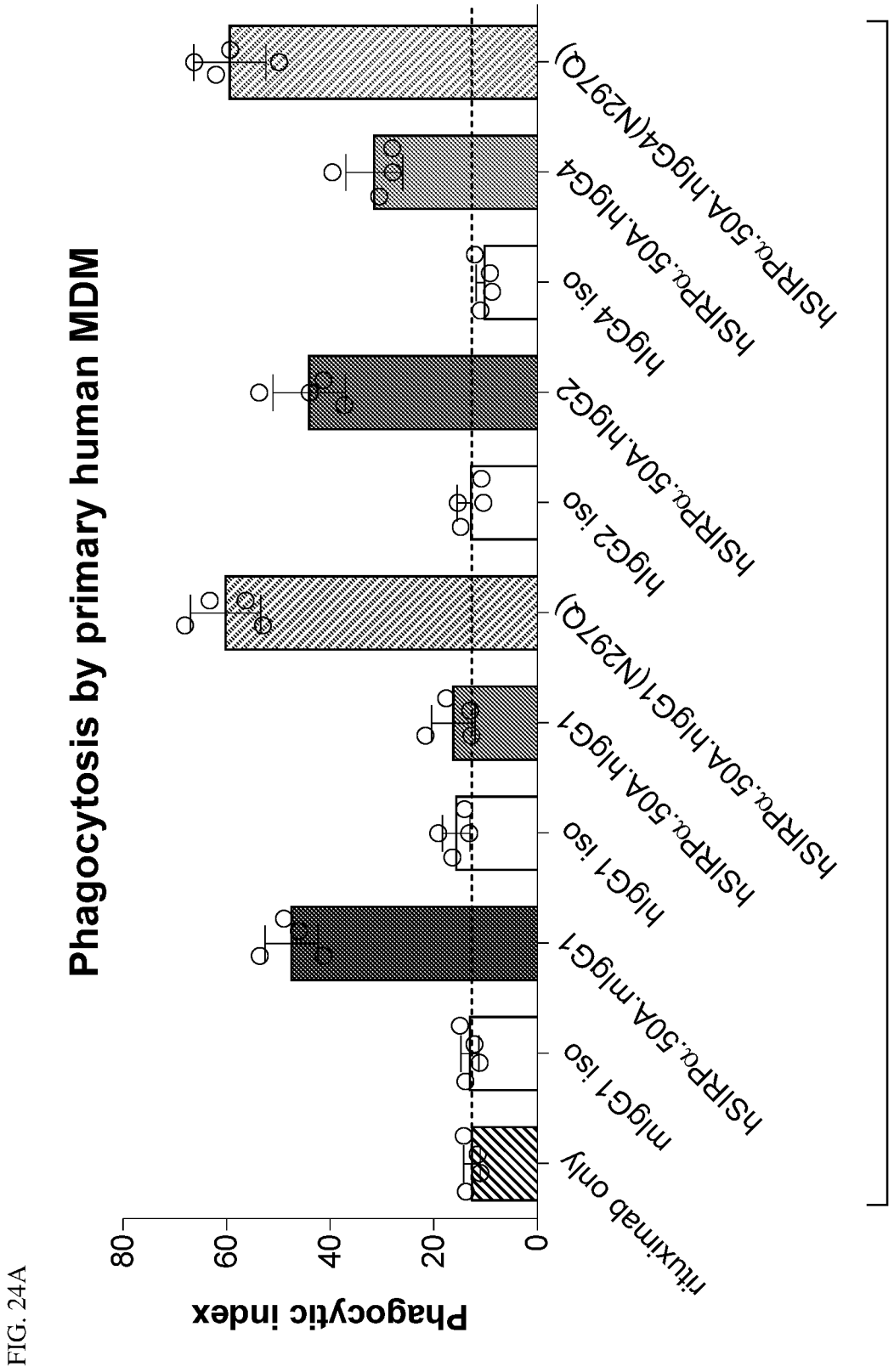

Phagocytosis by primary human MDM
Phagocytic index
0
20
40
60
80
rituximab only
mIgG1 iso
hSIRPα..50A.mIgG1
hIgG1 iso
hSIRPα..50A.hIgG1
hSIRPα..50A.hIgG1(N297Q)
hIgG2 iso
hSIRPα..50A.hIgG2
hIgG4 iso
hSIRPα..50A.hIgG4
hSIRPα..50A.hIgG4(N297Q)
+ 1 µg/ml rituximab

FIG. 24A

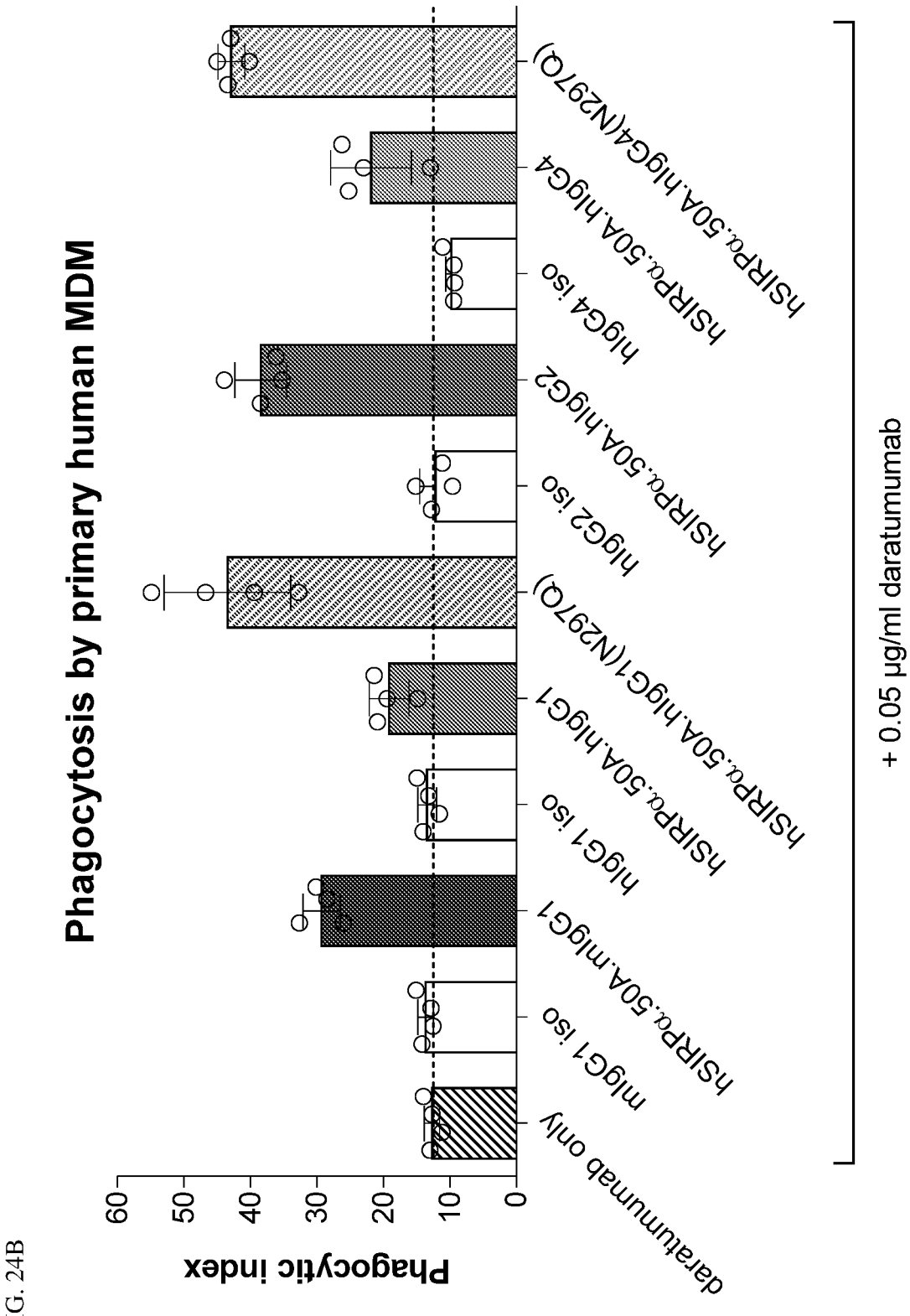

Phagocytosis by primary human MDM
Phagocytic index
0
10
20
30
40
50
60
daratumumab only
mIgG1 iso
hSIRPα..50A.mIgG1
hIgG1 iso
hSIRPα..50A.hIgG1
hSIRPα..50A.hIgG1(N297Q)
hIgG2 iso
hSIRPα..50A.hIgG2
hIgG4 iso
hSIRPα..50A.hIgG4
hSIRPα..50A.hIgG4(N297Q)
+ 0.05 µg/ml daratumumab

FIG. 24B

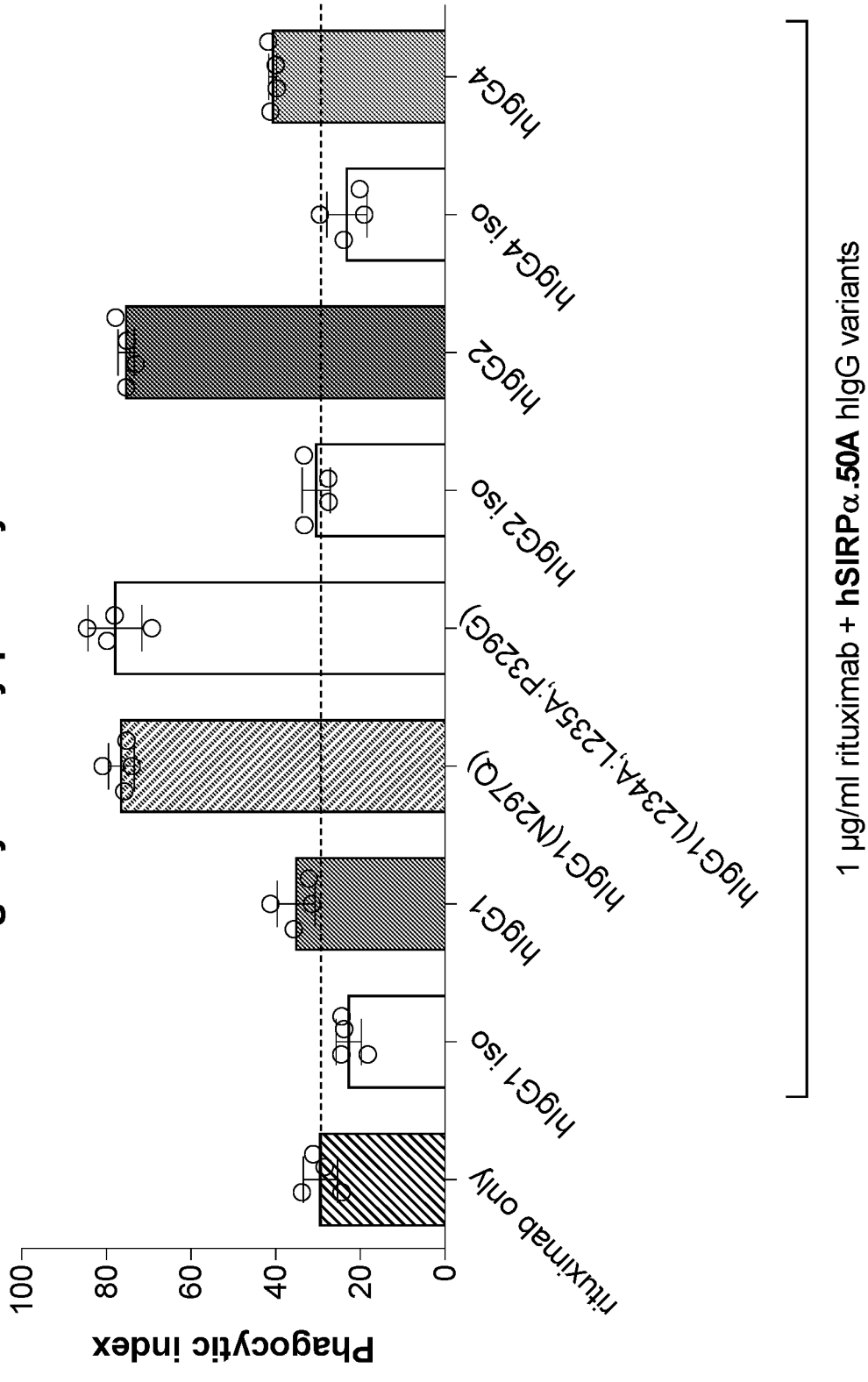

Phagocytosis by primary human MDM
Phagocytic index
100
80
60
40
20
0
rituximab only
hIgG1.iso
hIgG1
hIgG1(N297Q)
hIgG1(L234A.L235A.P329G)
hIgG2.iso
hIgG2
hIgG4.iso
hIgG4
1 µg/ml rituximab + hSIRPα.50A hIgG variants

FIG. 25