

SIRP ANTIBODIES FOR TREATMENT OF CANCER**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to U.S. provisional patent application number 63/591,737, filed on October 19, 2023, the contents of which are incorporated by reference herein in their entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (ELTH_006_01WO_SeqList_ST26.xml; Size: 58,297 bytes; and Date of Creation: October 17, 2024) are herein incorporated by reference in its entirety.

BACKGROUND

[0003] Signal regulatory proteins (SIRPs) are a family of cell-surface immune receptors. The SIRP family contains three family members (SIRP α , SIRP β , SIRP γ). SIRP α and SIRP β are expressed on myeloid cells of the immune system, including dendritic cells, macrophages, and monocytes. SIRP γ is expressed by lymphocytes such as T cells. Given the characteristic expression of the SIRP proteins in relation to the cell types implicated in certain cancers, the use of a SIRP $\alpha/\beta/\gamma$ -directed agents may modulate certain cancer pathologies. There is a need for agents and protocols for the treatment of cancer, provided herein are such agents and protocols.

SUMMARY

[0004] The use of a SIRP $\alpha/\beta/\gamma$ -directed antibody, through its multipronged effect, has the potential to target multiple SIRP α/β expressing myeloid cell types including but not limited to dendritic cells, monocytes, and macrophages, as well as SIRP γ expressing T cells, and can act to deplete cell types believed to be drivers of certain cancer pathologies. Provided are clinically relevant methods, for the treatment of cancer with selected SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure.

[0005] In one aspect, provided herein is a method of treating cancer in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of a SIRP $\alpha/\beta/\gamma$ binding antibody, in one or more treatment phases. In some embodiments, the heavy chain variable region (VH) of the SIRP $\alpha/\beta/\gamma$ binding antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the SIRP $\alpha/\beta/\gamma$ binding antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the SIRP $\alpha/\beta/\gamma$ binding antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

[0006] In another aspect, provided herein is a use of a SIRP $\alpha/\beta/\gamma$ binding antibody in the manufacture of a medicament for treating cancer in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of, in one or more treatment phases. In some embodiments, the heavy chain variable region (VH) of the SIRP $\alpha/\beta/\gamma$ binding antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the SIRP $\alpha/\beta/\gamma$ binding antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the SIRP $\alpha/\beta/\gamma$ binding antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

[0007] In another aspect, provided herein is a SIRP $\alpha/\beta/\gamma$ binding antibody for use in treating cancer in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of a, in one or more treatment phases. In some embodiments, the heavy chain variable region (VH) of the SIRP $\alpha/\beta/\gamma$ binding antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the SIRP $\alpha/\beta/\gamma$ binding antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto. In some embodiments, the SIRP $\alpha/\beta/\gamma$ binding antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

[0008] In another aspect, provided herein is a method of treating cancer in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of an anti-SIRP antibody, in one or more treatment phases, wherein the antibody comprises a means for binding human SIRP α , SIRP β , and SIRP γ proteins.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1A shows the S $\alpha\beta\gamma$ -01 safety and efficacy dosing study design schema.

[0010] FIG. 1B shows a schematic for the intra-participant dose escalation phase, individual fixed dose phase and additional exploration of schedule for a S $\alpha\beta\gamma$ -01 safety and efficacy dosing study.

[0011] FIG. 2 shows the subject demographics and baseline characteristics for the S $\alpha\beta\gamma$ -01 safety and efficacy dosing study.

[0012] FIG. 3 shows the S $\alpha\beta\gamma$ -01 dosing and added therapy for cancer and sHLH.

[0013] FIG. 4 shows the characteristics of sCD25 and ferritin biomarker response in three Cohort 1 subjects in clinical remission from cancer and sHLH at week 16.

[0014] FIG. 5 shows a summary table of anti-tumor activity with S $\alpha\beta\gamma$ -01 in T-Cell Malignancies (TCM).

DETAILED DESCRIPTION

Definitions

[0015] Where elements are presented in a list format (e.g., in a Markush group), it should be understood that each possible subgroup of the elements is also disclosed, and that any one or more elements can be removed from the list or group.

[0016] It should be understood that, unless clearly indicated, in any method described or disclosed herein that includes more than one act, the order of the acts is not necessarily limited to the order in which the acts of the method are recited, but the disclosure encompasses exemplary embodiments in which the order of the acts is so limited.

[0017] The terms used throughout the specification are defined as follows unless otherwise limited in specific instances. As used in the specification and the claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. All technical and scientific terms, acronyms, and abbreviations used in the specification and claims

have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains, unless defined or stated otherwise. All numerical ranges are inclusive of the values defining the range as well as all integer values in between, unless indicated or defined otherwise.

[0018] The term “priming dose phase” or “priming phase” refers to a phase to prepare the subject for a subsequent treatment phase. Without being held to theory or mechanism, the priming dose phase may introduce an antibody of the disclosure in such a way that minimizes adverse reactions such as hypersensitivity or toxicity related reactions. The term “priming dose” or “priming doses” or “prime dose” or “prime doses” refers to one or more doses within the priming dose phase. The term “priming” or “prime” refers to the act of administering a priming dose.

[0019] The term “treatment dose phase” or “treatment phase” refers to a phase which aims to treat one or more diseases or disorders in the subject. Without being held to theory or mechanism, the “treatment phase” aims to achieve one or more therapeutic effects. The term “treatment dose” or “treatment doses” refers to one or more doses within the treatment phase. In some embodiments, the treatment phase comprises one or more “loading dose phases” and/or one or more “maintenance dose phases”. The treatment phase need not include a loading dose phase. Thus, in some embodiments, the treatment phase may only comprise one or more “maintenance dose phases”.

[0020] The term “loading dose phase” or “loading phase” refers to a phase which aims to infuse the subject with a desired amount of a specified therapeutic. Without being held to theory or mechanism, the loading dose phase may aim to rapidly achieve a specified systemic therapeutic concentration of an antibody of the disclosure in the subject. The term “loading dose” or “loading doses” refers to one or more doses within the loading dose phase.

[0021] The term “maintenance dose phase” or “maintenance phase” refers to a phase which aims to sustain a desired amount of a specified therapeutic in the subject. Without being held to theory or mechanism, the maintenance dose phase may aim to maintain a specified systemic therapeutic concentration of an antibody of the disclosure in the subject. The term “maintenance dose” or “maintenance doses” refers to one or more doses within the maintenance dose phase.

[0022] In some embodiments, the dosing protocol comprises a priming dose phase followed by a subsequent treatment phase. In some embodiments, the protocol comprises multiple treatment phases, each optionally preceded by a priming dose phase. In some embodiments,

the treatment phase(s) comprise a maintenance dose phase. In some embodiments, the treatment phase(s) comprise a loading dose phase and a maintenance dose phase.

[0023] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

[0024] Provided herein are antibodies that bind to SIRP α , SIRP β , and SIRP γ , and methods of treating cancer using such antibodies. The antibodies may be useful for treating cancer by depleting SIRP α , SIRP β , and/or SIRP γ expressing cell types.

I. Antibodies

A. SIRP $\alpha/\beta/\gamma$ Antibodies

[0025] Provided herein are antibodies that bind to SIRP α , SIRP β , and SIRP γ , and are interchangeably referred to herein as SIRP $\alpha/\beta/\gamma$ antibodies, anti-SIRP $\alpha/\beta/\gamma$ antibodies, SIRP $\alpha/\beta/\gamma$ -directed antibodies and the like.

[0026] The skilled artisan will appreciate that, depending on context, a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure that has the ability to bind to SIRP α , SIRP β , and SIRP γ will encounter a binding surface (e.g. a cell) that may express only a subset of the targets to which the antibody is capable of binding. For example, an antibody that can bind SIRP α , SIRP β , and SIRP γ can bind to a cell expressing only SIRP γ , or a cell expressing only SIRP α . Alternatively, a binding surface, such as a cell, may express more than one, or all, of the targets to which the antibody can bind. In such a situation, the antibody is also expected to bind that surface. Thus, although the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure bind SIRP γ as well as SIRP α and SIRP β , the binding of all of the targets simultaneously is not required for activity. As such, in some embodiments, the antibodies of the disclosure comprise a means for binding human SIRP α , SIRP β , and SIRP γ proteins.

[0027] The term antibody as used herein throughout is used in the broadest sense and includes a monoclonal antibody, polyclonal antibody, human antibody, humanized antibody, non-human antibody, chimeric antibody, a monovalent antibody, and an antibody fragment.

[0028] In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are monoclonal antibodies (mAbs). In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are human antibodies. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are humanized antibodies. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are monoclonal human antibodies. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are chimeric antibodies. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are monoclonal chimeric antibodies.

[0029] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are antibody fragments, retaining SIRP α , SIRP β , and SIRP γ antigen binding specificity. In some embodiments, the antibody fragments are antigen-binding fragments (Fab), variable fragments (Fv) containing VH and VL sequences, single chain variable fragments (scFv) containing VH and VL sequences linked together in one chain, single chain antibody fragments (scAb) or other antibody variable region fragments, such as Fab', F(ab')₂, dsFv diabody, and Fd polypeptide fragments.

[0030] The SIRP α protein has been characterized to be highly polymorphic but does not appear to affect ligand binding properties. At least thirteen variants (polymorphs) have been characterized in humans, Variants 1-13, with V1 and V2 the most common. (Hatherley et al. JBC 289: 10024-10028, 2014). SIRP α also has at least three isoforms. Accordingly, the term "SIRP α " as used herein is inclusive of all variants and isoforms of SIRP α . Such isoforms are described in greater detail in WO2021226591, the contents of which are incorporated by reference in their entirety herein.

[0031] The amino acid sequence of human SIRP α (hSIRP α) isoform 1, variant 1 (V1) is provided in SEQ ID NO: 9 and referred to herein as hSIRP α V1.

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1  MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVLVAAGET ATLRCTATSL
61  IPVGPIQWFR GAGPGRELIY NQKEGHFPRV TTVSDLTKRN NMDFSIRIGN ITPADAGTYY
121 CVKFRKGSPD DVEFKSGAGT ELSVRAKPSA PVVSGPAARA TPQHTVSFTC ESHGFSPRDI
181 TLKWFKNENE LSDFQTNVDP VGESVSYSIH STAKVVLTRE DVHSQVICEV AHVTLQGDPL
241 RGTANLSETI RVPPTLEVTQ QPVRANQVN VTCQVRKFYP QRLQLTWLEN GNVSRTEAS
301 TVTENKDGTY NWMSWLLVNV SAHRDDVKLT CQVEHDGQPA VSKSHDLKVS AHPKEQGSNT
361 AAENTGSNER NIYIVGVVC TLLVALLMAA LYLVRIRQKK AQGSTSSTRL HEPEKNAREI
421 TQDTNDITYA DLNLPKGKKP APQAAEPNNH TEYASIQTSP QPASEDTLTY ADLDMVHLNR
481 TPKQPAPKPE PSFSEYASVQ VPRK (SEQ ID NO: 9)

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[0032] The amino acid sequence of hSIRP α isoform 1, variant 2 (V2) is provided in SEQ ID NO: 10 and referred to herein as hSIRP α V2.

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1  MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVSVAAGES AILHCTVTSL
61  IPVGPIQWFR GAGPARELIY NQKEGHFPRV TTVSESTKRE NMDFSISISN ITPADAGTYY
121 CVKFRKGSPD TEFKSGAGTE LSVRAKPSAP VVSGPAARAT PQHTVSFTCE SHGFSPRDIT
181 LKWKFKNGNEL SDFQTNVDPV GESVSYSIHS TAKVVLTRED VHSQVICEVA HVTLQGDPLR
241 GTANLSETIR VPPTLEVTQQ PVRAENQVNV TCQVRKFYPQ RLQLTWLENG NVSRTEAST
301 VTENKDGTYN WMSWLLNVNS AHRDDVKLTC QVEHDGQPAV SKSHDLKVS HPKEQGSNTA
361 AENTGSNERN IYIVGVVCT LLVALLMAAL YLVIRQKKA QGSTSSTR LH EPEKNAREIT
421 QVQSLDTNDI TYADLNLPKG KKPAPQAAEP NNHTEYASIQ TSPQPASEDT LTYADLDMVH
481 LNRTPKQPAP KPEPSFSEYA SVQVPRK (SEQ ID NO: 10)

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[0033] The amino acid sequence of hSIRP α isoform 2 is provided herein as SEQ ID NO: 11.

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1  MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVLVAAGET ATLRCTATSL
61  IPVGPIQWFR GAGPGRELIY NQKEGHFPRV TTVSDLTKRN NMDFSIRIGN ITPADAGTYY
121 CVKFRKGSPD DVEFKSGAGT ELSVRAKPSA PVVSGPAARA TPQHTVSFTC ESHGFSPRDI
181 TLKWKFKNGNE LSDFQTNVDP VGESVSYSIH STAKVVLTRE DVHSQVICEV AHVTLQGDPL
241 RGTANLSETI RVPPTLEVTQ QPVRAENQVN VTCQVRKFYP QRLQLTWLEN GNVSRTEAST
301 TVTENKDGTY NWMSWLLNVN SAHRDDVKLT CQVEHDGQPA VSKSHDLKVS AHPKEQGSNT
361 AAENTGSNER NIYIVGVVC TLLVALLMAA LYLVRIRQKK AQGSTSSTR LH HEPEKNAREI
421 TQVQSLDTND ITYADLNLPK GKKPAPQAAE PNNHTEYASI QTSPQPASED TLTYADLDMV
481 HLNRTPKQPA PKPEPSFSEY ASVQVPRK (SEQ ID NO: 11)

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[0034] The amino acid sequence of human SIRP α isoform 4 is provided in SEQ ID NO: 12.

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1  MEPAGPAPGR LGPLLCLLLA ASCAWSGVAG EEELQVIQPD KSVLVAAGET ATLRCTATSL
61  IPVGPIQWFR GAGPGRELIY NQKEGHFPRV TTVSDLTKRN NMDFSIRIGN ITPADAGTYY
121 CVKFRKGSPD VEFKSGAGTE LSVRAKPSAP VVSGPAARAT PQHTVSFTCE SHGFSPRDIT
181 LKWKFKNGNEL SDFQTNVDPV GESVSYSIHS TAKVVLTRED VHSQVICEVA HVTLQGDPLR
241 GTANLSETIR VPPTLEVTQQ PVRAENQVNV TCQVRKFYPQ RLQLTWLENG NVSRTEAST
301 VTENKDGTYN WMSWLLNVNS AHRDDVKLTC QVEHDGQPAV SKSHDLKVS HPKEQGSNTA
361 AENTGSNERN IYIVGVVCT LLVALLMAAL YLVIRQKKA QGSTSSTR LH EPEKNAREIT
421 QDTNDITYAD LNLPGKKPA PQAAEPNNHT EYASIQTSPQ PASEDTLTYA DLDMVHLNRT
481 PKQPAPKPEP SFSEYASVQV PRK (SEQ ID NO: 12)

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[0035] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of a SIRP α of a single species. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of a SIRP α of more than one species. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of

human SIRP α . In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of a non-human primate SIRP α , e.g. a cynomolgus monkey SIRP α .

[0036] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to a plurality of SIRP α variants found in a particular species, e.g. the SIRP $\alpha/\beta/\gamma$ antibodies bind to more than one of SIRP α human variants 1-13. In some embodiments the SIRP $\alpha/\beta/\gamma$ antibodies also bind to hSIRP α V1. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to hSIRP α V2. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to hSIRP α V1 and V2. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind the extracellular domain of SIRP α , e.g. hSIRP α V1 (e.g. Met1-Arg370 of V1, Gly27-Arg370 of V1, or Glu31-Arg370 of V1), or e.g. hSIRP α V2 (Met1-Arg369).

[0037] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure bind a plurality of SIRP α isoforms. For example, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure may bind to two or more SIRP α isoforms, or all SIRP α isoforms. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies bind to isoform 1, 2 and 4 of SIRP α .

[0038] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind specifically to hSIRP α V1. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind specifically to hSIRP α V2. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind specifically to hSIRP α V1 and hSIRP α V2. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind specifically to one or more variants of SIRP α , but show little or no binding to SIRP β .

[0039] Human SIRP β (hSIRP β) has at least 3 isoforms. SIRP β is also known in the literature as SIRP β 1, and these are used interchangeably herein. Such isoforms are described in greater detail in WO2021226591, the contents of which are incorporated by reference in their entirety herein. The amino acid sequence of hSIRP β isoform 1 is provided in SEQ ID NO: 13

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1  MPVPASWPHL  PSPFLLMTLL  LGRLTGUAGE  DELQVIQPEK  SVSVAAGESA  TLRCAMTSLI
61  PVGPIMWFRG  AGAGRELIYN  QKEGHFPRVT  TVSELTKRNN  LDFSISISNI  TPADAGTYYC
121 VKFRKGSDD  VEFKSGAGTE  LSVRAKPSAP  VVSGPAVRAT  PEHTVSFTCE  SHGFSRPDIT
181 LKWFKNENEL  SDFQTNVDPA  GDSVSYSIHS  TARVVLTRGD  VHSQVICEIA  HITLQGDPLR
241 GTANLSEAIR  VPPTLEVTTQ  PMRAENQANV  TCQVSNFYPR  GLQLTWLENG  NVSRTEAST
301 LIENKDGTYN  WMSWLLVNTC  AHRDDVVLTC  QVEHGGQAV  SKSYALEISA  HQKEHGSDIT
361 HEALAPTAP  LLVALLGPK  LLLVVGVSAT  YICWKQKA  (SEQ ID NO: 13)

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[0040] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of a SIRP β of a single species. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of a SIRP β of more than one species. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of human SIRP β . In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to one or more variants or isoforms of a non-human primate SIRP β , e.g. a cynomolgus monkey SIRP β .

[0041] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind to a plurality of SIRP β variants or isoforms found in a particular species, e.g. the SIRP $\alpha/\beta/\gamma$ antibodies bind to more than one of SIRP β human isoforms 1-3. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind the extracellular domain of SIRP β (e.g. amino acids 1-371 of SEQ ID NO: 13). In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies also bind specifically to one or more variants or isoforms of SIRP α , in addition to binding to SIRP γ and SIRP β .

[0042] Human SIRP γ has at least 4 isoforms. SIRP γ is also known as SIRP β 2, and SIRP β 2 is not to be confused with SIRP β which is referred to as SIRP β and SIRP β 1 interchangeably herein. The amino acid of hSIRP γ isoform 1 is provided as SEQ ID NO: 14.

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1  MPVPASWPHP  PGPFLLLTLL  LGLTEVAGEE  ELQMIQPEKL  LLVTVGKTAT  LHCTVTSLLP
61  VGPVLWFRGV  GPGRELIYNQ  KEGHFPRVTT  VSDLTKRNNM  DFSIRISSIT  PADVGTYTCV
121 KFRKGSPENV  EFKSGPGTEM  ALGAKPSAPV  VLGPAARTTP  EHTVSFTCES  HGFSPRDITL
181 KWFKNGNELS  DFQTNVDPTG  QSVAYSIRST  ARVVLDPWDV  RSQVICEVAH  VTLQGDPLRG
241 TANLSEAIRV  PPTLEVTQQP  MRVGNQVNVV  CQVRKFYPQS  LQLTWSSENG  VCQRETASTL
301 TENKDGTYNW  TSWFLVNISD  QRDDVVLTCQ  VKHDGQLAVS  KRLALEVTVA  QKDQSSDAP
361 GPASSLTALL  LIAVLLGPIY  VPWKQKKT (SEQ ID NO: 14)

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[0043] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies bind to one or more variants or isoforms of a SIRP γ of a single species. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies bind to one or more variants or isoforms of a SIRP γ of more than one species. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies bind to one or more variants or isoforms of human SIRP γ . In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies bind to one or more variants or isoforms of a non-human primate SIRP γ , e.g. a cynomolgus monkey SIRP γ .

[0044] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies bind to a plurality of SIRP γ variants or isoforms found in a particular species, e.g. the SIRP $\alpha/\beta/\gamma$ antibodies bind to more than one

of SIRP γ human isoforms 1-3. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies bind the extracellular domain of SIRP γ (e.g. amino acids 1-360 of SEQ ID NO: 14).

[0045] Also provided herein are Fc-containing SIRP γ antibodies. In some embodiments, Fc domain of (interchangeably referred to as a Fc sequence, Fc region, or simply Fc) of the SIRP γ antibody is a human Fc domain. In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is human IgG1, human IgG2, human IgG3, or human IgG4. In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is that of a mouse. In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is mouse IgG1 or mouse IgG2a. In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is that of a rat. In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is rat IgG1 or rat IgG2b. In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is that of a non-human primate, e.g. it is a cynomolgus monkey Fc domain.

[0046] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are full-length antibodies (comprising an intact tetrameric antibody containing two light chains and two heavy chains, each with a variable region, and a constant region). In some embodiments, the constant region of the full-length SIRP $\alpha/\beta/\gamma$ antibodies comprises a human Fc domain. In some embodiments, the Fc domain of a full-length SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG1, human IgG2, human IgG3, or human IgG4. In some embodiments, the Fc domain of a full-length SIRP $\alpha/\beta/\gamma$ antibody is that of a mouse immunoglobulin. In some embodiments, the Fc domain of a full-length SIRP $\alpha/\beta/\gamma$ antibody is that of a mouse IgG1 or mouse IgG2a. In some embodiments, the Fc domain of a full-length SIRP $\alpha/\beta/\gamma$ antibody is that of a rat. In some embodiments, the Fc domain of a full-length SIRP $\alpha/\beta/\gamma$ antibody is from a rat IgG1 or rat IgG2b. In some embodiments, the Fc domain of a full-length SIRP $\alpha/\beta/\gamma$ antibody is that of a non-human primate, e.g. it is a cynomolgus monkey Fc domain.

[0047] In some embodiments, the binding of the Fc-containing antibody to a SIRP-expressing cell can mediate effector cell-mediated depletion of the SIRP-expressing cell. In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is a human IgG1 Fc. Exemplary, but non-limiting, sequences of heavy chain constant regions (CH) of human IgG1 encompassing Fc domains of interest are provided as SEQ ID NO: 15-38, or a sequence with at least 80% identity thereto. Without being held by theory or mechanism, in some embodiments the Fc domains of interest may not include the terminal Lysine residue. Accordingly, exemplary, but non-limiting, sequences of heavy chain constant regions (CH) of

human IgG1 encompassing Fc domains of interest include any one of SEQ ID NOS: 15-38 without a terminal Lysine residue. SEQ ID NO: 15 provides the canonical human IgG1 heavy chain constant region (CH) sequence.

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 15)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 16)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 17)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 18)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PDVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 19)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 20)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PDVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 21)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 22)

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1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV LHEALHNHYT QKSLSLSPGK (SEQ ID NO: 23)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 24)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV LHEALHNHYT QKSLSLSPGK (SEQ ID NO: 25)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 26)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 27)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 28)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 29)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 30)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE

241 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 31)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSDHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 32)

[0048] In some embodiments, the constant region of human IgG1 heavy chain sequence encompassing a Fc domain of interest is SEQ ID NO: 33, wherein X1 is V or A.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX₁EP KSCDKTHTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTPEVTCVVVDVSDHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 33)

[0049] In some embodiments, the constant region of human IgG1 heavy chain sequence encompassing a Fc domain of interest is SEQ ID NO: 34, wherein X1 is V or A; X2 is G or A; X3 is S or D; and X4 is I or E.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX₁EP KSCDKTHTCP PCPAPELLX₂G
121 PX₃VFLFPPKP KDTLMISRTPEVTCVVVDVSDHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPX₄EKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 34)

[0050] In some embodiments, the constant region of human IgG1 heavy chain sequence encompassing a Fc domain of interest is SEQ ID NO: 35, wherein X1 is V or A.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX₁EP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSDHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV LHEALHSHYT QKSLSLSPGK (SEQ ID NO: 35)

[0051] In some embodiments, the constant region of human IgG1 heavy chain sequence encompassing a Fc domain of interest is SEQ ID NO: 36, wherein X1 is V or A; X2 is M or L; and X3 is N or S.

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX₁EP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSDHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV X₂HEALHX₃HYT QKSLSLSPGK (SEQ ID NO: 36)

[0052] In some embodiments, the constant region of human IgG1 heavy chain sequence encompassing a Fc domain of interest is SEQ ID NO: 37, wherein X1 is K or R; X2 is D or E; and X3 is L or M.

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1   ASTKGPSVFPLAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKX1VEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRX2E
241 X3TKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTPPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 37)

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[0053] In some embodiments, the constant region of human IgG1 heavy chain sequence encompassing a Fc domain of interest is SEQ ID NO: 38, and comprises L234A, L235A, P329G substitutions (referred to as LALA-PG substitutions).

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ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQ
PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 38)

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[0054] In some embodiments, the Fc domain of a Fc-containing SIRP $\alpha/\beta/\gamma$ antibody is a human IgG4 Fc. Exemplary, but non-limiting, sequences of heavy chain constant regions (CH) of human IgG4 encompassing Fc domains of interest are provided as SEQ ID NO: 39-46, or a sequence with at least 80% identity thereto. Without being held by theory or mechanism, in some embodiments the Fc domains of interest may not include the terminal Lysine residue. Accordingly, exemplary, but non-limiting, sequences of heavy chain constant regions (CH) of human IgG4 encompassing Fc domains of interest include any one of SEQ ID NOS: 39-46 without a terminal Lysine residue. SEQ ID NO: 39 provides the canonical human IgG4 heavy chain constant region (CH) sequence.

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ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYTCNVNHDHPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPPEVTCVVVDVSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 39)

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ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYTCNVNHDHPSNTKVDKRVESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPPEVTCVVVDVSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 40)

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ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYTCNVNHDHPSNTKVDKRVESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPPEVTCVVVDVSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE

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PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 41)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 42)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEALGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 43)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 44)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEAFAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 45)

[0055] In some embodiments, the constant region of human IgG4 heavy chain sequence encompassing a Fc domain of interest is SEQ ID NO: 46, wherein X1 is S or P; AND X2 is L or E.

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPX1CPAPEFX2GGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQ
EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQ
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQ
EGNVFSCSVMHEALHNHYTQKSLSLGLGK (SEQ ID NO: 46)

[0056] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies provided herein are chimeric and comprise a variable region from one species, and a constant region from another species, e.g. comprise a human variable region and a mouse constant region. In some embodiments, the mouse constant region is mouse IgG1, or mouse IgG2a. In some embodiments, the antibodies comprise a human variable region and a human constant region. In exemplary embodiments, the human constant region comprises sequences from human IgG1, human IgG2, human IgG3, or human IgG4.

[0057] The EU numbering scheme is one of many available antibody numbering schemes based on the residue numbers assigned to a canonical antibody sequence. Accordingly, a skilled artisan would understand that reference to a particular residue using the EU numbering scheme may or may not be exactly the residue in one of the SIRP $\alpha/\beta/\gamma$ antibodies

of the disclosure. For example, if a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure comprises a V215A substitution in the Fc, wherein the position number of the amino acid residue is of the EU numbering scheme, the residue may not be the actual residue 215 in that particular SIRP $\alpha/\beta/\gamma$ antibody. It may be actual residue number 213, or 214, or 215, or 216 or others. Accordingly, a skilled artisan will understand how to correspond the recited residue using the EU numbering scheme, to the actual residue in a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure. The EU numbering system for antibodies is known in the art and is described, for example, at imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html.

[0058] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG1 constant heavy chain (e.g. SEQ ID NO: 15), and heavy chain Fc substitutions are introduced to increase effector function (e.g. those that exhibit increased affinity to Fc γ R or promote complement protein binding).

[0059] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG1 constant heavy chain (e.g. SEQ ID NO: 15), and heavy chain Fc substitutions are introduced to decrease effector function (e.g. silence).

[0060] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG1 constant heavy chain (e.g. SEQ ID NO: 15), and heavy chain Fc substitutions are introduced to increase antibody half-life.

[0061] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG4 constant heavy chain (e.g. SEQ ID NO: 39), and heavy chain Fc substitutions are introduced to increase effector function (e.g. those that exhibit increased affinity to Fc γ R or promote complement protein binding).

[0062] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG4 constant heavy chain (e.g. SEQ ID NO: 39), and heavy chain Fc substitutions are introduced to decrease effector function (e.g. silence).

[0063] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG4 constant heavy chain (e.g. SEQ ID NO: 39), and heavy chain Fc substitutions are introduced to increase antibody half-life.

[0064] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is an IgG1 Fc domain (e.g. the Fc domain from any one of the IgG1 constant heavy chain sequences of SEQ ID

NOS: 15-38) or is an IgG4 human Fc domain (e.g. the Fc domain from any one of the IgG4 constant heavy chain sequences of SEQ ID NOS: 39-46).

[0065] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is an IgG1 Fc domain (e.g. the Fc domain from any one of the IgG1 constant heavy chain sequences of SEQ ID NOS: 15-38) or is an IgG4 human Fc domain (e.g. the Fc domain from any one of the IgG4 constant heavy chain sequences of SEQ ID NOS: 39, 40, or 46), and comprises at least one amino acid substitution in the heavy chain at a position selected from the group consisting of: 214, 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 356, 358, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0066] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from heavy chain SEQ ID NOS: 15-38, optionally with one or more heavy chain Fc amino acid substitutions, for example at least one amino acid substitution at a position selected from the group consisting of: 214, 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 356, 358, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme. Exemplary substitutions include one or more of K214R, V215A, G236A, S239D, I332E, D356E, L358M, M428L, N434S, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0067] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG1 constant heavy chain (e.g. SEQ ID NO: 15-38), and heavy chain Fc substitutions are introduced to, among other effects, increase effector function (e.g. one or more of FcR binding on an immune effector cell, and binding to complement C1q), selected from the group consisting of V215A, G236A, S239D, I332E, G236A/S239D, G236A/I332E, S239D/I332E, V215A/G236A/S239D/I332E, G236A/S239D/I332E, V215A/G236A/S239D/I332E, K326W/E333S, S267E/H268F/S324T, E345R, E430G, E345K, S440Y, K326W, E333S, S267E, H268F, S324T, and E345R/E430G/S440Y, F243L/R292P/Y300L/V305I/P396L, S239D/I332E, S298A/E333A/K334A,

L234Y/L235Q/G236W/S239M/H268D/D270E/S298A, and D270E/K326D/A330M/K334E wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0068] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG1 constant heavy chain (e.g. SEQ ID NO: 15-38), and heavy chain Fc substitutions are introduced to reduce (e.g. silence) effector function, including one or more of N297A, N297Q, N297G, L235E, L234A, L235A, K214R, P329G, D356E, and L358M, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0069] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG1 constant heavy chain (e.g. SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 38), and heavy chain Fc substitutions are introduced to reduce effector function (e.g. silence), including L234A, L235A, and P329G, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0070] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG4 constant heavy chain (e.g. SEQ ID NOS: 39, 40 or 46), and heavy chain Fc substitutions are introduced to reduce effector function, including one or more of L235E, and F234A/L235A, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0071] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG2 constant heavy chain, and heavy chain Fc substitutions are introduced to reduce effector function, including H268Q/V309L/A330S/P331S and V234A/G237A/P238S/H268A/V309L/A330S/P331S, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0072] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG4 constant heavy chain (e.g. SEQ ID NO: 39), and the antibody is prone to the dynamic process of Fab-arm exchange. Accordingly, in some embodiments the IgG4 heavy chain Fc domain comprises a S228P substitution, resulting in the reduction of Fab-arm exchange, wherein the position number of the amino acid residues are of the EU numbering scheme.

[0073] In some embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is from a human IgG4 constant heavy chain (e.g. SEQ ID NO: 39, 40 or 46), and one or more of the following heavy chain Fc substitution are introduced to reduce effector function: L235A, L235E, S228P, L235E/S228P, S228P/F234A, S228P/F234A/L235A, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0074] In other embodiments, the Fc domain of a SIRP $\alpha/\beta/\gamma$ antibody is altered to increase its serum half-life. Such alterations include heavy chain Fc substitutions of a human IgG1, IgG2, IgG3 or IgG4 such as M428L, N343S, T250Q/M428L, M252Y/S254T/T256E, M428L/N434S, S267E/L328F, N325S/L328F, and H433K/N434F, wherein the position number of the amino acid residues are of the EU numbering scheme.

i. Exemplary SIRP $\alpha/\beta/\gamma$ Antibodies – Complementarity Determining Region (CDR) Sequences

[0075] Provided herein are sequences for exemplary SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure. As referred below, a light chain variable (VL) domain CDR1 region is referred to as CDR-L1; a VL CDR2 region is referred to as CDR-L2; a VL CDR3 region is referred to as CDR-L3; a heavy chain variable (VH) domain CDR1 region is referred to as CDR-H1; a VH CDR2 region is referred to as CDR-H2; and a VH CDR3 region is referred to as CDR-H3. Table 1 provide exemplary CDR triplets for the light chains and heavy chains of SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure. In some embodiments, the antibodies of the disclosure comprise, the CDRs SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8. In some embodiments, the antibodies of the disclosure comprise, 1, 2, 3, or 4 modifications to one or more of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8.

Table 1: Exemplary SIRP $\alpha/\beta/\gamma$ antibody CDR Combination, Antibody S $\alpha\beta\gamma$ -01

Antibody ID.	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
S $\alpha\beta\gamma$ -01	QSLHNGNG FNY (SEQ ID NO: 3)	LGS (SEQ ID NO: 4)	MQGLQTPR T (SEQ ID NO: 5)	GGSISSSNW (SEQ ID NO: 6)	IYHSGST (SEQ ID NO: 7)	ARRGIWFG VGP (SEQ ID NO: 8)

ii. Exemplary SIRP $\alpha/\beta/\gamma$ Antibodies - Variable Region Sequences

[0076] The term variable region and variable domain are used interchangeably and refer to the portions of the light and heavy chains of an antibody that include the complementarity determining regions and framework regions (FRs).

[0077] Table 2 provides amino acid sequences for the variable domains of an exemplary SIRP $\alpha/\beta/\gamma$ antibody of the disclosure. Accordingly, in some embodiments a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 1 or at least 80% sequence identity thereto. In some embodiments a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure comprises a variable light chain comprising an amino acid sequence of SEQ ID NOS: 2 or at least 80% sequence identity thereto.

[0078] In some embodiments, a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure comprises the combination of VH/VL variable chain sequences of Antibody Sa $\beta\gamma$ -01 presented in Table 2. In some embodiments, a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure consist of the combination of VH/VL variable chain sequences of Antibody Sa $\beta\gamma$ -01 presented in Table 2.

[0079] Table 2: Exemplary Variable Heavy Chain and Variable Light Chain Amino Acid Sequences VH/VL pair of Antibody Sa $\beta\gamma$ -01

Antibody ID.	Variable Heavy Chain Amino Acid Sequence	Variable Light Chain Amino Acid Sequence
Sa $\beta\gamma$ -01	QVQLQESGPGLVKPSGTLSLTCAVSGG SISSNWWWSWVRQPPGKGLEWIGEIY HSGSTNYNPSLKSRTISVDKSKNQFSL KLSSVTAADTAVYYCARRGIWFGVGP WGQGTLTVSS (SEQ ID NO: 1)	DIVMTQSPLSLPVTGPGEPAISCRSSQSLH NGFNYLDWYLQKPGQSPQLLIYLGSNRASG VPDRFTGSGSGTDFTLKISRVEAEDVGVYYC MQGLQTPRTFGQGTKVEIK (SEQ ID NO: 2)

[0080] In some embodiments, provided herein is a SIRP $\alpha/\beta/\gamma$ antibody, wherein the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and wherein the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the heavy chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 1, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable domain of the antibody consists of the amino acid sequence of SEQ ID NO: 1, and the light chain variable domain of the antibody comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable

domain of the antibody comprises the amino acid sequence of SEQ ID NO: 1, and the light chain variable domain of the antibody consists the amino acid sequence of SEQ ID NO: 2. In some embodiments, the light chain variable domain comprises CDR sequences of SEQ ID NOS: 3, 4 and 5, and the heavy chain variable domain comprises CDR sequences of SEQ ID NOS: 6, 7 and 8.

II. Treatment of Cancer using SIRP $\alpha/\beta/\gamma$ Antibodies

[0081] Provided herein are antibodies that recognize and bind to SIRP α , SIRP β , and SIRP γ . The antibodies disclosed herein may be used for the treatment of cancer in a subject. In some embodiments, the subject is human. The subject can be of any age. In some embodiments, the subject is about 0 to about 12 years of age. In some embodiments, the subject is about 12 to about 18 years of age. In some embodiments, the subject is above about 18 to about 65 years of age. In some embodiments, the subject is at least 65 years of age or older. In some embodiments, the subject is treatment-naïve. In some embodiments, the subject has received one or more previous cancer treatments. In some embodiments, the subject is additionally suffering from hemophagocytic lymphohistiocytosis (HLH). These embodiments are discussed in further detail below.

A. Cancer and HLH Classifications

[0082] Cancer of the disclosure includes heme and non-heme cancers. In some embodiments, the heme-cancer is leukemia. In some embodiments, the heme-cancer is myeloma. In some embodiments, the heme-cancer is lymphoma. In some embodiments, the non-heme cancer is a solid tumor. In some embodiments, the cancer involves a pre-cancer, pre-HLH conditions, or pro-inflammatory genotypes identified by acquired clonal genetic variants in blood or inherited genetic variants or polymorphisms e.g., clonal hematopoiesis, clonal cytopenia of uncertain significance, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, and positive OHI index in cancer patients (ferritin and sCD25 meeting threshold).

[0083] Lymphomas of the disclosure includes, but is not limited to, Hodgkin as well as Non-Hodgkin lymphoma. Hodgkin lymphoma is marked by the presence of Reed-Sternberg lymphocytes. Non-Hodgkin lymphoma is any lymphoma that is not Hodgkin lymphoma and includes Diffuse Large B-cell lymphoma (DLBCL), Follicular lymphoma, Mantle Cell lymphoma, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Marginal Zone lymphoma, Burkitt lymphoma, T-cell lymphoma, Primary Central Nervous

System lymphoma (PCNSL), Lymphoplasmacytic lymphoma, and not otherwise specified (NOS) lymphoma.

[0084] In some embodiments, T-Cell Lymphoma comprises Cutaneous T-cell lymphoma, Adult T-cell lymphoma, Angioimmunoblastic T-cell lymphoma, Extranodal natural killer/T-cell lymphoma, Enteropathy-associated intestinal T-cell lymphoma (EATL), Anaplastic large cell lymphoma (ALCL), or Peripheral T-cell lymphoma (PTCL).

[0085] Leukemia of the disclosure includes, but is not limited to, Acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-cell ALL), Chronic myeloid leukemia (CML), or Chronic myelomonocytic leukemia (CMML).

[0001] In some embodiments, the patient additionally suffers from hemophagocytic lymphohistiocytosis (HLH), wherein the HLH is secondary HLH (sHLH).

[0086] sHLH includes immunosuppression mediated HLH, immunotherapy mediated HLH, idiopathic trigger mediated HLH, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated (fungal induced) HLH, autoimmune disease mediated HLH, or malignancy-triggered HLH.

[0087] In some embodiments, HLH comprises relapsed HLH. In some embodiments, HLH comprises refractory HLH.

[0088] In some embodiments, the sHLH is an infection-associated HLH, such as virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, or fungal-associated HLH. Examples of virus-associated HLH include, but are not limited to, EBV-associated HLH, CMV-associated HLH, HLH associated with other defined herpes virus infections, HIV-associated HLH, Influenza-associated HLH, and HLH associated with other virus infections. In exemplary embodiments, the infection-associated sHLH is associated with an infection from a coronavirus (e.g. COVID19, SARS (SARS-CoV), MERS), or Ebola. Examples of bacteria-associated HLH include mycobacterium associated HLH. Examples of parasite-associated HLH include Leishmania-associated or Plasmodium-associated HLH. Examples of fungal-induced HLH include Histoplasmosis-associated HLH.

[0089] In other embodiments, the sHLH is a malignancy-associated HLH, such as a malignancy-triggered HLH (e.g. HLH at onset, during, or end-stage of malignancy) and include hematological malignancies (e.g. T-cell lymphoblastic lymphoma/leukemia such as T-cell acute lymphoblastic leukemia (T-cell ALL), T-cell non-lymphoblastic lymphomas

such as peripheral T-cell lymphoma not otherwise specified, B-cell leukemias, B-cell lymphomas (non-Hodgkin's) such as Diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphomas, NK-cell lymphomas/leukemias, myeloid neoplasia such as acute myeloid leukemia (AML), other hematological malignancies), as well as solid tumors. In other embodiments, such sHLH is an HLH occurring during or as a result of treatment of malignancy (not triggered by the malignancy). In some embodiments, the sHLH is associated with a pre-hematologic malignancy.

[0090] In other embodiments, the sHLH is associated with defined rheumatologic conditions (e.g. Macrophage Activation Syndrome-HLH, or MAS-HLH). These include, but are not limited to HLH associated with systemic-onset juvenile idiopathic arthritis (SoJIA), HLH associated with adult-onset Still's disease, HLH associated with systemic lupus erythematosus (SLE), HLH associated with vasculitis, HLH associated with rheumatoid arthritis, as well as HLH associated with other defined autoimmune conditions and HLH associated with an undefined autoimmune condition.

[0091] In other embodiments, the sHLH is a transplant-related HLH, such as HLH associated with a kidney transplant, or hematologic stem cell transplants.

[0092] In some embodiments, the sHLH is associated with iatrogenic immune activation, e.g. associated with checkpoint inhibitors for the treatment of malignancies, associated with T cell therapy, for example chimeric antigen receptor – T cell therapy (CAR-T) or T cell receptor T cell therapy (TCR-T), associated with NK cell activating bispecific monoclonal antibody therapy, or associated with T cell activating bispecific monoclonal antibody therapy. In other embodiments, the sHLH is associated with iatrogenic immune suppression.

B. Administration of Therapeutic SIRP $\alpha/\beta/\gamma$ antibodies

[0093] As contemplated herein, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure, and pharmaceutical compositions comprising the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered for cancer treatment in therapeutically effective amounts, with the administration of at least one treatment phase. In some embodiments, the treatment phase comprises a maintenance dose phase. In some embodiments, the treatment phase comprises a loading dose phase and a maintenance dose phase. In some embodiments, the treatment phase is preceded by a priming dose phase. In some embodiments, the one or more treatment phases are preceded by a priming dose phase. In some embodiments the subject is administered in one or more treatment phases. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$

antibodies comprise the heavy chain variable domain of the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and the light chain variable domain of the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies comprise the CDR triplets of Table 1. In other embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure comprise, 1, 2, 3, or 4 modifications to SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8.

Treatment phase

[0094] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily during a treatment phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered at least two times per week during a treatment phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered at least three times per week during a treatment phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered weekly during a treatment phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered every 2, 3, 4, 5, or 6 weeks during a treatment phase.

[0095] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily during a loading dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered at least two times per week during a loading dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered at least three times per week during a loading dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered weekly during a loading dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered every 2, 3, 4, 5, or 6 weeks during a loading dose phase.

[0096] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily during a maintenance dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered at least two times per week during a maintenance dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present

disclosure are administered at least three times per week during a maintenance dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered weekly during a maintenance dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered every 2, 3, 4, 5, or 6 weeks during a maintenance dose phase.

[0097] In some embodiments, a treatment phase lasts for a duration of at least 1 week. In some embodiments, a treatment phase lasts for a duration of at least 2 weeks. In some embodiments, a treatment phase lasts for a duration of at least 3 weeks. In some embodiments, a treatment phase lasts for a duration of at least 4 weeks. In some embodiments, a treatment phase lasts for a duration of at least 5 weeks. In some embodiments, a treatment phase lasts for a duration of at least 6 weeks. In some embodiments, a treatment phase lasts for a duration of at least 7 weeks. In some embodiments, a treatment phase lasts for a duration of at least 8 weeks. In some embodiments, a treatment phase lasts for a duration of at least 9 weeks. In some embodiments, a treatment phase lasts for a duration of at least 10 weeks. In some embodiments, a treatment phase lasts for a duration of at least 11 weeks. In some embodiments, a treatment phase lasts for a duration of at least 12 weeks. In some embodiments, a treatment phase lasts for a duration of at least 13 weeks. In some embodiments, a treatment phase lasts for a duration of at least 14 weeks. In some embodiments, a treatment phase lasts for a duration of at least 15 weeks. In some embodiments, a treatment phase lasts for a duration of at least 16 weeks. In some embodiments, a treatment phase lasts for a duration of at least 17 weeks. In some embodiments, a treatment phase lasts for a duration of at least 18 weeks. In some embodiments, a treatment phase lasts for a duration of at least 19 weeks. In some embodiments, a treatment phase lasts for a duration of at least 20 weeks. In some embodiments, a treatment phase lasts for a duration of at least 21 weeks. In some embodiments, a treatment phase lasts for a duration of at least 22 weeks. In some embodiments, a treatment phase lasts for a duration of at least 23 weeks. In some embodiments, a treatment phase lasts for a duration of at least 24 weeks. In some embodiments, a treatment phase lasts for a duration of 24 weeks or more. In some embodiments, a treatment phase lasts indefinitely, e.g. until the initial symptoms have significantly decreased or until the condition has a reduced likelihood of returning or until the

condition has been cured. In some embodiments, a treatment phase is terminated and recommenced at a later time, e.g. if the cancer relapses.

[0098] In some embodiments, a loading dose phase lasts for a duration of at least 1 day. In some embodiments, a loading dose phase lasts for a duration of at least 2 days. In some embodiments, a loading dose phase lasts for a duration of at least 3 days. In some embodiments, a loading dose phase lasts for a duration of at least 4 days. In some embodiments, a loading dose phase lasts for a duration of at least 5 days. In some embodiments, a loading dose phase lasts for a duration of at least 6 days. In some embodiments, a loading dose phase lasts for a duration of at least 1 week. In some embodiments, a loading dose phase lasts for a duration of at least 2 weeks. In some embodiments, a loading dose phase lasts for a duration of at least 3 weeks. In some embodiments, a loading dose phase lasts for a duration of at least 4 weeks.

[0099] In some embodiments, a maintenance dose phase lasts for a duration of at least 1 week. In some embodiments, a maintenance dose phase lasts for a duration of at least 2 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 3 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 4 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 5 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 6 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 7 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 8 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 9 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 10 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 11 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 12 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 13 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 14 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 15 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 16 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 17 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 18 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 19 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 20 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 21 weeks.

weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 22 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 23 weeks. In some embodiments, a maintenance dose phase lasts for a duration of at least 24 weeks. In some embodiments, a maintenance dose phase lasts for a duration of 24 weeks or more. In some embodiments, a maintenance dose phase lasts indefinitely, e.g. until the initial symptoms have significantly decreased or until the condition has a reduced likelihood of returning or until the condition has been cured. In some embodiments, a maintenance dose phase is terminated and recommenced at a later time, e.g. if the cancer relapses.

[0100] The administration of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies during the treatment phase as described herein may be carried out intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, intrathecally, intraventricularly, intranasally, transmucosally, through implantation, or through inhalation. Intravenous administration may be carried out via injection or infusion. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered intravenously. In other exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered subcutaneously. In yet other exemplary embodiments, the treatment phase comprises both intravenous and subcutaneous administration of the SIRP $\alpha/\beta/\gamma$ antibodies.

[0101] The administration of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies during a loading dose phase as described herein may be carried out intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, intrathecally, intraventricularly, intranasally, transmucosally, through implantation, or through inhalation. Intravenous administration may be carried out via injection or infusion. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered intravenously. In other exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered subcutaneously. In yet other exemplary embodiments, a loading dose phase comprises both intravenous and subcutaneous administration of the SIRP $\alpha/\beta/\gamma$ antibodies.

[0102] The administration of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies during a maintenance dose phase as described herein may be carried out intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, intrathecally, intraventricularly, intranasally, transmucosally, through implantation, or through inhalation. Intravenous administration may be carried out via injection or infusion. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered intravenously. In other exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered

subcutaneously. In yet other exemplary embodiments, a maintenance dose phase comprises both intravenous and subcutaneous administration of the SIRP $\alpha/\beta/\gamma$ antibodies.

[0103] Administration of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies may be performed with any suitable pharmaceutically acceptable excipients, carriers, or other agents to provide suitable or improved tolerance, transfer, delivery, and the like.

[0104] In some embodiments a treatment phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of about 0.01 mg/kg, of about 0.03 mg/kg, of about 0.05 mg/kg, of about 0.1 mg/kg, of about 0.3 mg/kg, of about 0.5 mg/kg, of about 1.0 mg/kg, of about 3.0 mg/kg, or of about 5.0 mg/kg per dose. In some embodiments a treatment phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of at least about 0.01 mg/kg, of at least about 0.03 mg/kg, of at least about 0.05 mg/kg, of at least about 0.1 mg/kg, of at least about 0.3 mg/kg, of at least about 0.5 mg/kg, of at least about 1.0 mg/kg, of at least about 3.0 mg/kg, of at least 5.0 mg/kg or of at least about 10 mg/kg per dose. In some embodiments a treatment phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of about 0.01 mg/kg to about 0.03 mg/kg, of about 0.03 mg/kg to about 0.05 mg/kg, of about 0.05 mg/kg to about 0.1 mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.3 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 1.0 mg/kg, of about 1.0 mg/kg to about 3.0 mg/kg, of about 3.0 mg/kg to about 5.0 mg/kg, of about 5.0 mg/kg to about 10 mg/kg, of about 0.1 mg/kg to about 1 mg/kg, of about 0.3 mg/kg to about 3 mg/kg, of about 0.5 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 5 mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.01 mg/kg to about 0.05 mg/kg, of about 0.01 mg/kg to about 0.3 mg/kg, of about 0.03 mg/kg to about 0.1 mg/kg, of about 0.03 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 0.5 mg/kg, of about 0.05 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 3 mg/kg, of about 0.05 mg/kg to about 5 mg/kg, of about 0.1 mg/kg to about 3 mg/kg, 0.1 mg/kg to about 5 mg/kg, 0.3 mg/kg to about 1 mg/kg, 0.3 mg/kg to about 3 mg/kg, 0.3 mg/kg to about 5 mg/kg, or about 3.0 mg/kg to about 10 mg/kg.

[0105] In some embodiments a loading dose phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of about 0.01 mg/kg, of about 0.03 mg/kg, of about 0.05 mg/kg, of about 0.1 mg/kg, of about 0.3 mg/kg, of about 0.5 mg/kg, of about 1.0 mg/kg, of about 3.0 mg/kg, or of about 5.0 mg/kg per dose. In some embodiments a loading dose phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of at least about 0.01 mg/kg, of at least

about 0.03 mg/kg, of at least about 0.05 mg/kg, of at least about 0.1 mg/kg, of at least about 0.3 mg/kg, of at least about 0.5 mg/kg, of at least about 1.0 mg/kg, of at least about 3.0 mg/kg, of at least 5.0 mg/kg or of at least about 10 mg/kg per dose. In some embodiments a loading dose phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of about 0.01 mg/kg to about 0.03 mg/kg, of about 0.03 mg/kg to about 0.05 mg/kg, of about 0.05 mg/kg to about 0.1 mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.3 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 1.0 mg/kg, of about 1.0 mg/kg to about 3.0 mg/kg, of about 3.0 mg/kg to about 5.0 mg/kg, of about 5.0 mg/kg to about 10 mg/kg, of about 0.1 mg/kg to about 1 mg/kg, of about 0.3 mg/kg to about 3 mg/kg, of about 0.5 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 5 mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.01 mg/kg to about 0.05 mg/kg, of about 0.01 mg/kg to about 0.3 mg/kg, of about 0.03 mg/kg to about 0.1 mg/kg, of about 0.03 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 0.5 mg/kg, of about 0.05 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 3 mg/kg, of about 0.05 mg/kg to about 5 mg/kg, of about 0.1 mg/kg to about 3 mg/kg, 0.1 mg/kg to about 5 mg/kg, 0.3 mg/kg to about 1 mg/kg, 0.3 mg/kg to about 3 mg/kg, 0.3 mg/kg to about 5 mg/kg, or about 3.0 mg/kg to about 10 mg/kg.

In some embodiments a maintenance dose phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of about 0.01 mg/kg, of about 0.03 mg/kg, of about 0.05 mg/kg, of about 0.1 mg/kg, of about 0.3 mg/kg, of about 0.5 mg/kg, of about 1.0 mg/kg, of about 3.0 mg/kg, or of about 5.0 mg/kg per dose. In some embodiments a maintenance dose phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of at least about 0.01 mg/kg, of at least about 0.03 mg/kg, of at least about 0.05 mg/kg, of at least about 0.1 mg/kg, of at least about 0.3 mg/kg, of at least about 0.5 mg/kg, of at least about 1.0 mg/kg, of at least about 3.0 mg/kg, of at least 5.0 mg/kg or of at least about 10 mg/kg per dose. In some embodiments a maintenance dose phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of about 0.01 mg/kg to about 0.03 mg/kg, of about 0.03 mg/kg to about 0.05 mg/kg, of about 0.05 mg/kg to about 0.1 mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.3 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 1.0 mg/kg, of about 1.0 mg/kg to about 3.0 mg/kg, of about 3.0 mg/kg to about 5.0 mg/kg, of about 5.0 mg/kg to about 10 mg/kg, of about 0.1 mg/kg to about 1 mg/kg, of about 0.3 mg/kg to about 3 mg/kg, of about 0.5 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 5

mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.01 mg/kg to about 0.05 mg/kg, of about 0.01 mg/kg to about 0.3 mg/kg, of about 0.03 mg/kg to about 0.1 mg/kg, of about 0.03 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 0.5 mg/kg, of about 0.05 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 3 mg/kg, of about 0.05 mg/kg to about 5 mg/kg, of about 0.1 mg/kg to about 3 mg/kg, 0.1 mg/kg to about 5 mg/kg, 0.3 mg/kg to about 1 mg/kg, 0.3 mg/kg to about 3 mg/kg, 0.3 mg/kg to about 5 mg/kg, or about 3.0 mg/kg to about 10 mg/kg.

Priming dose phase

[0106] As noted above, in some embodiments the subject is administered one or more priming doses during the one or more priming dose phases prior to the one or more treatment phases. Without being held to theory or mechanism, the priming dose is thought to reduce infusion reaction severity.

[0107] In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered for a period of 1 day during the priming dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily for a period of 2 days or at least 2 days during the priming dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily for a period of 3 days, or at least 3 days during the priming dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily for a period of 4 days, or at least 4 days during the priming dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily for a period of 5 days, or at least 5 days during the priming dose phase. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered daily for a period of more than 5 days during the priming dose phase.

[0108] In some embodiments, one or more additional priming dose phases may be administered after the first treatment phase is terminated and before a subsequent treatment phase is recommenced.

[0109] The administration of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies during the priming dose phase as described herein may be carried out intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, intrathecally, intraventricularly, intranasally, transmucosally, through implantation, or through inhalation. Intravenous administration during the priming dose phase may be carried out via injection or

infusion. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered intravenously during the priming dose phase. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered subcutaneously during the priming dose phase. In exemplary embodiments the SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure are administered subcutaneously and intravenously during the priming dose phase. Administration of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies during the priming dose phase may be performed with any suitable excipients, carriers, or other agents to provide suitable or improved tolerance, transfer, delivery, and the like.

[0110] In some embodiments the priming dose phase comprises administering one or more doses of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure at a concentration of about 0.01 mg/kg to about 0.03 mg/kg, of about 0.03 mg/kg to about 0.05 mg/kg, of about 0.05 mg/kg to about 0.1 mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.3 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 1.0 mg/kg, of about 1.0 mg/kg to about 3.0 mg/kg, of about 3.0 mg/kg to about 5.0 mg/kg, of about 5.0 mg/kg to about 10 mg/kg, of about 0.1 mg/kg to about 1 mg/kg, of about 0.3 mg/kg to about 3 mg/kg, of about 0.5 mg/kg to about 0.5 mg/kg, of about 0.5 mg/kg to about 5 mg/kg, of about 0.1 mg/kg to about 0.3 mg/kg, of about 0.01 mg/kg to about 0.05 mg/kg, of about 0.01 mg/kg to about 0.3 mg/kg, of about 0.03 mg/kg to about 0.1 mg/kg, of about 0.03 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 0.5 mg/kg, of about 0.05 mg/kg to about 0.3 mg/kg, of about 0.05 mg/kg to about 3 mg/kg, of about 0.05 mg/kg to about 5 mg/kg, of about 0.1 mg/kg to about 3 mg/kg, 0.1 mg/kg to about 5 mg/kg, 0.3 mg/kg to about 1 mg/kg, 0.3 mg/kg to about 3 mg/kg, 0.3 mg/kg to about 5 mg/kg, or about 3.0 mg/kg to about 10 mg/kg.

[0111] The administered dose and/or frequency of administration of a SIRP $\alpha/\beta/\gamma$ antibody of the disclosure during the priming dose phase, treatment phase, loading dose phase, or maintenance dose phase may be modified based on certain subject response criteria. A modified dose may be either a dose reduction or escalation or an increase or decrease in the frequency of administration of said dose. In some embodiments, the modified dose is reverted once the certain subject response criteria has resolved.

[0112] The timing of administration of the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure may also be referenced based on a daily timeline. For instance, "Day 1" refers to the first day on which the first single administration is initiated, regardless of whether the dose is part of the priming dose phase, treatment phase, loading dose phase, or maintenance phase. Subsequent administrations may be scheduled relative to this initial dose. In some embodiments, the subject

is administered a priming dose on Day 1. In some embodiments, the subject is administered a loading dose on Day 2, Day 3 and Day 4. In some embodiments, the subject is administered a maintenance dose at least two times per week starting on Days 8 and 11, respectively.

C. Pharmaceutical Compositions

[0113] The disclosure also provides pharmaceutical compositions comprising any one of the SIRP $\alpha/\beta/\gamma$ antibodies disclosed herein, and optionally a pharmaceutical acceptable excipient or carrier. In some embodiments, the pharmaceutical composition is sterile. The pharmaceutical compositions may be formulated to be compatible with their intended routes of administration. In some embodiments, the pharmaceutical compositions of the disclosure are suitable for administration to a human subject.

D. Combination Therapies

[0114] The administration of any one of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies provided herein may be in combination with any other known, suspected, and experimental drugs or treatments for diseases or conditions. In some embodiments, the disease or condition is associated with overactivation and/or hyperproliferation of myeloid cells, lymphocytes, or other cells expressing SIRP α , SIRP β , or SIRP γ . In some embodiments, the disease or condition is an autoimmune disease or condition. In some embodiments, the disease or condition is a neoplastic disorder or malignancy. In some embodiments, a therapeutic SIRP $\alpha/\beta/\gamma$ antibody may be used in combination with corticosteroids (e.g. – dexamethasone).

[0115] In some embodiments, a therapeutic SIRP $\alpha/\beta/\gamma$ antibody provided herein to treat cancer, is used in combination with one or more additional therapeutic or investigational agents is selected from listing consisting of: a chemotherapeutic agent, an immunotherapeutic agent, a CAR T therapeutic agent, a JAK inhibitor, a radiotherapeutic agent, methotrexate, azathioprine, dexamethasone, a biological therapeutic agent, a TNF inhibitor, anakinra, antimicrobials, etoposide, tocilizumab, emapalumab, alemtuzumab, cyclosporin, intravenous immunoglobulin (IVIG), rituximab, other corticosteroids, or any combination chemotherapy regimens. In some embodiments, the chemotherapeutic agent is selected from the group consisting of: ICE (ifosfamide, carboplatin, and etoposide phosphate), HyperCVAD (dexamethasone, cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (adriamycin), methotrexate, cytarabine), AAVD (brentuximab vedotin (Adcetris), doxorubicin, vinblastine, and dacarbazine), azacitidine, venetoclax, GemEtop (gemcitabine

hydrochloride and), GemOx (gemcitabine hydrochloride and etoposide), and CHOP (cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (oncovin), and prednisone), or any combination or modified iteration thereof.

E. Evaluation of SIRP $\alpha/\beta/\gamma$ Antibody Therapy

[0001] In some embodiments, a predicted prognosis and/or likelihood of response to treatment is obtained by evaluating a ratio of sCD25/ferritin. In some embodiments, a predicted prognosis and/or likelihood of response to treatment is obtained by measuring circulating monocyte and lymphocyte counts. In some embodiments, a predicted prognosis and/or likelihood of response to treatment is obtained by measuring CRP. In some embodiments, a predicted prognosis and/or likelihood of response to treatment is obtained by measuring % reduction of any of these markers (ferritin, sCD25, CRP). In some embodiments, a predicted prognosis and/or likelihood of response to treatment is obtained by any other known assessment.

[0116] Evaluation of the SIRP $\alpha/\beta/\gamma$ antibody therapy may be carried out by any known response assessment. In some embodiments, evaluation of the SIRP $\alpha/\beta/\gamma$ antibody therapy in a subject with HLH comprises measuring one or more biomarkers from a biological sample obtained from the subject which may include ferritin, sCD25, sCD25/ferritin ratio, C-reactive protein (CRP), fibrinogen, CXCL9, CXCL10, sCD163, LDH, IFN-gamma, IL-6, TNF-alpha, IL-8, IL-10, IL-18, GDF-15, IL-1RA, MDC, ST2, IL-16, CD163, Epithelial-Derived Neutrophil-Activating Protein 78 (ENA-78), Factor VII, ICAM-1, Interferon gamma Induced Protein 10 (IP-10), IL-12p40, IL-16, Macrophage-Derived Chemokine (MDC), Macrophage Inflammatory Protein-1 alpha (MIP-1 alpha), Macrophage Inflammatory Protein-1 beta (MIP-1 beta), Matrix Metalloproteinase-3 (MMP-3), Matrix Metalloproteinase-9 (MMP-9) Monocyte Chemotactic Protein 1 (MCP-1), and Monokine Induced by Gamma Interferon (MIG).

III. Exemplary Enumerated Embodiments

[0117] The following non-limiting enumerated embodiments are provided as exemplary.

[0118] Embodiment I-1. A method of treating a cancer in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 10 mg/kg per dose of a SIRP $\alpha/\beta/\gamma$ binding antibody, in one or more treatment phases.

[0119] Embodiment I-2. The method of I-1, wherein the heavy chain variable region (VH) of the antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto.

[0120] Embodiment I-3. The method of I-1 or I-2, wherein the antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

[0121] Embodiment I-4. The method of any one of I-1 to I-3, wherein the antibody comprises an Fc domain.

[0122] Embodiment I-5. The method of I-4, wherein the Fc domain is selected from the group consisting of human IgG1, IgG2, IgG3, and IgG4.

[0123] Embodiment I-6. The method of claim I-5, wherein the Fc domain is from the heavy chain IgG amino acid sequences of SEQ ID NO: 15 or SEQ ID NO: 39, optionally with one or more Fc amino acid substitutions.

[0124] Embodiment I-7. The method of claim I-5, wherein the Fc domain is from the heavy chain IgG amino acid sequences of any one of SEQ ID NOS: 15-46, optionally lacking a terminal lysine.

[0125] Embodiment I-8. The method of I-5, wherein the heavy chain Fc domain comprises one or more amino acid substitutions relative to SEQ ID NO: 15 or SEQ ID NO: 39 at a position selected from the group consisting of: 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme.

[0126] Embodiment I-9. The method of any one of I-1 to I-8, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered as a pharmaceutical composition, wherein the pharmaceutical composition comprises the antibody, and a pharmaceutically acceptable carrier.

[0127] Embodiment I-10. The method of any one of I-1 to I-9, wherein the treatment phase comprises a loading dose phase and a maintenance dose phase.

[0128] Embodiment I-11. The method of any one of I-1 to I-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the treatment phase.

- [0129] Embodiment I-12. The method of any one of I-1 to I-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the treatment phase.
- [0130] Embodiment I-13. The method of any one of I-1 to I-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the treatment phase.
- [0131] Embodiment I-14. The method of any one of I-1 to I-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the treatment phase.
- [0132] Embodiment I-15. The method of any one of I-1 to I-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the loading dose phase.
- [0133] Embodiment I-16. The method of any one of I-1 to I-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the loading dose phase.
- [0134] Embodiment I-17. The method of any one of I-1 to I-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the loading dose phase.
- [0135] Embodiment I-18. The method of any one of I-1 to I-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the loading dose phase.
- [0136] Embodiment I-19. The method of any one of I-1 to I-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the maintenance dose phase.
- [0137] Embodiment I-20. The method of any one of I-1 to I-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the maintenance dose phase.
- [0138] Embodiment I-21. The method of any one of I-1 to I-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the maintenance dose phase.
- [0139] Embodiment I-22. The method of any one of I-1 to I-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the maintenance dose phase.
- [0140] Embodiment I-23. The method of any one of I-1 to I-22, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered daily during the loading dose phase.

- [0141] Embodiment I-24. The method of any one of I-1 to I-23, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered weekly during the maintenance dose phase.
- [0142] Embodiment I-25. The method of any one of I-1 to I-23, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject at least two times per week during the maintenance dose phase.
- [0143] Embodiment I-26. The method of any one of I-1 to I-25, wherein the treatment phase lasts for a duration of at least 12 weeks.
- [0144] Embodiment I-27. The method of any one of I-1 to I-25, wherein the treatment phase lasts for a duration of less than 12 weeks.
- [0145] Embodiment I-28. The method of any one of I-1 to I-27, wherein the treatment phase comprises one or more doses of about 0.1mg/kg to about 1mg/kg.
- [0146] Embodiment I-29. The method of any one of I-1 to I-27, wherein the loading phase comprises one or more doses of about 0.3 mg/kg to about 1.0 mg/kg.
- [0147] Embodiment I-30. The method of any one of I-1 to I-27 or Embodiment I-29, wherein the maintenance dose phase comprises one or more doses of about 0.3 mg/kg to about 1.0 mg/kg.
- [0148] Embodiment I-31. The method of any one of I-1 to I-28, wherein the method further comprises a priming dose phase.
- [0149] Embodiment I-32. The method of I-31, wherein the priming dose occurs over a duration of 1 to 5 days.
- [0150] Embodiment I-33. The method of I-31 or I-32, wherein the priming comprises one or more doses of about 0.01 mg/kg, about 0.03 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 3 mg/kg, or about 5 mg/kg.
- [0151] Embodiment I-34. The method of I-33, wherein the subject is administered a priming dose of about 0.1 mg/kg on Day 1.
- [0152] Embodiment I-35. The method of I-34, wherein the subject is administered a loading dose of about 0.3 mg/kg on Days 2, 3, and 4.
- [0153] Embodiment I-36. The method of I-35, wherein the subject is administered a maintenance dose of about 0.5 mg/kg at least two times per week starting on Days 8 and 11 respectively.
- [0154] Embodiment I-37. The method of any one of I-31 to I-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the priming dose phase.

- [0155] Embodiment I-38. The method of any one of I-31 to I-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the priming dose phase.
- [0156] Embodiment I-39. The method of any one of I-31 to I-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the priming dose phase.
- [0157] Embodiment I-40. The method of any one of I-31 to I-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the priming dose phase.
- [0158] Embodiment I-41. The method of any one of I-1 to I-40, wherein the method comprises at least two treatment phases, each preceded by a priming dose phase.
- [0159] Embodiment I-42. The method of any one of I-1 to I-41, wherein the subject is below about 0 to about 12 years of age.
- [0160] Embodiment I-43. The method of any one of I-1 to I-41, wherein the subject is about 12 to about 18 years of age.
- [0161] Embodiment I-44. The method of any one of I-1 to I-41, wherein the subject is about 18 to about 65 years of age.
- [0162] Embodiment I-45. The method of any one of I-1 to I-41, wherein the subject is above about 65 years of age.
- [0163] Embodiment I-46. The method of any one of I-1 to I-45, wherein the subject is not treatment-naïve.
- [0164] Embodiment I-47. The method of I-46, wherein the subject has previously been administered one or more of the following: etoposide, dexamethasone, cyclosporin, anakinra, Tocilizumab, JAK inhibitors, alemtuzimab, intravenous immunoglobulin (IVIG), rituximab, other corticosteroids, emapalumab or any combination chemotherapy regimens.
- [0165] Embodiment I-48. The method of any one of I-1 to I-45, wherein the subject is treatment-naïve.
- [0166] Embodiment I-49. The method of any one of I-1 to I-48, wherein the cancer is a heme-based cancer.
- [0167] Embodiment I-50. The method of I-49, wherein the heme-based cancer is selected from the group consisting of lymphoma, leukemia, and myeloma.
- [0168] Embodiment I-51. The method of I-50, wherein the leukemia is Acute myeloid leukemia (AML), Chronic myeloid leukemia (CML), or Chronic myelomonocytic leukemia (CMML).

- [0169] Embodiment I-52. The method of I-50, wherein the lymphoma is Hodgkin lymphoma or non-Hodgkin lymphoma.
- [0170] Embodiment I-53. The method of I-52, wherein the non-Hodgkin lymphoma comprises Diffuse Large B-cell lymphoma (DLBCL), Follicular lymphoma, Mantle Cell lymphoma, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Marginal Zone lymphoma, Burkitt lymphoma, T-cell lymphoma, Primary Central Nervous System lymphoma (PCNSL), Lymphoplasmacytic lymphoma, or not otherwise specified (NOS) lymphoma.
- [0171] Embodiment I-54. The method of I-53, wherein the T-Cell Lymphoma comprises Cutaneous T-cell lymphoma, Adult T-cell lymphoma, Angioimmunoblastic T-cell lymphoma, Extranodal natural killer/T-cell lymphoma, Enteropathy-associated intestinal T-cell lymphoma (EATL), Anaplastic large cell lymphoma (ALCL), or Peripheral T-cell lymphoma (PTCL).
- [0172] Embodiment I-55. The method of any one of I-1 to I-54, wherein the patient additionally suffers from hemophagocytic lymphohistiocytosis (HLH), wherein the HLH is secondary HLH.
- [0173] Embodiment I-56. The method of I-55, wherein the sHLH is selected from the group consisting of immunosuppression or immunotherapy mediated HLH, idiopathic trigger mediated HLH, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated (fungal induced) HLH, autoimmune disease mediated HLH, malignancy-triggered HLH, non-mendelian secondary HLH (sHLH) and mendelian associated sHLH.
- [0174] Embodiment I-57. The method of I-56, wherein the malignancy-triggered HLH comprises an HLH triggered by a hematological malignancy or solid tumor.
- [0175] Embodiment I-58. The method of I-56, wherein the HLH comprises a relapsed or refractory sHLH.
- [0176] Embodiment I-59. The method of I-56, wherein the sHLH is an infection-associated HLH.
- [0177] Embodiment I-60. The method of I-56, wherein the sHLH is associated with a rheumatologic condition.
- [0178] Embodiment I-61. The method of I-56, wherein the sHLH is associated with a kidney transplant or hematologic stem cell transplant.
- [0179] Embodiment I-62. The method of I-56, wherein the sHLH is associated immune checkpoint inhibitors or T cell therapy (CAR-T) or T cell receptor T cell therapy (TCR-T).

[0180] Embodiment I-63. The method of any one of I-1 to I-62, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered as single agent, or in combination with at least one additional therapeutic agent in the treatment phase and/or the prime dosing phase.

[0181] Embodiment I-64. The method of I-63, wherein the one or more additional therapeutic or investigational agents is selected from listing consisting of: a chemotherapeutic agent, an immunotherapeutic agent, a CAR T therapeutic agent, a JAK inhibitor, a radiotherapeutic agent, methotrexate, azathioprine, dexamethasone, a biological therapeutic agent, a TNF inhibitor, anakinra, antimicrobials, etoposide, tocilizumab, emapalumab, and alemtuzumab.

[0182] Embodiment I-65. The method of any one of I-1 to I-64, wherein the method comprises measuring one or more biomarkers in a biological sample obtained from the subject.

[0183] Embodiment I-66. The method of I-65, wherein the biomarkers comprise one or more of ferritin, sCD25, sCD25/ferritin ratio, C-reactive protein (CRP), fibrinogen, CXCL9, CXCL10, sCD163, LDH, IFN-gamma, IL-6, TNF-alpha, IL-8, IL-10, IL-18, GDF-15, IL-1RA, MDC, ST2, IL-16, circulating monocyte counts, and circulating lymphocyte counts, CD163, Epithelial-Derived Neutrophil-Activating Protein 78 (ENA-78), Factor VII, ICAM-1, Interferon gamma Induced Protein 10 (IP-10), IL-12p40, Macrophage-Derived Chemokine (MDC), Macrophage Inflammatory Protein-1 alpha (MIP-1 alpha), Macrophage Inflammatory Protein-1 beta (MIP-1 beta), Matrix Metalloproteinase-3 (MMP-3), Matrix Metalloproteinase-9 (MMP-9) Monocyte Chemotactic Protein 1 (MCP-1), and Monokine Induced by Gamma Interferon (MIG).

[0184] Embodiment I-67. Use of a SIRP $\alpha/\beta/\gamma$ binding antibody in the manufacture of a medicament for treating cancer in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of, in one or more treatment phases.

[0185] Embodiment I-68. The use of I-67, wherein the heavy chain variable region (VH) of the antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto.

[0186] Embodiment I-69. The use of I-67 or I-68, wherein the antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

[0187] Embodiment I-70. A SIRP $\alpha/\beta/\gamma$ binding antibody for use in treating cancer in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of a, in one or more treatment phases.

[0188] Embodiment I-71. The antibody for use of I-70, wherein the heavy chain variable region (VH) of the antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto.

[0189] Embodiment I-72. The antibody for use of I-70 or I-71, wherein the antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

[0190] Embodiment I-73. A method of treating cancer in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of an anti-SIRP antibody, in one or more treatment phases, wherein the antibody comprises a means for binding human SIRP α , SIRP β , and SIRP γ proteins.

[0191] The following Examples are merely illustrative and are not meant to limit any aspects of the present disclosure in any way.

EXAMPLES

Example 1: Sa β γ -01 Dosing Study Design and Criteria

[0192] A Phase 1b, open-label, multicenter study was designed to investigate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of Sa β γ -01 following administration of Sa β γ -01 in subjects with lymphoma and sHLH. The study comprised up to 4 cohorts with a 1-week screening period, a 12-week treatment period, optional extension phase treatment period, and 4-week follow-up period (**FIG. 1A-1B**).

[0193] Cohort 1 was designed to establish dose level/regimen in sHLH/lymphoma patients for utilization in Cohorts 2-4. Eligible subjects for cohort 1 were ≥ 12 years of age. The subject of any cohort was excluded from the study if they met any of the following: known or previous treatment for primary HLH; any other significant concurrent, uncontrolled medical

condition that contraindicated participation in the study; hemopoietic stem cell transplant (HSCT) within 100 days of the first dose of Sa β γ -01; ongoing administration of any therapies used primarily to treat HLH excluding dexamethasone; live or attenuated vaccine received within 6 weeks or bacille Calmette-Guerin (BCG) vaccine within 12 weeks prior to screening; history of hypersensitivity or allergy to dexamethasone; history of hypersensitivity or allergy to any components of Sa β γ -01; or currently breastfeeding. Subject demographics and baseline characteristics for Cohorts 1 and 2 can be found in **FIG. 2**.

[0194] Cohort 1 included up to 4 dose levels of Sa β γ -01 (**Table 1.1**). The initial starting dose (Dose Level 1) for Cohort 1 was 0.1 mg/kg and was administered to the first 3 subjects sequentially. Successive subjects in Cohort 1 were not dosed until the preceding subject had received and tolerated at least one dose for a minimum of 24 hours. Newly enrolled subjects then started at Dose Level 2 and received a priming dose of 0.1 mg/kg on Day 1, and loading doses of 0.3 mg/kg on Days 2, 3, and 4. After the loading dose, the maintenance dose was initiated, and was escalated during an intra-subject dose escalation phase until that subject: (1) demonstrated biomarker evidence of improvement, (2) developed dose-limiting toxicities (DLT), or (3) received a maximum dose of 3 mg/kg. Intravenous (IV) administration occurred over 6 hours on Day 1 and for the first dose of each new dose level, and then over 60 minutes for subsequent doses if the first dose was tolerated. Highest dose escalation level and added treatments for each individual subject in Cohorts 1 and 2 can be found in **FIG. 3**.

Table 1.1: Estimated Sa β γ -01 Doses Level for Cohort 1

Dose Levels	Sa β γ -01 Doses (mg/kg)
Dose Level 1	0.1
Dose Level 2	0.3
Dose Level 3	1.0
Dose Level 4	3.0

[0195] Cohort 2 was designed to be initiated with a single fixed dose phase to further evaluate a dose level and regimen determined from Cohort 1, via intravenous (IV) infusion or subcutaneous (SC) injection in the subjects (**FIG. 1B**). The dose level and regimen may be adjusted (increased or decreased) for the cohort as deemed appropriate. Subjects may be transitioned from an IV to a SC dosing schedule. Total treatment duration was designed up to 12 weeks.

[0196] Cohorts 3 and 4 were additionally designed to investigate less frequent dosing regimens of Sαβγ-01 at a dose informed by previous cohorts and no higher than 3 mg/kg.

[0197] Cohort 2 was designed to be open to all eligible participants (i.e., those 6- <12 years of age who have relapsed or refractory sHLH and participants ≥ 12 years of age who were treatment-naïve or had relapsed or refractory sHLH). All Cohort 2-4 participants were enrolled at a fixed dose regimen with either IV or SC routes of administration. IV administration was to be given over 3-6 hours for the first dose and then over 60 minutes for subsequent doses, if the first dose was well tolerated.

Example 2: Evaluation of Sαβγ-01 Dosing Study

[0198] PK was evaluated by measuring plasma concentrations of Sαβγ-01. For participants < 12 years of age, a PK sample was collected pre-dose (within 1 hour of dosing) prior to each dose administered. No other PK samples were to be collected for this age group. For participants ≥ 12 years of age, a maximum of 5 samples may be collected at additional time points during the study if warranted. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

[0199] Biomarkers were additionally measured in participants ≥ 12 years of age only, blood samples were collected periodically and used as the basis for multiple assays to evaluate the effect of Sαβγ-01. Analyses may include, but not be limited to, plasma cytokines, tumor necrosis factor (TNF) alpha, IFN γ , IL-2, IL-4, IL-6, IL-10, IL-13 IL-17, IL23, ferritin, sCD25, CRP, D-dimer, fibrinogen, CXCL9, CXCL10, CD163, and LDH. (**FIG. 4**).

[0200] **FIG. 4** focuses on the overall clinical course and maximum biomarker response in the 3 patients with partial responses in Cohort 1; the figure shows the characteristics of sCD25 and ferritin biomarker response in three Cohort 1 subjects in clinical remission from cancer and sHLH at week 16. All 3 patients demonstrated cancer remission based on imaging and/or bone marrow evaluation depending on standard of care practices for evaluation of their underlying malignancy. All 3 patients had low sCD25/ferritin ratio and their sHLH disease characteristics were not expected to respond to combination chemotherapy. (Zou H. J Cancer Res Clin Oncol.;149(11):8521-8533, 2023). Achieving clinical remission of both the sHLH and cancer, and therefore, suggesting anti-tumor and anti-HLH effects that are synergistic with combination chemotherapy.

[0201] FIG. 5 shows a summary table of anti-tumor activity with S α β γ -01 in T-Cell Malignancies (TCM). TCMs are generally considered chemotherapy-resistant malignancies with high unmet needs. Five chemotherapy-refractory peripheral T cell lymphoma (PTCL) patients had their tumor response evaluated around week 4 of study (except for Patient 13 who had testing on Day 40) using the same modality that best measured their baseline disease activity (PET or marrow evaluation, or both). 4 of 5 (80%) of these patients achieved complete tumor responses (may be a compartmental assessment) based on the modality of choice per clinician discretion after S α β γ -01 treatment in combination with clinician choice of anti-cancer directed therapies. The targeted depletion of SIRP-positive myeloid cells and T lymphocytes by S α β γ -01 may exert anti-tumor effects directly by cytotoxic killing of tumor cells, indirectly by altering the tumor microenvironment) and/or by other mechanisms. SIRPs may be overexpressed in the tumor microenvironment, as was demonstrated in GBM (Vlaminck et al. 2021 Front. Immunol. 12:777524). ELA026 activity in TCM is being evaluated in the ongoing sHLH Phase 1b study and in other future studies.

CLAIMS

1. A method of treating a cancer in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 10 mg/kg per dose of a SIRP $\alpha/\beta/\gamma$ binding antibody, in one or more treatment phases.
2. The method of claim 1, wherein the heavy chain variable region (VH) of the antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto.
3. The method of claim 1 or 2, wherein the antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.
4. The method of any one of claims 1-3, wherein the antibody comprises an Fc domain.
5. The method of claim 4, wherein the Fc domain is selected from the group consisting of human IgG1, IgG2, IgG3, and IgG4.
6. The method of claim 5, wherein the Fc domain is from the heavy chain IgG amino acid sequences of SEQ ID NO: 15 or SEQ ID NO: 39, optionally with one or more Fc amino acid substitutions.
7. The method of claim 5, wherein the Fc domain is from the heavy chain IgG amino acid sequences of any one of SEQ ID NOS: 15-46, optionally lacking a terminal lysine.
8. The method of 5, wherein the heavy chain Fc domain comprises one or more amino acid substitutions relative to SEQ ID NO: 15 or SEQ ID NO: 39 at a position selected from the group consisting of: 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 396, 428, 430, 433, 434, and 440 wherein the position numbers of the amino acid residues are of the EU numbering scheme.
9. The method of any one of claims 1-8, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered as a pharmaceutical composition, wherein the pharmaceutical composition comprises the antibody, and a pharmaceutically acceptable carrier.
10. The method of any one of claims 1-9, wherein the treatment phase comprises a loading dose phase and a maintenance dose phase.

11. The method of any one of claims 1-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the treatment phase.
12. The method of any one of claims 1-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the treatment phase.
13. The method of any one of claims 1-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the treatment phase.
14. The method of any one of claims 1-10, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the treatment phase.
15. The method of any one of claims 1-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the loading dose phase.
16. The method of any one of claims 1-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the loading dose phase.
17. The method of any one of claims 1-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the loading dose phase.
18. The method of any one of claims 1-14, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the loading dose phase.
19. The method of any one of claims 1-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the maintenance dose phase.
20. The method of any one of claims 1-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the maintenance dose phase.
21. The method of any one of claims 1-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the maintenance dose phase.
22. The method of any one of claims 1-18, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the maintenance dose phase.
23. The method of any one of claims 1-22, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered daily during the loading dose phase.

24. The method of any one of claims 1-23, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered weekly during the maintenance dose phase.
25. The method of any one of claims 1-23, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject at least two times per week during the maintenance dose phase.
26. The method of any one of claims 1-25, wherein the treatment phase lasts for a duration of at least 12 weeks.
27. The method of any one of claims 1-25, wherein the treatment phase lasts for a duration of less than 12 weeks.
28. The method of any one of claims 1-27, wherein the treatment phase comprises one or more doses of about 0.1 mg/kg to about 1 mg/kg.
29. The method of any one of claims 1-27, wherein the loading phase comprises one or more doses of about 0.3 mg/kg to about 1.0 mg/kg.
30. The method of any one of claims 1-27 or 29, wherein the maintenance dose phase comprises one or more doses of about 0.3 mg/kg to about 1.0 mg/kg.
31. The method of any one of claims 1-28, wherein the method further comprises a priming dose phase.
32. The method of claim 31, wherein the priming dose occurs over a duration of 1 to 5 days.
33. The method of claim 31 or 32, wherein the priming comprises one or more doses of about 0.01 mg/kg, about 0.03 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 3 mg/kg, or about 5 mg/kg.
34. The method of claim 33, wherein the subject is administered a priming dose of about 0.1 mg/kg on Day 1.
35. The method of claim 34, wherein the subject is administered a loading dose of about 0.3 mg/kg on Days 2, 3, and 4.
36. The method of claim 35, wherein the subject is administered a maintenance dose of about 0.5 mg/kg at least two times per week starting on Days 8 and 11 respectively.
37. The method of any one of claims 31-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject subcutaneously during the priming dose phase.
38. The method of any one of claims 31-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered to the subject intravenously during the priming dose phase.

39. The method of any one of claims 31-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject intravenously and subsequently administered subcutaneously during the priming dose phase.
40. The method of any one of claims 31-36, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is initially administered to the subject subcutaneously and subsequently administered intravenously during the priming dose phase.
41. The method of any one of claims 1-40, wherein the method comprises at least two treatment phases, each preceded by a priming dose phase.
42. The method of any one of claims 1-41, wherein the subject is below about 0 to about 12 years of age.
43. The method of any one of claims 1-41, wherein the subject is about 12 to about 18 years of age.
44. The method of any one of claims 1-41, wherein the subject is about 18 to about 65 years of age.
45. The method of any one of claims 1-41, wherein the subject is above about 65 years of age.
46. The method of any one of claims 1-45, wherein the subject is not treatment-naïve.
47. The method of claim 46, wherein the subject has previously been administered one or more of the following: etoposide, dexamethasone, cyclosporin, anakinra, Tocilizumab, JAK inhibitors, alemtuzimab, intravenous immunoglobulin (IVIG), rituximab, other corticosteroids, emapalumab or any combination chemotherapy regimens.
48. The method of any one of claims 1-45, wherein the subject is treatment-naïve.
49. The method of any one of claims 1-48, wherein the cancer is a heme-based cancer.
50. The method of claim 49, wherein the heme-based cancer is selected from the group consisting of lymphoma, leukemia, and myeloma.
51. The method of claim 50, wherein the leukemia is Acute myeloid leukemia (AML), Chronic myeloid leukemia (CML), or Chronic myelomonocytic leukemia (CMML).
52. The method of claim 50, wherein the lymphoma is Hodgkin lymphoma or non-Hodgkin lymphoma.
53. The method of claim 52, wherein the non-Hodgkin lymphoma comprises Diffuse Large B-cell lymphoma (DLBCL), Follicular lymphoma, Mantle Cell lymphoma, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Marginal Zone lymphoma, Burkitt lymphoma, T-cell lymphoma, Primary Central Nervous System

lymphoma (PCNSL), Lymphoplasmacytic lymphoma, or not otherwise specified (NOS) lymphoma.

54. The method of claim 53, wherein the T-Cell Lymphoma comprises Cutaneous T-cell lymphoma, Adult T-cell lymphoma, Angioimmunoblastic T-cell lymphoma, Extranodal natural killer/T-cell lymphoma, Enteropathy-associated intestinal T-cell lymphoma (EATL), Anaplastic large cell lymphoma (ALCL), or Peripheral T-cell lymphoma (PTCL).
55. The method of any one of claims 1-54, wherein the patient additionally suffers from hemophagocytic lymphohistiocytosis (HLH), wherein the HLH is secondary HLH.
56. The method of claim 55, wherein the sHLH is selected from the group consisting of immunosuppression or immunotherapy mediated HLH, idiopathic trigger mediated HLH, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated (fungal induced) HLH, autoimmune disease mediated HLH, malignancy-triggered HLH, non-mendelian secondary HLH (sHLH) and mendelian associated sHLH.
57. The method of claim 56, wherein the malignancy-triggered HLH comprises an HLH triggered by a hematological malignancy or solid tumor.
58. The method of claim 56, wherein the HLH comprises a relapsed or refractory sHLH.
59. The method of claim 56, wherein the sHLH is an infection-associated HLH.
60. The method of claim 56, wherein the sHLH is associated with a rheumatologic condition.
61. The method of claim 56, wherein the sHLH is associated with a kidney transplant or hematologic stem cell transplant.
62. The method of claim 56, wherein the sHLH is associated immune checkpoint inhibitors or T cell therapy (CAR-T) or T cell receptor T cell therapy (TCR-T).
63. The method of any one of claims 1-62, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered as single agent, or in combination with at least one additional therapeutic agent in the treatment phase and/or the prime dosing phase.
64. The method of claim 63, wherein the one or more additional therapeutic or investigational agents is selected from listing consisting of: a chemotherapeutic agent, an immunotherapeutic agent, a CAR T therapeutic agent, a JAK inhibitor, a radiotherapeutic agent, methotrexate, azathioprine, dexamethasone, a biological therapeutic agent, a TNF inhibitor, anakinra, antimicrobials, etoposide, tocilizumab, emapalumab, and alemtuzumab.

65. The method of any one of claims 1-64, wherein the method comprises measuring one or more biomarkers in a biological sample obtained from the subject.
66. The method of claim 65, wherein the biomarkers comprise one or more of ferritin, sCD25, sCD25/ferritin ratio, C-reactive protein (CRP), fibrinogen, CXCL9, CXCL10, sCD163, LDH, IFN-gamma, IL-6, TNF-alpha, IL-8, IL-10, IL-18, GDF-15, IL-1RA, MDC, ST2, IL-16, circulating monocyte counts, and circulating lymphocyte counts, CD163, Epithelial-Derived Neutrophil-Activating Protein 78 (ENA-78), Factor VII, ICAM-1, Interferon gamma Induced Protein 10 (IP-10), IL-12p40, Macrophage-Derived Chemokine (MDC), Macrophage Inflammatory Protein-1 alpha (MIP-1 alpha), Macrophage Inflammatory Protein-1 beta (MIP-1 beta), Matrix Metalloproteinase-3 (MMP-3), Matrix Metalloproteinase-9 (MMP-9) Monocyte Chemotactic Protein 1 (MCP-1), and Monokine Induced by Gamma Interferon (MIG).
67. Use of a SIRP $\alpha/\beta/\gamma$ binding antibody in the manufacture of a medicament for treating cancer in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of, in one or more treatment phases.
68. The use of claim 67, wherein the heavy chain variable region (VH) of the antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto.
69. The use of claim 67 or 68, wherein the antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.
70. A SIRP $\alpha/\beta/\gamma$ binding antibody for use in treating cancer in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of a, in one or more treatment phases.
71. The antibody for use of claim 70, wherein the heavy chain variable region (VH) of the antibody comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence with at least 80% sequence identity thereto, and wherein the light chain variable region (VL) of the antibody comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence with at least 80% sequence identity thereto.

72. The antibody for use of claim 70 or 71, wherein the antibody comprises complementarity determining region (CDR) sequences of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.
73. A method of treating cancer in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 10.0 mg/kg per dose of an anti-SIRP antibody, in one or more treatment phases, wherein the antibody comprises a means for binding human SIRP α , SIRP β , and SIRP γ proteins.