

SIRP ANTIBODIES FOR TREATMENT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent application number 63/591,736, 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_005_01WO_SeqList_ST26.xml; Size: 58,325 bytes; and Date of Creation: October 17, 2024) are herein incorporated by reference in its entirety.

BACKGROUND

[0003] Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening inflammatory syndrome characterized by dysregulated immune function. The disease is associated with a massive systemic inflammatory response for which patients require immediate and aggressive treatment with intensive care. HLH is classically divided into 2 types, primary (pHLH) and secondary (sHLH), although it is increasingly recognized as a syndrome including complex interactions of host genetics and extrinsic challenges. There are no formal guidelines regarding the diagnosis and treatment of sHLH. Pathogenesis of HLH is initiated upon antigen presentation by myeloid cells, such as dendritic cells, to cytolytic lymphocytes, resulting in lymphocyte activation, proliferation, and production of pro-inflammatory cytokines such as interferon gamma (IFN γ), leading to further pro-inflammatory cytokine production, tissue infiltration, and cellular damage. Myeloid cells and activated lymphocytes are believed to play a role in multiple pathological processes in HLH including antigen presentation, cytokine production, cellular activation, hemophagocytosis, and end organ damage.

[0004] 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 HLH, the use of SIRP $\alpha/\beta/\gamma$ -directed agents may modulate HLH pathology. There is a need for agents and protocols for the treatment of HLH, provided herein are such agents and protocols.

SUMMARY

[0005] 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, thereby depleting the cell types believed to be driving HLH pathology. Provided are clinically relevant methods, for the treatment of HLH with selected SIRP $\alpha/\beta/\gamma$ antibodies of the disclosure.

[0006] In one aspect, provided herein is a method of treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 5.0 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.

[0007] In another aspect, provided herein is a use of a SIRP $\alpha/\beta/\gamma$ binding antibody in the manufacture of a medicament for treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 5.0 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.

[0008] In another aspect, provided herein is a SIRP $\alpha/\beta/\gamma$ binding antibody for use in treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 5.0 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.

[0009] In another aspect, provided herein is a method of treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 5.0 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

[0010] FIG. 1A shows the Sa $\beta\gamma$ -01 sHLH safety and efficacy dosing study design schema.

[0011] FIG. 1B shows a schematic for the intra-participant dose escalation phase, individual fixed dose phase and additional exploration of schedule for the Sa $\beta\gamma$ -01 sHLH safety and efficacy dosing study.

[0012] FIG. 2 shows the subject demographics and baseline characteristics for the Sa $\beta\gamma$ -01 sHLH safety and efficacy dosing study.

[0013] FIG. 3 shows the Sa $\beta\gamma$ -01 dosing and added therapy for cancer and sHLH for Cohorts 1 and 2.

[0014] FIGS. 4A-4B shows the individual response criterion and overall response assessment. FIG. 4A is directed to ten Sa $\beta\gamma$ -01 dosed patients from Cohorts 1 and 2. FIG. 4B is directed to 12 Sa $\beta\gamma$ -01 dosed patients in a frontline setting.

[0015] **FIGS. 5A-5B** shows pharmacokinetic profiles of eight patients observed during the indicated $\text{Sa}\beta\gamma\text{-01}$ dose regimen.

[0016] **FIG. 6** shows the characteristics of sCD25 and ferritin biomarker response in three subjects from Cohort 1 in clinical remission from cancer and sHLH at week 16.

[0017] **FIG. 7** shows the maximum reductions from baseline of sCD25, ferritin, and CRP biomarkers in twelve patients receiving $\text{Sa}\beta\gamma\text{-01}$ in a frontline setting.

[0018] **FIG. 8** shows pharmacodynamic effects observed during windows of $\text{Sa}\beta\gamma\text{-01}$ monotherapy at the indicated doses for 3 patients.

[0019] **FIG. 9** shows an early and rapid effect of $\text{Sa}\beta\gamma\text{-01}$ treatment, at the indicated doses for two patients, on C-reactive protein (CRP), associated with reduction of HLH-associated cytokines and biomarkers.

[0020] **FIG. 10** shows the HLH biomarker reduction over time in a single relapsed/refractory T-cell lymphoma-triggered mHLH patient treated with $\text{Sa}\beta\gamma\text{-01}$.

[0021] **FIG. 11** shows the HLH biomarker reduction over time in mHLH patients treated with $\text{Sa}\beta\gamma\text{-01}$ in a frontline setting during monotherapy windows. Panel A shows the summary of seven patients for ferritin and CRP. Panel B shows reductions of several biomarkers in a single patient.

[0022] **FIG. 12** shows the HLH biomarker reduction over time in a sHLH patient (not triggered by malignancy) treated with $\text{Sa}\beta\gamma\text{-01}$.

[0023] **FIG. 13** shows additional inflammatory biomarker responses as fold-change from baseline in six patients treated with $\text{Sa}\beta\gamma\text{-01}$ in a frontline setting.

[0024] **FIGS. 14A-14B** show swimmer plots of patients that were treated with $\text{Sa}\beta\gamma\text{-01}$. **FIG. 13A** shows twelve mHLH patients that were treated with $\text{Sa}\beta\gamma\text{-01}$ in frontline settings. **FIG. 13B** shows the survival and response of all patients receiving $\text{Sa}\beta\gamma\text{-01}$ in the study.

[0025] **FIG. 15** shows recorded adverse events. Combined terms: sepsis includes sepsis and septic shock, platelet count decrease includes platelet count decrease and thrombocytopenia, neutrophil count decrease includes neutrophil count decrease and neutropenia, peripheral swelling includes peripheral swelling and oedema peripheral, rash includes rash and rash maculopapular.

DETAILED DESCRIPTION

Definitions

[0026] 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.

[0027] 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.

[0028] 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 abbreviates 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.

[0029] 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.

[0030] 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”.

[0031] The term “loading dose phase” or “loading phase” refers to a phase which aims to deliver 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. The term “loading” or “load” refers to the act of administering a loading dose.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] Provided herein are antibodies that bind to SIRP α , SIRP β , and SIRP γ , and methods of treating HLH using such antibodies. The antibodies may be useful for treating HLH by depleting SIRP α , SIRP β , and/or SIRP γ expressing cell types, involved in HLH pathology.

I. Antibodies

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

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] The SIRP α protein has been characterized to be highly polymorphic but this 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.

[0042] 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 ITPADAGTTY
121 CVKFRKGSPD DVEFKSGAGT ELSVRAKPSA PVVSGPAARA TPQHTVSFTC ESHGFSPRDI
181 TLKWFKNONE LSDFQTNVDP VGESVSYSIH STAKVVLTRE DVHSQVICEV AHVTIQGDPL
241 RGTANLSETI RVPPTLEVTQ QPVAENQVN VTCQVRKFYP QRLQLTWLEN GNVSRTEAS
301 TVTENKDGTY NMSWLLVNV SAHRDDVKLT CQVEHDGQPA VSKSHDLKVS AHPKEQGSNT
361 AAENTGSNER NIYIVGVVVC TLLVALLMAA LYLVRIRQKK AQGSTSSTRL HEPEKNAREI
421 TQDNDITTYA DLNLPKGKKP APQAAEPNNH TEYASIQTSP QPASEDTLTY ADLDMVHLNR
481 TPKQPAPKPE PSFSEYASVQ VPRK (SEQ ID NO: 9)

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[0043] 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 ITPADAGTTY
121 CVKFRKGSPD TEFKSGAGTE LSVRAKPSAP VVSGPAARAT PQHTVSFTCE SHGFSPRDI
181 LKWFKNONE LSDFQTNVDPV GESVSYSIHS TAKVVLTRER VHSQVICEVA HVTIQGDPLR
241 GTANLSETIR VPPTLEVTQQ PVRAENQVN TCQVRKFYPQ RLQLTWLENG NVSRTEAST
301 VTENKDGTYN WMSWLLVNV SAHRDDVKLT CQVEHDGQPAV SKSHDLKVS AHPKEQGSNTA
361 AENTGSNER NIYIVGVVCT LLVALLMAAL YLVRIRQKKA QGSTSSTRLH EPEKNAREIT
421 QVQSLDNDI TYADLNLPKG KKPAPQAAEP NNHTEYASIQ TSPQASEDT LTYADLDMVH
481 LNRTPKQPAP KPEPSFSEYA SVQVPRK (SEQ ID NO: 10)

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[0044] 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

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61  IPVGPIQWFR GAGPGRELIY NQKEGHFPRV TTVSDLTKRN NMDFSIRIGN ITPADAGTYY
121 CVKFRKGSPD DVEFKSGAGT ELSVRAKPSA PVVSGPAARA TPQHTVSFTC ESHGFSPRDI
181 TLKWFKNONE LSDFQTNVDP VGESVSYSIH STAKVVLTRE DVHSQVICEV AHVTLQGDPL
241 RGTANLSETI RVPPTLEVTD QPVAENQVN VTCQVRKFYP QRLQLTWLEN GNVSRTEAS
301 TVTENKDGTY NMSWLLVNV SAHRDDVKLT CQVEHDGQPA VSKSHDLKVS AHPKEQGSNT
361 AAENTGSNER NIYIVGVVVC TLLVALLMAA LYLVRIRQKK AQGSTSSTRL HEPEKNAREI
421 TQVQSLDTND ITYADLNLPK GKKPAPQAAE PNNHTEYASI QTSPQPASED TLTYADLDMV
481 HLNRTPKQPA PKPEPSFSEY ASVQVPRK (SEQ ID NO: 11)

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[0045] 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 SHGFSPRDI
181 LKWFKNONE SDFQTNVDPV GESVSYSIH TAKVVLTRD VHSQVICEVA HVTQLQGDPLR
241 GTANLSETIR VPPTLEVTDQ PVAENQVNV TCQVRKFYPQ RLQLTWLENG NVSRTEAST
301 VTENKDGTYN WMSWLLVNV SAHRDDVKLT CQVEHDGQPAV SKSHDLKVSA HPKEQGSNTA
361 AENTGSNER NIYIVGVVCT LLVALLMAAL YLVRIRQKKA QGSTSSTRLH EPEKNAREIT
421 QDTNDITYAD LNLPGKKPA PQAAEPNNHT EYASIQTSPQ PASEDTLYA DLDVMHLNRT
481 PKQPAPKPEP SFSEYASVQV PRK (SEQ ID NO: 12)

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[0046] 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 .

[0047] 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).

[0048] 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 .

[0049] 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 .

[0050] 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  TVSELTNRNN  LDFSISISNI  TPADAGTYYC
121 VKFRKGSDD  VEFKSGAGTE  LSVRAKPSAP  VVSGPAVRAT  PEHTVSFTCE  SHGFSPRDI
181 LKWFKNLDEL  SDFQTNVDP  GDSVSYSIHS  TARVVLTRGD  VHSQVICEIA  HITLQGDPLR
241 GTANLSEAIR  VPPTLEVTQQ  PMRAENQANV  TCQVSNFYPR  GLQLTWLENG  NVSRTEAST
301 LIENKDGTYN  WMSWLLVNTC  AHRDDVVLTC  QVEHGGQAV  SKSYALEISA  HQKEHGSIT
361 HEALAPTAP  LLVALLGPK  LLLVVGVSAT  YICWKQKA (SEQ ID NO: 13)

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[0051] 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 .

[0052] 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 .

[0053] 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  HGFSPRDLTL
181 KWFKNNGNELS  DFQTNVDPTG  QSVAYSIRST  ARVVLDPWDV  RSQVICEVAH  VTLQGDPLRG
241 TANLSEAIRV  PPTLEVTQQP  MRVGNQVNVV  CQVRKFYPQS  LQLTWSENGN  VCQRETASTL
301 TENKDGTYNW  TSWFLVNISD  QRDDVVLTCQ  VKHDGQLAVS  KRLALEVTVA  QKDQSSDATP
361 GPASSLTALL  LIAVLLGPIY  VPWKQKT (SEQ ID NO: 14)

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[0054] 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 .

[0055] 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).

[0056] Also provided herein are Fc-containing SIRP $\alpha/\beta/\gamma$ antibodies. In some embodiments, Fc domain of (interchangeably referred to as a Fc sequence, Fc region, or simply Fc) of the SIRP $\alpha/\beta/\gamma$ 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.

[0057] 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.

[0058] 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 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: 15)

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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 MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 16)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLGG

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121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTLC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 17)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTLC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 18)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTLC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 19)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTLC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 20)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKHTTCP PCPAPELLGG
121 PDVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTLC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 21)

1 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKHTTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTLC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 22)

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

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 26)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 27)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 28)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 29)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 30)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 31)

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKAEP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 32)

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[0059] 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.

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1   ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61  GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX1EP KSCDKTHTCP PCPAPELLAG
121 PDVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNEWYVDGVEVHNA KTKPREEQYN
181 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPEEKTIS KAKGQPREPQ VYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW
301 QQGNVFSCSV MHEALHSHYT QKSLSLSPGK (SEQ ID NO: 33)

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[0060] 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.

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1  ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX1EP KSCDKTHTCP PCPAPELLX2G
121 PX3VFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKALPAPK4EKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 34)

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[0061] 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.

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1  ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKX1EP KSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
301 QQGNVFSCSV LHEALHSHYT QKSLSLSPGK (SEQ ID NO: 35)

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[0062] 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 KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
241 LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
301 QQGNVFSCSV X2HEALHX3HYT QKSLSLSPGK (SEQ ID NO: 36)

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[0063] 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.

```

1  ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
61 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKX1VEPKSCDKTHTCP PCPAPELLGG
121 PSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
181 STYRVVSVLT VLNQDNLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRX2E
241 X3TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
301 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 37)

```

[0064] 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).

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 38)

[0065] 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.

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 39)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 40)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 41)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 42)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEALGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 43)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 44)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNYHTQKSLSLSLGK (SEQ ID NO: 45)

[0066] 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.

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQKTYTCNVDHKPSNTKVDKRVESKYGPPCPX1CPAPEFX2GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNYHTQKSLSLSLGK (SEQ ID NO: 46)

[0067] 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.

[0068] 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.

[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), 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).

[0070] 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).

[0071] 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.

[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 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).

[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), and heavy chain Fc substitutions are introduced to decrease effector function (e.g. silence).

[0074] 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.

[0075] 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).

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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

[0086] 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 Sa $\beta\gamma$ -01

Antibody ID.	CDR-L1	CDR-L2	CDR-L3	CDR-H1	CDR-H2	CDR-H3
Sa $\beta\gamma$ -01	QSLHGNNG FNY (SEQ ID NO: 3)	LGS (SEQ ID NO: 4)	MQQLQTPR T (SEQ ID NO: 5)	GGSISSNW (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

[0087] 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).

[0088] 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.

[0089] 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.

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
S $\alpha\beta\gamma$ -01	QVQLQESGPGLVKPSGTLSTCAVSGG SISSSNWWSWVRQPPGKLEWIGEIY HSGSTNYNPSLKSRTISVDKSKNQFSL KLSSVTAADTAVYYCARRGIWFGVGP WGQGTLVTVSS (SEQ ID NO: 1)	DIVMTQSPLSLPVTPGEPASISCRSSQSLH NGFNYLDWYLQKPGQSPQLLIYLG SNRASGVPDRFTGSGSGTDFTLKISRVEAEDVGVYYC MQGLQTPRTFGQGTKVEIK (SEQ ID NO: 2)

[0090] 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 HLH using SIRP $\alpha/\beta/\gamma$ Antibodies

[0091] 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 HLH in a subject. In some embodiments, the subject is human. The subject can be of any age. In some embodiments, the subject is below about 6 years of age. In some embodiments, the subject is about 6 to about 12 years of age. In some embodiments, the subject is above about 12 years of age. In some embodiments, the subject is treatment-naïve. In some embodiments, the subject has received one or more previous HLH treatments. In some embodiments, the subject is suffering from

primary HLH (pHLH). In some embodiments, the subject has one or more polymorphisms that make them more susceptible to pHLH. In some embodiments, the subject is suffering from secondary (sHLH). In some embodiments, the subject has one or more polymorphisms that make them more susceptible to sHLH. These embodiments are discussed in further detail below.

A. Hemophagocytic lymphohistiocytosis (HLH) Classifications

[0092] Hemophagocytic lymphohistiocytosis of the disclosure include primary HLH (pHLH) as well as secondary HLH (sHLH). 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 (mHLH).

[0093] In some embodiments, HLH comprises relapsed HLH. In some embodiments, HLH comprises refractory HLH.

[0094] Relapsed sHLH can be when the subject initially responds to an HLH therapy (e.g. an HLH therapy such as but not limited to etoposide, dexamethasone, cyclosporin, anakinra, tocilizumab, JAK inhibitors, alemtuzumab, intravenous immunoglobulin (IVIG), rituximab, other corticosteroids, emapalumab, any combination chemotherapy regimens, or other HLH therapy) but subsequently experiences a recurrence of disease symptoms. Refractory sHLH can be when the subject has failed to sufficiently respond to treatment with an HLH therapy (e.g. an HLH therapy such as but not limited to etoposide, dexamethasone, cyclosporin, anakinra, tocilizumab, JAK inhibitors, alemtuzumab, intravenous immunoglobulin (IVIG), rituximab, other corticosteroids, emapalumab, any combination chemotherapy regimens, or other HLH therapy). In some embodiments, the subject has failed to respond to about 2 weeks of an HLH therapy. In some embodiments, the subject has failed to respond to 2 weeks of treatment with tocilizumab, anakinra, or other HLH therapy with a less than 50% decrease in serum ferritin. In some embodiments, the subject has received ~4 doses of etoposide with a less than 50% decrease in serum ferritin 72 hours after last dose.

[0095] In some embodiments the subject is treatment naïve. In other embodiments, the subject is not treatment naïve, and has previously been administered etoposide, dexamethasone, cyclosporin, anakinra, tocilizumab, JAK inhibitors, alemtuzumab, intravenous immunoglobulin (IVIG), rituximab, other corticosteroids, emapalumab any combination chemotherapy regimens, or other HLH therapy.

[0096] 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.

[0097] In other embodiments, the sHLH is a malignancy-associated HLH (mHLH), 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 treatment or at any stage of a malignancy, 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.

[0098] 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.

[0099] In other embodiments, the sHLH is a transplant-related HLH, such as HLH associated with a kidney transplant, or hematologic stem cell transplants.

[0100] 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

[0101] 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 HLH 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 subject is administered in one or more treatment phases. In some embodiments, the one or more treatment phases are preceded by a priming dose phase. 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

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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 HLH relapses.

[0106] 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. In exemplary embodiments, a loading dose phase lasts for a duration of 3 days.

[0107] 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.

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. 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 HLH relapses.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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, or of at least 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 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, about 3.0 mg/kg to about 5.0 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.

[0113] 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, or of at least 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 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, about 3.0 mg/kg to about 5.0 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. In exemplary 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 0.3 mg/kg.

[0114] 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, or of at least 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 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, about 3.0 mg/kg to about 5.0 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. In exemplary 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 0.5 mg/kg.

Priming dose phase

[0115] 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 may serve several roles, e.g., may reduce infusion reaction severity, improve the responsiveness of the subject during the treatment phase and/or allow for the target concentration of the antibody treatment to be achieved rapidly.

[0116] 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. In exemplary embodiments, the SIRP $\alpha/\beta/\gamma$ antibodies of the present disclosure are administered for a period of 1 day during the priming dose phase.

[0117] 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.

[0118] 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.

[0119] 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, about 3.0 mg/kg

to about 5.0 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. In exemplary 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 0.1 mg/kg.

[0120] 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. In some embodiments, the dose is reduced in response to the event of grade 4 thrombocytopenia sustained for 7 or more days. In some embodiments, the dose is reduced in response to the event of grade 4 thrombocytopenia sustained for 7 or more days. In some embodiments, the dose is reduced in response to the event of febrile neutropenia (any grade). In some embodiments, the dose is reduced in response to non-hematologic toxicities grade 2 or above. In some embodiment, the maintenance dose is reduced from 0.5 mg/kg twice weekly to 0.3 mg/kg twice weekly. In some embodiment, the maintenance dose is reduced from 0.3 mg/kg twice weekly to 0.3 mg/kg weekly.

[0121] 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

[0122] 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

[0123] The administration of any one of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies provided herein may be in combination with any other known or investigational 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).

[0124] In some embodiments, a therapeutic SIRP $\alpha/\beta/\gamma$ antibody is provided to treat sHLH that occurs due to infections, in combination with the appropriate antiviral for the treatment of a viral infection, or in combination with the appropriate antibiotic therapy for the treatment of a bacterial infection. By way of example only, a therapeutic antibody of the disclosure could be administered in combination with an antiviral therapy for example, an antiviral therapy for COVID-19, SARS (SARS-CoV), MERS, Ebola, or Epstein Barr virus, or in combination with an antibiotic therapy, for example an antibiotic therapy for the treatment of sepsis. In some embodiments, the SIRP $\alpha/\beta/\gamma$ antibody is administered in combination with a standard therapy for the infection.

[0125] In some embodiments, a therapeutic SIRP $\alpha/\beta/\gamma$ antibody provided herein to treat sHLH that occurs due to malignancies, is used in combination with the appropriate chemotherapeutic or malignancy-associated treatment of an oncological indication. In some embodiments, a therapeutic SIRP $\alpha/\beta/\gamma$ antibody provided herein to treat sHLH that occurs due to an autoimmune disorder, such as a rheumatological disorder including systemic lupus

erythematosus or rheumatoid arthritis, in combination with the appropriate treatment of such a disorder. Exemplary appropriate treatments include, but are not limited to, corticosteroids.

[0126] In some embodiments, a therapeutic SIRP $\alpha/\beta/\gamma$ antibody provided herein to treat sHLH, 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, and alemtuzumab. 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 (bentuximab 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

[0127] Diagnostic criteria may be utilized to initially diagnose HLH in a subject and/or to evaluate the mitigation HLH in a subject after administration of any one of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies provided herein. In some embodiments, the diagnostic criteria used is the H-Score system. In exemplary embodiments, the H-Score system comprises up to 9 variables which may include known underlying immunosuppression, high temperature, organomegaly, triglycerides, ferritin, serum glutamic oxaloacetic transaminase, fibrinogen levels, cytopenia, and/or hemophagocytosis features on bone marrow aspirate. The H-Score scoring system is freely available at <https://saintantoine.aphp.fr/score/>. In other embodiments, diagnostic criteria used is an OHI index which can be used as a marker for malignancies with an inflammatory phenotype, deranged immune system, and/or defective anti-tumor immunogenic reactions. (Zoref-Lorenz A. et al. Blood. 139(7):1098-1110, 2022). In exemplary embodiments, an OHI index demonstrating CD25 > 3900 U/mL and ferritin >1000 ng/mL accurately identifies malignancy-associated HLH. In some embodiments,

CD25 > 3900 U/mL may be presented as pg/mL (approximately 6-8 fold to convert from U/ml to pg/mL).

[0128] In some embodiments, a predicted prognosis and/or likelihood of response to chemotherapy is obtained by evaluating a ratio of sCD25/ferritin. (Tabata C. and Tabata R. Ann Hematol. (1):63-71, 2012).

[0129] Diagnostic criteria may be utilized to initially diagnose HLH in a subject and/or to evaluate the mitigation HLH in a subject after administration of any one of the therapeutic SIRP $\alpha/\beta/\gamma$ antibodies provided herein. In some embodiments, the diagnostic criteria used is the H-Score system. In exemplary embodiments, the H-Score system comprises 9 variables which may include known underlying immunosuppression, high temperature, organomegaly, triglycerides, ferritin, serum glutamic oxaloacetic transaminase, fibrinogen levels, cytopenia, and/or hemophagocytosis features on bone marrow aspirate. In other embodiments, diagnostic criteria used is an OHI index. In exemplary embodiments, an OHI index demonstrating CD25 > 3900 U/mL and ferritin >1000 ng/mL accurately identifies malignancy-associated HLH.

[0130] In some embodiments, a predicted prognosis and/or likelihood of response to chemotherapy 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.

[0131] 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

[0132] The following non-limiting enumerated embodiments are provided as exemplary.

[0133] Embodiment I-1. A method of treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 5.0 mg/kg per dose of a SIRP $\alpha/\beta/\gamma$ binding antibody, in one or more treatment phases.

[0134] 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.

[0135] 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.

[0136] Embodiment I-4. The method of any one of I-1 to I-3, wherein the antibody comprises an Fc domain.

[0137] 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.

[0138] Embodiment I-6. The method of 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.

[0139] Embodiment I-7. The method of 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

- [0152] 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.
- [0153] 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.
- [0154] 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.
- [0155] 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.
- [0156] Embodiment I-24. 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.
- [0157] 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 weekly during the maintenance dose phase.
- [0158] 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.
- [0159] 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.
- [0160] 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 0.3 mg/kg to about 1.0 mg/kg.
- [0161] Embodiment I-29. The method of any one of I-1 to I-28, wherein the loading phase comprises one or more doses of about 0.3 mg/kg.
- [0162] Embodiment I-30. The method of any one of I-1 to I-29, wherein the maintenance dose phase comprises one or more doses of about 0.5 mg/kg.
- [0163] Embodiment I-31. The method of any one of I-1 to I-30, wherein the method further comprises a priming dose phase.
- [0164] Embodiment I-32. The method of I-31, wherein the priming dose phase occurs over a duration of 1 to 5 days.
- [0165] Embodiment I-33. The method of I-31 or I-32, wherein the priming dose phase 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.

[0166] 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.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] 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.

[0171] 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.

[0172] 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.

[0173] 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.

[0174] Embodiment I-42. The method of any one of I-1 to I-41, wherein the subject is below about 6 years of age.

[0175] Embodiment I-43. The method of any one of I-1 to I-41, wherein the subject is about 6 to about 12 years of age.

[0176] Embodiment I-44. The method of any one of I-1 to I-41, wherein the subject is above about 12 years of age.

[0177] Embodiment I-45. The method of any one of I-1 to I-44, wherein the subject is not treatment-naïve.

[0178] Embodiment I-46. The method of I-45, 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.

[0179] Embodiment I-47. The method of any one of I-1 to I-44, wherein the subject is treatment-naïve.

[0180] Embodiment I-48. The method of any one of I-1 to I-47, wherein the HLH is a primary HLH.

[0181] Embodiment I-49. The method of any one of I-1 to I-47, wherein the HLH is a secondary HLH (sHLH).

[0182] Embodiment I-50. The method of I-49, wherein the sHLH is selected from the group consisting of immunosuppression therapy mediated HLH, immunotherapy mediated HLH, idiopathic trigger mediated HLH, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated HLH, autoimmune disease-mediated HLH, and malignancy-triggered HLH.

[0183] Embodiment I-51. The method of I-50, wherein the malignancy-triggered HLH comprises an HLH triggered by a hematological malignancy.

[0184] Embodiment I-52. The method of I-50, wherein the malignancy-triggered HLH comprises an HLH triggered by a solid tumor.

[0185] Embodiment I-53. The method of I-50, wherein the sHLH comprises a relapsed or refractory sHLH.

[0186] Embodiment I-54. The method of I-50, wherein the sHLH is an infection-associated HLH.

[0187] Embodiment I-55. The method of I-50, wherein the sHLH is associated with a rheumatologic condition.

[0188] Embodiment I-56. The method of I-50, wherein the sHLH is associated with a kidney transplant or hematologic stem cell transplant.

[0189] Embodiment I-57. The method of I-50, wherein the immune therapy mediated sHLH is associated with therapy with immune checkpoint inhibitors, a CAR T cell therapy (CAR T) or a T cell receptor T cell therapy (TCR-T).

[0190] Embodiment I-58. The method of any one of I-1 to I-57, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered as single agent during the treatment phase and/or the priming dose phases.

[0191] Embodiment I-59. The method of any one of I-1 to I-57, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered in combination with at least one additional therapeutic agent during the treatment phase and/or the priming dose phases.

[0192] Embodiment I-60. The method of I-59, wherein the at least one additional therapeutic agent is selected from group consisting of a corticosteroid-based therapy, a chemotherapeutic agent, an immunotherapeutic agent, a CAR T therapy, a JAK inhibitor, a radiotherapeutic agent, methotrexate, azathioprine, a TNF inhibitor, tocilizumab, anakinra, antimicrobials, etoposide, anakinra, tocilizumab, emapalumab, and alemtuzumab.

[0193] Embodiment I-61. The method of any one of I-1 to I-60, wherein the method comprises measuring one or more biomarkers in a biological sample obtained from the subject.

[0194] Embodiment I-62. The method of I-61, 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, 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).

[0195] Embodiment I-63. The method of any one of I-1 to I-62, wherein the method comprises diagnosing and predicting prognosis, and/or likelihood of response to chemotherapy in the subject utilizing an H-Score system.

[0196] Embodiment I-64. The method of any one of I-1 to I-62, wherein the method comprises diagnosing and predicting prognosis, and/or likelihood of response to chemotherapy in the subject utilizing an OHI index.

[0197] Embodiment I-65. The method of any one of I-1 to I-64, wherein the method comprises evaluating a ration of sCD25/ferritin to diagnose and predict prognosis, and/or likelihood of response to chemotherapy in the subject.

[0198] Embodiment I-66. The method of any one of I-1 to I-65, a predicted prognosis and/or likelihood of response to treatment is obtained by measuring circulating monocyte and lymphocyte counts.

[0199] Embodiment I-67. The method of any one of I-1 to I-66, wherein the method comprises monitoring sCD25 and ferritin peak, minimum, maximum, and reduction prospectively to diagnose and predict prognosis, and/or likelihood of response to chemotherapy in the subject.

[0200] Embodiment I-68. Use of a SIRP $\alpha/\beta/\gamma$ binding antibody in the manufacture of a medicament for treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 5.0 mg/kg per dose of, in one or more treatment phases.

[0201] Embodiment I-69. The use of I-68, 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.

[0202] Embodiment I-70. The use of I-68 or I-69, 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.

[0203] Embodiment I-71. A SIRP $\alpha/\beta/\gamma$ binding antibody for use in treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 5.0 mg/kg per dose of a, in one or more treatment phases.

[0204] Embodiment I-72. The antibody for use of I-71, 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.

[0205] Embodiment I-73. The antibody for use of I-71 or I-72, 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.

[0206] Embodiment I-74. A method of treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 5.0 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.

[0207] 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

[0208] 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 either treatment naïve or relapsed/refractory sHLH. sHLH was confirmed with a diagnosis based on fulfilling at least 5 of the 8 modified HLH-2004 criteria in Henter et al. (Pediatr Blood Cancer 48(2): 124-131, 2007).

Relapsed/refractory sHLH includes the situation where (1) the subject has failed to respond to 2 weeks of treatment with tocilizumab, anakinra, or other HLH therapy with a less than 50% decrease in serum ferritin, or (2) the subject has received 4 doses of etoposide with a less than 50% decrease in serum ferritin 72 hours after last dose, or (3) on a case-by-case basis. 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**).

[0209] Cohort 1 was designed to establish dose level/regimen in sHLH 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 1-3 and mHLH specific subjects with frontline settings (treatment naïve or early refractory sHLH) can found in **FIG. 2**.

[0210] 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 Sαβγ-01 Doses Level for Cohort 1

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

[0211] Biomarker evidence of improvement for the study was defined as: (1) monocyte reduction and (2) serum ferritin reduction $\geq 20\%$ compared to baseline or the most recent value prior to the next dose level dosing if baseline levels ≥ 3000 ng/mL, or if baseline levels < 3000 ng/mL, any decrease in ferritin levels accompanied by an improvement in one or more of: fasting triglyceride levels, coagulation parameters, or sIL2 receptor levels compared to baseline.

[0212] DLT was determined by the occurrence of clinically significant, non-hematologic toxicities Common Terminology Criteria for Adverse Events (CTCAE) grade of ≥ 3 if at least probably related to Sαβγ-01. In participants with a baseline CTCAE grade of 0, 1, or 2 neutropenia and/or thrombocytopenia, the occurrence of Grade 4 neutropenia and/or thrombocytopenia, sustained for 7 or more days while on treatment, was considered a delayed DLT if at least probably related to Sαβγ-01.

[0213] 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.

[0214] Cohorts 3 and 4 were additionally designed to investigate less frequent dosing regimens of Sa β γ -01 at a dose informed by previous cohorts and no higher than 3 mg/kg.

[0215] Patients in Cohorts 2 and 3 received fixed-dose regimens consisting of a priming dose (0.1 mg/kg, IV), three daily loading doses (0.3 mg/kg, IV), and maintenance doses of 1.0 mg/kg IV weekly (Cohort 2) or 0.5 mg/kg IV twice weekly (Cohort 3). Fractionation of the 1 mg/kg weekly dose in Cohort 3 was implemented to optimize mid-week PD effects, reduce potential effects on platelet count, and provide additional options for dose modification. Sa β γ -01 was administered IV at drug initiation and while hospitalized, but subcutaneous administration was permitted after hospital discharge. Investigators were to provide routine supportive care including management of infusion reactions, blood product needs, and antimicrobial prophylaxis per institutional guidelines. Measures to reduce infusion reactions included premedication with dexamethasone, a priming dose of 0.1 mg/kg IV, and longer infusion times (up to 6 hours). Dose modifications were permitted if needed to manage cytopenias.

[0216] 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 $\geq$ 12 years of age who were treatment-naïve or had relapsed or refractory sHLH). Cohort 2 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. In Cohort 3, only patients with treatment naïve or early refractory sHLH (frontline settings) were eligible for enrollment. Early refractory was defined as <1 week of any HLH-directed therapy with insufficient clinical or laboratory response as judged by the investigator. Cohort 3 included 2 early refractory and 8 treatment-naïve sHLH patients.

Example 2: Evaluation of Sa β γ -01 Dosing Study

[0217] Several assessments were conducted throughout the span of the study. Efficacy assessments were conducted using the Clinical Response Criteria laid out in **Table 1.2** and defined as either a complete response (CR), a modified complete response (mCR), a partial response (PR), or HLH improvements (**FIG. 4A-4B**). (Locatelli, F. N Engl J Med; 382:1811-

1822, 2020). FIG. 4A shows clinical response criteria for Cohorts 1 and 2. FIG. 4B shows clinical response criteria for frontline setting mHLH patients across all cohorts.

Table 1.2: Response Criteria

Complete Response (CR)	- No fever = body temperature $<37.5^{\circ}\text{C}$ - Normal spleen size as measured by 3D abdominal ultrasound - No cytopenia = absolute neutrophil count $\geq 1.0 \times 10^9/\text{L}$ and platelet count $\geq 100 \times 10^9/\text{L}$ (absence of granulocyte colony stimulating factor [G-CSF] and transfusion support must be documented for at least 4 days to report no cytopenia) - No hyperferritinemia = serum level is $<2000 \mu\text{g/L}$ (or ng/mL) - No evidence of coagulopathy, i.e., normal D-Dimer and/or normal ($>150 \text{ mg/dL}$) fibrinogen levels - No neurological and cerebrospinal fluid (CSF) abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are >2-fold higher than baseline)
Modified Complete Response (mCR)	- No fever = body temperature $<37.5^{\circ}\text{C}$ - No hyperferritinemia = serum level is $<2000 \mu\text{g/L}$ (or ng/mL) - No evidence of coagulopathy, ie, normal D-Dimer and/or normal ($>150 \text{ mg/dL}$) fibrinogen levels - No neurological and CSF abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are >2-fold higher than baseline)
Partial Response (PR)	- At least 3 of the HLH clinical and laboratory abnormalities meet the above-mentioned criteria for "Complete Response" - There is no progression of other aspects of HLH disease pathology (eg, jaundice, liver size, oedema, central nervous system [CNS] clinical alterations)
HLH Improvement	Improvement ($>50\%$ change from baseline) of at least 3 HLH clinical and laboratory abnormalities (including CNS involvement).

[0218] PK was evaluated by measuring plasma concentrations of $\text{S}\alpha\beta\gamma\text{-01}$. 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. 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.

[0219] The Cohort 3 regimen achieved a steady state drug concentration above the target threshold of 100 ng/mL without evidence of drug accumulation in patients with sufficient sampling for evaluation within the first four weeks of study (**FIG. 5A-5B**).

[0220] The intended PD effect of $\text{S}\alpha\beta\gamma\text{-01}$ is to exert an anti-inflammatory effect which was primarily measured via ferritin, sCD25, CRP, LDH, monocytes counts and lymphocyte

counts (**FIGS. 6-12**). Other markers of inflammation were also monitored including IFN γ , IL-18, IL-10, CXCL9, CXCL10, ALT, sCD163, neutrophil counts, and platelet counts (**FIGS. 9, 10, and 12**).

[0221] **FIG. 6** 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 sHLH at week 16. 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).

[0222] Ferritin, sCD25, and CRP were evaluated in the frontline setting mHLH population (n = 12) for maximum percent reduction from baseline by week 4 of study (**FIG. 7**). Patient baseline was determined from either study day 1 pre-dose values or screening values if the day 1 pre-dose data was not available. With the exception of Patient 19's sCD25 response, all biomarkers showed depletion within the 4 week period for all patients, with at least 50% of patients experiencing a 50% or greater reduction for ferritin, sCD25, or CRP.

[0223] **FIG. 8** shows a reduction in monocyte and lymphocyte counts over a course of 8 to 15 days in 3 patients from Cohorts 1 and 2. Patients received varying S $\alpha\beta\gamma$ -01 dose regimens as indicated in the figure and additional cancer therapies and notable events are indicated as well. S $\alpha\beta\gamma$ -01 dosing is indicated by the dotted lines and initiation of chemotherapy is indicated by the dotted line with drug label. There was an overall downtrend of monocytes and lymphocytes with repeated dosing. The top row shows monocyte count and the bottom row shows lymphocyte count. Patients 6 and 9 from **FIG. 8** were also monitored from CXCL9, CXCL10, CD163 and CRP (**FIG. 9**) which also demonstrated a rapid reduction by day 8.

[0224] **FIG. 10** shows additional biomarkers for Patient 6, who was enrolled in Cohort 1 (S $\alpha\beta\gamma$ -01 dosing was 0.1 mg/kg IV daily) and had an 8 day window without concurrent chemotherapy treatment. Although anakinra was an added therapy on Day 3 for CNS defects related to central pontine myelinolysis (a baseline medical condition), anakinra is not known to affect monocyte and lymphocyte counts. Thus, the progressive monocyte and lymphocyte decrease is attributed to S $\alpha\beta\gamma$ -01 and the CRP was substantially decreasing before anakinra was added. Among the PD effects evaluated on study, monocyte count, lymphocyte count, and CRP appear to respond the quickest, including to the first dose. Further, Patient 6's CRP

response overlaid with key inflammatory and HLH-related cytokines. The left axis shows the corresponding cytokine units and is plotted in blue, and the right axis shows the CRP units (mg/L) and is plotted in black. Overall, there is strong concordance amongst the cytokines and they closely mirror the CRP reduction in the 8 day window. All changes were closely linked to CRP decreases. CRP is a validated marker of inflammation and has been employed as a primary endpoint for registration clinical trials such as for giant cell arteritis (GCA). The observation that CRP declined early in the patient with elevated CRP following S α β γ -01 therapy supports that the drug is exerting its intended anti-inflammatory effect.

[0225] Additionally, patients samples were collected and evaluated during >1-week windows of S α β γ -01 therapy without chemotherapy effects (**FIG. 11**). **FIG. 11** shows pharmacodynamic effects observed during windows of S α β γ -01 monotherapy. The figure shows a case summary of 7 patients with relapsed/refractory T-cell Lymphoma-triggered mHLH that had a more than 1 week chemotherapy-free window that allowed evaluation of S α β γ -01 monotherapy and its pharmacodynamic (PD) effects ferritin and CRP (panel A). Panel B shows additional biomarkers including monocyte count, lymphocyte count, CRP, Ferritin, sCD25, and LDH for Patient 16.

[0226] FIG. 12 demonstrates similar biomarker response profiles to S α β γ -01 in a non-malignancy triggered sHLH patient. Patient 14 was the first infection case of (EBV)-triggered HLH treated with S α β γ -01. The patient presented with neurological symptoms, liver abnormalities, and severe neutropenia. Upon starting S α β γ -01 with background dexamethasone, the patient's HLH-associated abnormalities quickly resolved (clinical and laboratory variables). Dexamethasone presumably contributed to the therapeutic effects. There was a robust recovery of cellular counts upon sHLH disease activity control. This coincided with improved neurological symptoms per the Investigator. Patient 14 had achieved a mCR at Week 2 and a CR by Week 8 and was discharged from the hospital and continued to receive S α β γ -01 0.5 mg/kg SC twice weekly and finished the full 12-week course. This is the first patient experience that illustrates that in a normal functioning marrow (i.e., without active hematologic malignancy and/or cyclic multiagent chemotherapy), S α β γ -01 produced no clinically significant neutropenia or thrombocytopenia given as 0.5 mg/kg IV/SC twice weekly. There was no cumulative toxicity or progressive cytopenia with continued S α β γ -01 dosing. Counts were in normal range and patient had no clinically significant SAEs. Of note, the recovery of lymphocytes and monocytes to normal ranges in this patient in the presence of

steady-state therapeutic drug concentrations >100 ng/mL of ELA026 through week 12 suggests a therapeutic index against native vs. activated or pathologic immune cells.

[0227] 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 S $\alpha\beta\gamma$ -01. Analyses included, but were not limited to, plasma cytokines, tumor necrosis factor (TNF) alpha, IFN γ , IL-2, IL-4, IL-6, IL-10, IL-13 IL-17, IL-18 IL-23, ferritin, sCD25, CRP, D-dimer, fibrinogen, CXCL9, CXCL10, CD163, LDH, 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). **FIG.13** presents cytokine data as a fold-change from baseline for mHLH patients treated with S $\alpha\beta\gamma$ -01 in frontline settings (n = 6) where a baseline sample was collected and could be used to determine the change in cytokine response after S $\alpha\beta\gamma$ -01 treatment.

[0228] Immunogenicity was additionally assessed. Blood samples were collected from all participants periodically. Blood samples were screened for antibodies binding to S $\alpha\beta\gamma$ -01 and the titer of confirmed positive samples reported.

[0229] Survival and overall response were evaluated by **FIG. 14A** which shows a swimmer plot of mHLH patients that were treated with S $\alpha\beta\gamma$ -01 in frontline settings, and **FIG. 14B** which shows a swimmer plot of all patients receiving S $\alpha\beta\gamma$ -01. Survival is calculated from the date of HLH diagnosis, allowing comparisons to survival estimates established from natural history studies with available therapies. Grey bars to the left of Day 0 in FIG. 14A show time prior to study start after diagnosis. Survival at Day 60 is 11 of 12 (92% survival). A meta-analysis in mHLH patients with available therapies shows a survival of 50-60% at Day 60 indicating S $\alpha\beta\gamma$ -01 may offer survival benefits. Furthermore, there were no inpatient deaths. The 100% hospital discharge alive is also favorable compared with inpatient mortality of 20-30% with available therapies. Six patients remain alive at time of the data cutoff. Response was evaluated using modified HLH-2004 response criteria adapted from (Locatelli 2020).

[0230] Severity of adverse events was classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Adverse event percentages were

determined from the occurrence of a specific AE in a number of individual patients out of the total patients who experienced any AE and received at least one dose of study drug (n = 22) (**FIG. 15**). No dose-limiting toxicities occurred with dose escalation in Cohort 1, therefore, a maximum tolerated dose was not defined. All patients experienced treatment-emergent adverse events (TEAE) and 19 of 22 (86%) experienced a serious adverse event (SAE).

CLAIMS

1. A method of treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 5.0 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 to the subject at least two times per week 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 weekly 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 0.3 mg/kg to about 1.0 mg/kg.
29. The method of any one of claims 1-28, wherein the loading phase comprises one or more doses of about 0.3 mg/kg.
30. The method of any one of claims 1-29, wherein the maintenance dose phase comprises one or more doses of about 0.5 mg/kg.
31. The method of any one of claims 1-30, wherein the method further comprises a priming dose phase.
32. The method of claim 31, wherein the priming dose phase occurs over a duration of 1 to 5 days.
33. The method of claim 31 or 32, wherein the priming dose phase 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 6 years of age.
43. The method of any one of claims 1-41, wherein the subject is about 6 to about 12 years of age.
44. The method of any one of claims 1-41, wherein the subject is above about 12 years of age.
45. The method of any one of claims 1-44, wherein the subject is not treatment-naïve.
46. The method of claim 45, 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.
47. The method of any one of claims 1-44, wherein the subject is treatment-naïve.
48. The method of any one of claims 1-47, wherein the HLH is a primary HLH.
49. The method of any one of claims 1-47, wherein the HLH is a secondary HLH (sHLH).
50. The method of claim 49, wherein the sHLH is selected from the group consisting of immunosuppression therapy mediated HLH, immunotherapy mediated HLH, idiopathic trigger mediated HLH, virus-associated HLH, bacteria-associated HLH, parasite-associated HLH, fungal-associated HLH, autoimmune disease-mediated HLH, and malignancy-triggered HLH.
51. The method of claim 50, wherein the malignancy-triggered HLH comprises an HLH triggered by a hematological malignancy.
52. The method of claim 50, wherein the malignancy-triggered HLH comprises an HLH triggered by a solid tumor.
53. The method of claim 50, wherein the sHLH comprises a relapsed or refractory sHLH.
54. The method of claim 50, wherein the sHLH is an infection-associated HLH.
55. The method of claim 50, wherein the sHLH is associated with a rheumatologic condition.

56. The method of claim 50, wherein the sHLH is associated with a kidney transplant or hematologic stem cell transplant.
57. The method of claim 50, wherein the immune therapy mediated sHLH is associated with therapy with immune checkpoint inhibitors, a CAR T cell therapy (CAR T) or a T cell receptor T cell therapy (TCR-T).
58. The method of any one of claims 1-57, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered as single agent during the treatment phase and/or the priming dose phases.
59. The method of any one of claims 1-57, wherein the SIRP $\alpha/\beta/\gamma$ binding antibody is administered in combination with at least one additional therapeutic agent during the treatment phase and/or the priming dose phases.
60. The method of claim 59, wherein the at least one additional therapeutic agent is selected from group consisting of a corticosteroid-based therapy, a chemotherapeutic agent, an immunotherapeutic agent, a CAR T therapy, a JAK inhibitor, a radiotherapeutic agent, methotrexate, azathioprine, a TNF inhibitor, tocilizumab, anakinra, antimicrobials, etoposide, anakinra, tocilizumab, emapalumab, and alemtuzumab.
61. The method of any one of claims 1-60, wherein the method comprises measuring one or more biomarkers in a biological sample obtained from the subject.
62. The method of claim 61, 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, 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).
63. The method of any one of claims 1-62, wherein the method comprises diagnosing and predicting prognosis, and/or likelihood of response to chemotherapy in the subject utilizing an H-Score system.
64. The method of any one of claims 1-62, wherein the method comprises diagnosing and predicting prognosis, and/or likelihood of response to chemotherapy in the subject utilizing an OHI index.

65. The method of any one of claims 1-64, wherein the method comprises evaluating a ration of sCD25/ferritin to diagnose and predict prognosis, and/or likelihood of response to chemotherapy in the subject.
66. The method of any one of claims 1-65, a predicted prognosis and/or likelihood of response to treatment is obtained by measuring circulating monocyte and lymphocyte counts.
67. The method of any one of claims 1-66, wherein the method comprises monitoring sCD25 and ferritin peak, minimum, maximum, and reduction prospectively to diagnose and predict prognosis, and/or likelihood of response to chemotherapy in the subject.
68. Use of a SIRP $\alpha/\beta/\gamma$ binding antibody in the manufacture of a medicament for treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 5.0 mg/kg per dose of, in one or more treatment phases.
69. The use of claim 68, 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.
70. The use of claim 68 or 69, 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.
71. A SIRP $\alpha/\beta/\gamma$ binding antibody for use in treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, wherein the antibody is administered to the subject at least about 0.01 mg/kg to about 5.0 mg/kg per dose of a, in one or more treatment phases.
72. The antibody for use of claim 71, 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.
73. The antibody for use of claim 71 or 72, 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.

74. A method of treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof, comprising administering to the subject at least about 0.01 mg/kg to about 5.0 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.