(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 May 2025 (15.05.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/101901 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/18* (2006.01)
A61P 31/14 (2006.01) *C07K 14/705* (2006.01)

(21) International Application Number:
PCT/US2024/055127

(22) International Filing Date:
08 November 2024 (08.11.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/598,051 10 November 2023 (10.11.2023) US
63/695,805 17 September 2024 (17.09.2024) US

(71) Applicant: **THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY** [US/US]; Office of the General Counsel, Building 170, 3rd Floor, Main Quad, P.O. Box 20386, Stanford, CA 94305-2038 (US).

(72) Inventors: **WANG, Taia, T.**; 240 Pasteur Drive, Room 3400 (Laboratory), Biomedical Innovations Building, Palo Alto, CA 94304 (US). **GONZÁLEZ, Joseph**; 240 Pasteur Drive, Room 3400 (Laboratory), Biomedical Innovations Building, Palo Alto, CA 94304 (US). **CHAKRABORTY, Saborni**; 240 Pasteur Drive, Room 3400 (Laboratory), Biomedical Innovations Building, Palo Alto, CA 94304 (US). **CHENG, Yik, Ling, Bowie**; 240 Pasteur Drive, Room 3400 (Laboratory), Biomedical Innovations Building, Palo Alto, CA 94304 (US).

(74) Agent: **CHHEDA, Jennifer, J.** et al.; Jones Day, 250 Vesey Street, New York, NY 10281-1047 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: USE OF SIALYLATED IVIG OR IGG FC REGION-CONTAINING PROTEIN FOR PREVENTING OR TREATING RESPIRATORY VIRUS DISEASES

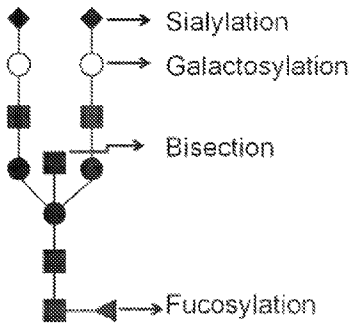


FIG. 1A

(57) Abstract: In one aspect, provided herein are methods for preventing and/or treating respiratory virus diseases (*e.g.*, moderate to severe respiratory virus diseases) comprising administering to a subject (*e.g.*, a human subject) hypersialylated intravenous immunoglobulin (IVIg), a protein comprising a sialylated IgG Fc region, or a protein comprising a modified IgG Fc region that mimics IgG Fc sialylation. In another aspect, provided herein are methods for improving lung function or preserving lung function in a subject with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus diseases) comprising administering to a subject (*e.g.*, a human subject) hypersialylated intravenous immunoglobulin (IVIg), a protein comprising a sialylated IgG Fc region, or a protein comprising a modified IgG Fc region that mimics IgG Fc sialylation.

WO 2025/101901 A1

USE OF SIALYLATED IVIG OR IgG Fc REGION-CONTAINING PROTEIN FOR PREVENTING OR TREATING RESPIRATORY VIRUS DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/695,805, filed September 17, 2024 and U.S. Provisional Patent Application No. 63/598,051, filed November 10, 2023, the disclosure of each of which is incorporated by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with Government support under contract AI139119 awarded by the National Institutes of Health. The Government has certain rights in the invention.

SEQUENCE LISTING

[0003] This application contains an electronic Sequence Listing which has been submitted in XML file format with this application, the entire content of which is incorporated by reference herein in its entirety. The Sequence Listing XML file submitted with this application is entitled "14790-003-228_SEQ_LISTING.xml", was created on November 1, 2024, and is 17,377 bytes in size.

1. INTRODUCTION

[0004] In one aspect, provided herein are methods for preventing and/or treating respiratory virus diseases (*e.g.*, moderate to severe respiratory virus diseases) comprising administering to a subject (*e.g.*, a human subject) hypersialylated intravenous immunoglobulin (IVIg), a protein comprising a sialylated or hypersialylated IgG Fc region, or a protein comprising a modified IgG Fc region that mimics IgG Fc sialylation. In another aspect, provided herein are methods for improving lung function or preserving lung function in a subject with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus diseases) comprising administering to a subject (*e.g.*, a human subject) hypersialylated intravenous immunoglobulin (IVIg), a protein comprising a sialylated IgG Fc region or

hypersialylated, or a protein comprising a modified IgG Fc region that mimics IgG Fc sialylation.

2. BACKGROUND

[0005] A balanced inflammatory response during respiratory viral infections is essential for clearance of virus and infection-associated debris in the tissue and maintenance of adequate lung function. While most respiratory viral infections resolve with little or no harm to the host, a minority of infections trigger an aberrant inflammatory response that contributes to damage of lung tissue and the compromised gas exchange that is often associated with severe or fatal infections (Kalil, A. C. & Thomas, P. G. Influenza virus-related critical illness: pathophysiology and epidemiology. Crit Care 23, 258, doi:10.1186/s13054-019-2539-x (2019); Fukuyama, S. & Kawaoka, Y. The pathogenesis of influenza virus infections: the contributions of virus and host factors. Current opinion in immunology 23, 481-486, doi:10.1016/j.coi.2011.07.016 (2011); and Gill, J. R. et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Arch Pathol Lab Med 134, 235-243, doi:10.5858/134.2.235 (2010)). Regulators of the lung inflammatory response during these infections are not well defined and there is a need for methods for treating such respiratory virus infections.

3. SUMMARY

[0006] In one aspect, provided herein is a method for treating a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject), comprising administering to the subject an agent described herein (*e.g.*, hypersialylated intravenous immunoglobulin (IVIg), or an IgG Fc region-containing protein comprising hypersialylated IgG Fc region). In another aspect, provided herein is a method for treating moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids. In another aspect, provided herein is a method for improving lung function or preserving lung function in a subject (*e.g.*, human subject) with a moderate to severe respiratory virus disease, comprising administering to the subject an agent described herein (*e.g.*, hypersialylated intravenous immunoglobulin (IVIg), or an IgG Fc region-containing

protein comprising hypersialylated IgG Fc region). In another aspect, provided herein is a method for improving lung function or preserving lung function in a subject (*e.g.*, human subject) with a moderate to severe respiratory virus disease, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids. In another aspect, provided herein is a method for reducing inflammation associated with moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an agent described herein (*e.g.*, hypersialylated intravenous immunoglobulin (IVIg), or an IgG Fc region-containing protein comprising hypersialylated IgG Fc region). In another aspect, provided herein is a method for reducing inflammation associated with moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids. In some embodiments, the hypersialylated IVIg comprises α2,3-linked sialic acids. In some embodiments, the IgG Fc region-containing protein comprises α2,3-linked sialic acids. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing dyspnoea, tachypnoea, and/or hypoxia. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein has a sustained fever, such as, e.g., a fever over 102° F (*e.g.*, about 102.5° F, about 103° F, about 103.5° F, about 104° F, about 104.5° F, about 105° F, about 105.5° F, or about 106° F). In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing moderate to severe chest or stomach pain.

[0007] In another aspect, provided herein is a method for preventing moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an agent described herein (*e.g.*, hypersialylated intravenous immunoglobulin (IVIg), or an IgG Fc region-containing protein comprising hypersialylated IgG Fc region). In another aspect, provided herein is a method for preventing moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject

hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids. In some embodiments, the hypersialylated IVIg comprises α2,3-linked sialic acids. In some embodiments, the IgG Fc region-containing protein comprises α2,3-linked sialic acids. In some embodiments, the subject (*e.g.*, human subject) is diagnosed with a respiratory virus infection and is at high risk for moderate to severe respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) is diagnosed with a mild respiratory virus disease and is at high risk for moderate to severe respiratory disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease. In some embodiments, the subject is a human subject at high risk for moderate to severe respiratory virus disease is less than 5 years old (*e.g.*, about 1 years old, about 2 years old, about 3 years old, or about 4 years old) or 50 years old or older (*e.g.*, about 65 years old or older, about 70 years old or older, or about 75 years old or older). In some embodiments, the subject (*e.g.*, human subject) at high risk for moderate to severe respiratory virus disease has diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system.

[0008] In some embodiments, the subject (*e.g.*, human subject) has 10% or less of total IgG1 sialylated in a serum sample from the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein. In some embodiments, the subject (*e.g.*, human subject) has 10% or less of IgG1 G2SFS in a serum sample from the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

[0009] In some embodiments, the respiratory virus is influenza virus. In some embodiments, the influenza virus is an influenza A virus. In some embodiments, the influenza A virus is an H1 or H3 subtype.

[0010] In some embodiments, the respiratory virus is a human respiratory syncytial virus. In some embodiments, the respiratory virus is a human metapneumovirus. In some embodiments, the respiratory virus is a human parainfluenza virus. In some embodiments, the respiratory virus is an adenovirus or coronavirus. In some embodiments, the respiratory virus is a severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or a severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2). In some embodiments, the respiratory virus is a human bocavirus.

[0011] In some embodiments, no significant difference in neutralization of the respiratory virus by the hypersialylated IVIg or the IgG Fc region-containing protein relative to asialylated IVIg or the same IgG Fc region-containing protein in which the sialylation has been removed, respectively, is detected as assessed in an *in vitro* neutralization assay. In some embodiments, no significant difference means that there is no statistically significant difference at p value of less than 0.05 in the amount of neutralization detected.

[0012] In some embodiments, the hypersialylated IVIg or the IgG Fc region-containing protein does not prevent binding of the respiratory virus to its host cell receptor as assessed in an *in vitro* assay.

[0013] In some embodiments, the levels of one or more proinflammatory cytokines in a bronchoalveolar lavage (BAL) sample from the subject (*e.g.*, human subject) are reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to the levels of the one or more proinflammatory cytokines in a BAL sample from the same subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein. In some embodiments, the one or more proinflammatory cytokines include one or more of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1 alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-gamma, and TNF-beta.

[0014] In some embodiments, the levels of one or more monocyte/macrophage chemotactic factors in a BAL sample from the subject (*e.g.*, human subject) are reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to the levels of the one or more monocyte/macrophage chemotactic in a BAL sample from the same subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein. In some embodiments, the one or more monocyte/macrophage chemotactic factors include one or more of GM-CSF, CXCL1, CXCL2, CXCL5, CXCL10, and CXCL11.

[0015] In some embodiments, neutrophil and monocyte infiltration in a BAL sample from the subject (*e.g.*, human subject) is reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to neutrophil and monocyte infiltration in a BAL sample from the same subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

[0016] In some embodiments, no significant difference in the titer of the respiratory virus is detected following administration of the hypersialylated IVIg or the IgG Fc region-containing protein to an animal model for the respiratory virus relative to the titer of the respiratory virus detected following administration of asialylated IVIg, the same IgG Fc region-containing protein in which the sialylation has been removed, or phosphate buffered saline to the same type of animal model. In some embodiments, no significant difference means less than a log or less than 0.5 logs difference in respiratory virus titer. In some embodiments, the titer of the respiratory virus in a BAL sample is assessed.

[0017] In some embodiments, the hypersialylated IVIg or the IgG Fc region-containing protein suppresses the expression one or more of genes induced by the respiratory virus that are involved in the inflammatory response. In some embodiments, the hypersialylated IVIg or the IgG Fc region-containing protein upregulates the expression of DC-SIGN. In some embodiments, the hypersialylated IVIg or the IgG Fc region-containing protein upregulates the expression of Siglec G. In some embodiments, the hypersialylated IVIg or the IgG Fc region-containing protein induces REST. In some embodiments, the hypersialylated IVIg or the IgG Fc region-containing protein induces nuclear REST expression in cells, such as immune cells, such as monocytes and/or macrophages (*e.g.*, alveolar macrophages). In some embodiments, the hypersialylated IVIg or the IgG Fc region-containing protein suppresses NF-KB signaling in cells, such as immune cells (*e.g.*, monocytes and/or macrophages (*e.g.*, alveolar macrophages)).

[0018] In some embodiments, the hypersialylated IVIg comprises higher α2,6-linked sialic acid in the N-linked glycans of Fc regions than an unmodified IVIg composition. In some embodiments, the hypersialylated IVIg comprises at least 20% (*e.g.*, at least 25%, at least 27%, at least 30%, about 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, or at least 80%) higher α2,6-linked sialic acid in the N-linked glycans of Fc regions than an unmodified IVIg composition.

[0019] In some embodiments, the hypersialylated IVIg includes antibody that binds to an antigen of the respiratory virus. In some embodiments, the hypersialylated IVIg includes antibody that binds to an envelope protein or glycoprotein of the respiratory virus.

[0020] In some embodiments, the IgG Fc region-containing protein is binds to an antigen of the respiratory virus. In some embodiments, the antigen of the respiratory virus is an envelope protein or glycoprotein.

[0021] In some embodiments, the IgG Fc region-containing protein comprises an antibody. In some embodiments, the antibody binds to an antigen of the respiratory virus. In

some embodiments, the antigen of the respiratory virus is an envelope protein or glycoprotein.

[0022] In some embodiments, the IgG Fc region-containing protein consists of a hypersialylated IgG Fc region. In some embodiments, the hypersialylated IgG Fc region is a sialylated human IgG1 Fc region.

[0023] In some embodiments, the hypersialylated IgG Fc region is at least 90% or at least 95%, identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the hypersialylated IgG Fc region is at least 96%, at least 97%, at least 98%, or at least 99%, identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the hypersialylated IgG Fc region consists of the amino acid sequence of SEQ ID NO:1.

[0024] In another aspect, provided herein is a method for treating a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject), comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region described herein. In another aspect, provided herein is a method for treating moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN. In another aspect, provided herein is a method for improving lung function or preserving lung function in a subject (*e.g.*, human subject) with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region described herein. In another aspect, provided herein is a method for improving lung function or preserving lung function in a subject (*e.g.*, human subject) with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN. In another aspect, provided herein is a method for reducing inflammation associated with moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region described herein. In another aspect, provided herein is a method for reducing inflammation associated with moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on

DC-SIGN. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing dyspnoea, tachypnoea, and/or hypoxia. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein has a sustained fever, such as, e.g., a fever over 102° F (*e.g.*, about 102.5° F, about 103° F, about 103.5° F, about 104° F, about 104.5° F, about 105° F, about 105.5° F, or about 106° F). In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing moderate to severe chest or stomach pain.

[0025] In another aspect, provided herein is a method for preventing moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region described herein. In another aspect, provided herein is a method for preventing moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN. In some embodiments, the subject (*e.g.*, human subject) is diagnosed with a respiratory virus infection and is at high risk for moderate to severe respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) is diagnosed with a mild respiratory virus disease and is at high risk for moderate to severe respiratory disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease. In some embodiments, the subject is a human subject at high risk for moderate to severe respiratory virus disease is less than 5 years old (*e.g.*, about 1 years old, about 2 years old, about 3 years old, or about 4 years old) or 50 years old or older (*e.g.*, about 65 years old or older, about 70 years old or older, or about 75 years old or older). In some embodiments, the subject (*e.g.*, human subject) at high risk for moderate to severe respiratory virus disease has diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system.

[0026] In some embodiments, the subject (*e.g.*, human subject) has 10% or less of total IgG1 sialylated in a serum sample from the subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein. In some embodiments, the subject (*e.g.*, human subject) has 10% or less of IgG1 G2SFS in a serum sample from the

subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

[0027] In some embodiments, the respiratory virus is influenza virus. In some embodiments, the influenza virus is an influenza A virus. In some embodiments, the influenza A virus is an H1 or H3 subtype.

[0028] In some embodiments, the respiratory virus is a human respiratory syncytial virus. In some embodiments, the respiratory virus is a human metapneumovirus. In some embodiments, the respiratory virus is a human parainfluenza virus. In some embodiments, the respiratory virus is an adenovirus or coronavirus. In some embodiments, the respiratory virus is a severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In some embodiments, the respiratory virus is a human bocavirus.

[0029] In some embodiments, no significant difference in neutralization of the respiratory virus by the IgG Fc region-containing protein relative to the same IgG Fc region-containing protein in which the sialylation has been removed, is detected as assessed in an *in vitro* neutralization assay. In some embodiments, no significant difference means that there is no statistically significant difference at p value of less than 0.05 in the amount of neutralization detected.

[0030] In some embodiments, the IgG Fc region-containing protein does not prevent binding of the respiratory virus to its host cell receptor as assessed in an *in vitro* assay (*e.g.*, an immunoassay, such as an ELISA).

[0031] In some embodiments, the levels of one or more proinflammatory cytokines in a bronchoalveolar lavage (BAL) sample from the subject (*e.g.*, human subject) are reduced after administration of the IgG Fc region-containing protein relative to the levels of the one or more proinflammatory cytokines in a BAL sample from the same subject prior to administration of the IgG Fc region-containing protein. In some embodiments, the one or more proinflammatory cytokines include one or more of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1 alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-gamma, and TNF-beta.

[0032] In some embodiments, the levels of one or more monocyte/macrophage chemotactic factors in a BAL sample from the subject (*e.g.*, human subject) are reduced after administration of the IgG Fc region-containing protein relative to the levels of the one or more monocyte/macrophage chemotactic factors in a BAL sample from the same subject prior to administration of the IgG Fc region-containing protein. In some embodiments, the

one or more monocyte/macrophage chemotactic factors include one or more of GM-CSF, CXCL1, CXCL2, CXCL5, CXCL10, and CXCL11.

[0033] In some embodiments, neutrophil and monocyte infiltration in a BAL sample from the subject (*e.g.*, human subject) is reduced after administration of the IgG Fc region-containing protein relative to neutrophil and monocyte infiltration in a BAL sample from the same subject prior to administration of the IgG Fc region-containing protein.

[0034] In some embodiments, no significant difference in the titer of the respiratory virus is detected following administration of the IgG Fc region-containing protein to an animal model for the respiratory virus relative to the titer of the respiratory virus detected following administration of the same IgG Fc region-containing protein in which the sialylation has been removed, or phosphate buffered saline to the same type of animal model. In some embodiments, no significant difference means less than a log or less than 0.5 logs difference in respiratory virus titer. In some embodiments, the titer of the respiratory virus in a BAL sample is assessed.

[0035] In some embodiments, the IgG Fc region-containing protein suppresses the expression of one or more of genes induced by the respiratory virus that are involved in the inflammatory response. In some embodiments, the IgG Fc region-containing protein upregulates the expression of DC-SIGN. In some embodiments, the IgG Fc region-containing protein upregulates the expression of Siglec G. In some embodiments, the IgG Fc region-containing protein induces REST. In some embodiments, the IgG Fc region-containing protein induces nuclear REST expression in cells, such as immune cells, such as monocytes and/or macrophages (*e.g.*, alveolar macrophages). In some embodiments, the IgG Fc region-containing protein suppresses NF-KB signaling in cells, such as immune cells (e.g., monocytes and/or macrophages (*e.g.*, alveolar macrophages)).

[0036] In some embodiments, the IgG Fc region-containing protein is binds to an antigen of the respiratory virus. In some embodiments, the antigen of the respiratory virus is an envelope protein or glycoprotein.

[0037] In some embodiments, the IgG Fc region-containing protein comprises an antibody. In some embodiments, the antibody binds to an antigen of the respiratory virus. In some embodiments, the antigen of the respiratory virus is an envelope protein or glycoprotein.

[0038] In some embodiments, the modified IgG Fc region comprises the amino acid sequence of SEQ ID NO:2.

[0039] In some embodiments, the protein consists of the modified IgG Fc region. In some embodiments, the modified IgG Fc region consists of the amino acid sequence of SEQ ID NO:2.

[0040] In some embodiments, IgG Fc region-containing protein includes α2,6-linked sialic acids and/or mimics the activity of hypersialylated IgG1 Fc. In some embodiments, the IgG Fc region containing protein comprises at least about 20% (*e.g.*, at least 25%, at least 27%, at least 30%, about 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, or at least 80%) higher α2,6-linked sialic acids in N-linked glycans of Fc regions than an unmodified IVIg composition. In some embodiments, the modified IgG Fc comprises α2,3-linked sialic acids.

3.1 Terminology

[0041] The terms "about" and "approximate" in reference to a number includes the number and the number plus or minus 1% to 20% (*e.g.*, 5%, 10%, 15%, or 20%) of the number.

[0042] The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0043] An antibody can include, for example, a monoclonal antibody, a monospecific antibody, a multi-specific antibody, a bispecific antibody, a human antibody, a humanized antibody, a chimeric antibody, a synthetic antibody, a tetrameric antibody comprising two heavy chain and two light chain molecule, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain-antibody heavy chain pair, intrabodies, heteroconjugate antibody, monovalent antibody, and antigen-binding fragments of any of the above. In specific embodiments, an antibody comprises an IgG (*e.g.*, IgG_1) Fc region. In some embodiments, an antibody comprises two or more IgG (*e.g.*, IgG_1) Fc regions. In some embodiments, antibodies described herein refer to polyclonal antibody populations. In specific embodiments, an antibody is an IgG. In some embodiments, an antibody is IgG1, IgG2, IgG3, or IgG4.

[0044] As used herein, the terms "comprising" and "including" can be used interchangeably. The terms "comprising" and "including" are to be interpreted as specifying

the presence of the stated features or components as referred to, but does not preclude the presence or addition of one or more features, or components, or groups thereof. Additionally, the terms "comprising" and "including" are intended to include examples encompassed by the term "consisting of". Consequently, the term "consisting of" can be used in place of the terms "comprising" and "including" to provide for more specific embodiments.

[0045] Percent identity: Techniques known to one of skill in the art can be used to determine the percent identity between two amino acid sequences or between two nucleotide sequences. Generally, to determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.,* gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.,* % identity = number of identical overlapping positions/total number of positions X 100%). In one embodiment, the two sequences are the same length. In a certain embodiment, the percent identity is determined over the entire length of an amino acid sequence or nucleotide sequence.

[0046] The determination of percent identity between two sequences (*e.g.,* amino acid sequences or nucleic acid sequences) can also be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264 2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873 5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.*, 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.,* for score=100, wordlength=12 to obtain nucleotide sequences homologous to nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.,* to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, 1997, Nucleic Acids Res. 25:3389 3402. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped

BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.*, of XBLAST and NBLAST) can be used (*see*, *e.g.*, National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[0047] The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

[0048] As used herein, terms "subject" or "patient" are used interchangeably to refer to an animal (*e.g.*, birds, reptiles, and mammals). In some embodiments, a subject is a bird. In some embodiments, a subject is a mammal including a non-primate (*e.g.*, a camel, donkey, zebra, cow, pig, horse, goat, sheep, cat, dog, rat, and mouse) and a primate (*e.g.*, a monkey, chimpanzee, and a human). In some embodiments, a subject is a non-human animal. In some embodiments, a subject is a non-human mammal. In some embodiments, a subject is a farm animal (*e.g.*, a horse, a pig, a cow, a goat, etc.) or pet (*e.g.*, a cat, a dog, etc.). In specific embodiments, a subject is a human.

[0049] In some embodiments, suppresses refers to a detectable reduction. In some embodiments, suppresses refers to at least a 10%, at least a 15%, at least a 20%, or at least a 25% reduction. In some embodiments, a decrease refers to at least a 10%, at least a 15%, at least a 20%, or at least a 25% reduction. In some embodiments an increase refers to at least a 10%, at least a 15%, at least a 20%, or at least a 25% increase.

4. DESCRIPTION OF THE FIGURES

[0050] **FIGS. 1A-1B**. Schematic diagram of IgG1 Fc glycan. (FIG. 1A) The Fc glycan present at N297 within the CH2 domain shown with all possible glycan modifications. Composition of the core Fc glycan (boxed) can be modified by addition of specific saccharide units (fucose [F], N-acetylglucosamine, galactose [G] and sialic acid [S]). (FIG. 1B) The various possible galactose and sialic acid residues that can be added to the core agalactosylated and fucosylated variant (G0F) of IgG1.

[0051] FIGS. 2A-2D. Characterization of anti-HA Fc glycoforms in influenza patients. (FIG. 2A) Distribution of anti-HA IgG1 Fc glycoforms from influenza patients who developed symptoms requiring hospitalization (H) (n=10) or who maintained mild symptoms and were not hospitalized (NH) (n=16). (FIG. 2B) IgG1 sialic acid distribution in hospitalized and non-hospitalized patients where G1 represents one and G2 represents 2 galactose residues on the biantennary N-glycan branches. (FIG. 2C) IgG1 Fc G2FS area under the receiver-operating-characteristic curve (AUC) with 95% confidence interval. (FIG. 2D) Half-maximal neutralizing titers (pNT50) against a H1 pseudotyped virus (A/Hawaii/70/2019) in plasma of hospitalized and non-hospitalized influenza patients collected at acute and convalescent time points. Median values are depicted in FIG. 2A and FIG. 2B with a solid black line. p values in (FIG. 2A) were calculated using unpaired Student's test with Welch's correction, in (FIG. 2B) with two-way ANOVA with Tukey's correction and in (FIG. 2D) using mixed effect analysis with Sidak's correction. In FIG. 2B, the H is to the left and NH is to the right in the graph for each of G1FS and G2FS. In FIG. 2D, the H is to the left and NH is to the right for each of acute and convalescent.

[0052] FIGS. 3A-3E. Characterization of enzymatically modified human IgG (IVIg). (FIG. 3A) Purified IgG pooled from thousands of donors (IVIg) was enzymatically treated to enhance sialylation by treatment with ST6Gal 1 (S IVIg) or was neuraminidase treated to remove existing sialic acids (S0 IVIg). The level of 2,6-sialic acid of the IVIg preparations was assessed by SNL lectin blot (left) and as loading control, the amount of protein loaded was shown with anti-human IgG antibody staining (right). (FIG. 3B) Level of IgG1 sialylation of modified IVIg determined by mass spectroscopy. (FIG. 3C) Size exclusion chromatograms of unmodified, asialyated (S0) and sialylated (S) IVIg. (FIG. 3D) Neutralization curves of A/Netherlands/602/2009 H1N1 and A/X31 H3N2 viruses in MDCK cells with unmodified, S0 and S IVIg Error bars indicate the range of technical replicates. (FIG. 3E): EC50 values of unmodified, S0 and S IVIg against A/Netherlands/602/2009 H1N1 and A/X31 H3N2 viruses.

[0053] FIGS. 4A-4E. IgG sialylation protects against influenza disease in a SIGN-R1 dependent manner. (FIG. 4A) Experimental design. FcγR humanized C57/Bl6 mice were challenged intranasally with 5LD of A/Netherlands/2009 H1N1 or A/X31 H3N2 viruses, and received either no treatment (Virus only), sialylated IVIg (S) or asialylated IVIg (S0) prior to infection, followed by daily monitoring of weight and survival. (FIG. 4B) Body weight and (FIG. 4C) survival for mice challenged with A/Netherlands/10/2009 (H1N1) (n=11 for the S and S0 IVIg groups, n=4 for the virus only group). (FIG. 4D) Body weight

and (FIG. 4E) survival for mice challenged with X31 (H3N2) (n=7 for the S and n=8 for the S0 IVIg groups, n=6 for the virus only group). Each line represents one single mouse and triangles indicate mice that succumbed to challenge. Statistical significance was determined by two-way ANOVA with Bonferroni correction for multiple comparison in (FIGS. 4B, 4D) (Asterisk denotes statistical significance between S IVIg vs S0 IVIg. *$P=<0.05$, **$P=<0.01$, #$P=< 0.001$. Each triangle represents a mouse that went below 85% of their original body weight). For mice that died, their body weight would be defined as 85% for statistical analysis. For the survival curves, the statistical significance was determined by log-rank Mantel–Cox tests against the Virus only group in (FIGS. 4C, 4E).

[0054] FIGS. 5A-5H. Sialylation of IgG reduces lung inflammation and protects lung function in influenza-infected mice. (FIG. 5A) Experimental design. FcγR humanized C57/Bl6 mice were infected with A/Netherland/09 H1N1 or A/X31 H3N2 influenza strains, and received either no treatment (virus only, Vir), S or S0 IVIg prior to infection. (FIG. 5B) IVIg in BAL fluid collected 7 days post A/Netherland/09 H1N1 infection (n=9-10 for S/S0 groups; n=3 no IVIg control group). (FIG. 5C) Lung viral titers on day 4 and/or day 7 post-infection (mice who received virus alone had succumbed to infection on day 7) (n=3-5 per group). (FIG. 5D) Neutrophil count in BAL fluid on day 4. (FIG. 5E) Heat map showing the BAL fluid cytokines on Day 7 post-H1N1 infection. The scale denotes the level of cytokines, with deep red and deep blue showing the highest and the lowest level of cytokine respectively. (n=3 per group). Associated p values in adjacent table. (FIG. 5F) The absolute number of neutrophils (left) and monocytes (right) on day 7 post H1N1-infection. (FIG. 5G) Experimental design to test SIGN-R1 dependence and survival of mice challenged with H1N1 with or without S IVIg in addition to either isotype control or SIGN-R1 blocking antibody (n=4 for isotype (iso) and αSIGNR1 group, n=15-17 for S IVIg with iso or with αSIGNR1 antibody groups). (FIG. 5H) The level of O2 and CO2 in the cardiac arterial blood collected from H1N1-infected mice on Day 5. Statistical significance was determined by one-way ANOVA for (FIG. 5B), (FIG. 5C) and (FIG. 5D), by two-tailed Student's t-test in (FIG. 5E) and (FIG. 5F) and by log-rank Mantel–Cox tests against the S IVIg + iso group in (FIG. 5G).

[0055] FIG. 6. Immune cell profiling in lungs of mice receiving variously sialylated IVIg. Day 7 BAL fluid immune cells in FcγR humanized C57/Bl6 mice treated S or S0 IVIg, or received no treatment (Vir, virus only) followed by 5LD A/Netherlands/09 challenges. Significance was calculated using Welch's t-test.

[0056] FIGS. 7A-7C. A recombinantly expressed sialylated Fc domain protects against influenza virus disease. (FIG. 7A) Experimental design. Humanized FcγR C57/BL6 mice received intranasal infection of A/Netherlands/09 influenza strain, then received either no treatment or sialylated Fc (sFc) on day 2, 4 and 6 post-infection. (FIG. 7B) Weight curves of mice that received either no treatment (Virus only, each dashed line represents one mouse) (n=7) or sFc treatment (each solid line represents one mouse) (n=10) post-A/Netherlands/09 challenge. (FIG. 7C) Survival curves of mice that received either no treatment (Virus only) or sFc treatment (sFc) post-infection. Statistical significance was inferred by (FIG. 7B) two-way ANOVA with Bonferroni correction for multiple comparison and (FIG. 7C) log-rank Mantel–Cox tests. For mice that died, their body weight would be defined as 85% for statistical analysis.

[0057] FIGS. 8A-8C. Sialylated IgG are actively anti-inflammatory through SIGN-R1. (FIG. 8A) Mouse model of immune response to human IgG immune complexes within the lung. Mice were intratracheally administered sialylated (FS/-), asialylated (F/-), or no (-/-) immune complexes. SIGN-R1 blockade prior to sialylated immune complex administration (FS/+). (FIG. 8B) BAL neutrophil content and (FIG. 8C) soluble factors in BAL fluid from immune complex-treated mice, 4 hours post administration. P-values in B were determined by two-way ANOVA with post-hoc Tukey HSD test. P-values in FIG. 8C were determined by one-way ANOVA with post-hoc Tukey HSD test. The absence of a corresponding p-value indicates a non-significant comparison.

[0058] FIGS. 9A-9F. Sialylated and afucosylated IgG elicit distinct transcriptional changes in lung resident cells, promoting inverse transcriptional regulation of key immune functions. (FIGS. 9A, 9B) Alveolar macrophage (Amφ), interstitial macrophage (Imφ), monocytes (mono), and dendritic cells (DCs) within the FcγR-humanized mouse whole lung were assessed for (FIG. 9A) abundance as well as (FIG. 9B) CD16 and SIGN-R1 expression by flow cytometry. (FIGS. 9C-9F) Amφ were isolated from bronchoalveolar lavage fluid of mice 4 hours after immune complex administration. Isolated Amφ underwent bulk RNA sequencing and transcriptomic analysis. (FIG. 9C) Principal component analysis of transcriptional profiles of Amφ isolated from mice that received afucosylated (F0), fucosylated (F), or sialylated (FS) immune complexes. (FIGS. 9D-9F) Differential genes (red) expressed between mice that received (FIG. 9D) afucosylated or (FIG. 9E) sialylated immune complexes compared to fucosylated immune complexes. (FIG. 9F) DEGs of mice that received sialylated immune complexes after blockade with anti-SIGN-R1 antibody or an isotype control. Annotated genes include the most differentially expressed genes as well as

genes encoding soluble factors that were assess in BAL fluid. P-values in (FIGS. 9A, 9B) were determined by one-way ANOVA with post-hoc Tukey HSD test and in (FIGS. 9D-9F) were determined by ANOVA using the factoextra R package. The absence of a corresponding p-value indicates a non-significant comparison.

[0059] FIGS. 10A-10C. Volcano plots of M2 macrophage differentially expressed genes (DEGs). –Log10P cutoff = 5, Log2FC = +/-0.584963 (+/-1.5). Labeled points indicate DEGs that meet both significance and fold-change criteria. (FIG. 10A) DEGs of Cd209+ M2 macrophage stimulated with sFc versus unstimulated (PBS). (FIG. 10B) DEGs of Cd209-knocked down M2 macrophage stimulated with sFc versus Cd209+ M2 macrophage stimulated with sFc. (FIG. 10C) DEGs of unstimulated Cd209-knocked down M2 macrophage versus unstimulated CD209+ M2 macrophage. Il4i1 – IL-4 induced gene. A checkpoint molecule (PMID: 32818467); Mmp25 – matrix metalloproteinase involved in CD16 downregulation (PMID: 23851692); Qpct – enzymatic modifier of the CD47 – SIRPα checkpoint axis (PMID: 30833751); Lilrb1 – CD85j. Checkpoint molecule containing ITIM domains (PMID: 26636629); Ly75 – CD205. Myeloid cell receptor that induces tolerance toward ligand/binding partners (PMID: 33679806); and Ccl17 – One of two ligand of CCR4, present on regulatory T cells (PMID: 28723576).

[0060] FIGS. 11A-11B. Enrichment plots of (FIG. 11A) **Influenza infection and** (FIG. 11B) **NRSF/REST pathways by GSEA** comparing murine alveolar macrophage isolated from mice treated with sialylated immune complexes (ICs) versus asialylated ICs.

[0061] FIGS. 12A-12C. Pathways and genes commonly increased in expression in virus only (Vir) and asialylated (S0) IVIg groups when compared to sialylated (S) IVIg group (FIG. 12A) Commonly upregulated pathways in Vir versus S groups and S0 versus S groups, and the genes that are specific to these pathways. (FIG. 12B) Differentially expressed genes involved in the commonly upregulated pathways. (FIG. 12C) Sialic acid binding receptors on AM were down-regulated in virus only (Vir) and asialylated (S0) IVIg groups when compared to sialylated (S) IVIg group. CD209b was down-regulated in S0 group compared to S group, and Siglecg was down-regulated in both Vir group and S0 group when compared to S group.

[0062] FIGS. 13A-13H. IgG sialylation predicts the severity of human influenza disease and protects mice against divergent influenza strains. (FIG. 13A) IgG1 sialic acid distribution in hospitalized (n=10, white open circles) and non-hospitalized (n=16, closed grey circles) patients where G1 represents one and G2 represents 2 galactose residues on the biantennary N-glycan branches. Median values are depicted with a solid black line and

statistical significance was two-way ANOVA with Tukey's correction. (FIG. 13B) IgG1 Fc G2FS area under the receiver-operating-characteristic curve (AUC) with 95% confidence interval. (FIG. 13C) FcγR-humanized mice received either no treatment (Virus only), sialylated (S) human IgG (hIgG) or asialylated hIgG (S0) prior to lethal challenge with A/Netherlands/2009 (H1N1) or A/X-31 (H3N2) viruses. (FIG. 13D) Body weight (left) and survival (right) of mice challenged with A/Netherlands/10/2009 (H1N1). For body weight, statistical significance was determined by two-way ANOVA with Bonferroni correction for multiple comparison and body weight of sacrificed mice was defined as 85% (humane end-point) for statistical analyses. For survival analysis, statistical significance was determined by log-rank Mantel–Cox tests against the Virus only group. (*P<0.05, **P<0.01, #P< 0.001). The experiment was performed twice, and representative data are shown (n=11 for the S (solid grey line) and S0 (dotted black line) hIgG groups, n=4 for the virus only group (solid black line)). (FIG. 13E) Body weight (left) and survival (right) for mice challenged with X31 (H3N2). For body weight, statistical significance was determined by two-way ANOVA with Bonferroni correction for multiple comparison and body weight of sacrificed mice was defined as 85% for statistical analyses. For survival analysis, statistical significance was determined by log-rank Mantel–Cox tests against the Virus only group. (*P<0.05, **P<0.01, #P< 0.001). Data from one experiment performed once (n=7 for the S (solid grey line) and n=8 for the S0 hIgG (dotted black line) groups, n=6 for the virus only group (solid black line)). (FIG. 13F) Lung viral titers of H1N1 infected mice on day 4 and/or day 7 post-infection. One-way ANOVA and two tailed student's T-test analysis were used in day 4 and day 7 analysis respectively. Mice received no treatment (Virus only, Vir), sialylated (S) human IgG (hIgG) or asialylated hIgG (S0) prior to lethal challenge. Data are represented as mean ± SEM and are pooled from two independent experiments (for day 4 titers n = 12 per group, for day 7 titers, n=9 for S and n=7 for S0). (FIG. 13G) Lung viral titers of H3N2 infected mice on day 7 post-infection. Two tailed student's T-test analysis was for statistical analysis. Mice received sialylated (S) human IgG (hIgG) or asialylated hIgG (S0) prior to lethal challenge. Experiment was performed once. Data are shown as mean ± SEM (n=5 per group). (FIG. 13H) FcγR humanized C57BL/6 mice were either pre-treated with S hIgG or received no pretreatment followed by H1N1 challenge in addition to either isotype hIgG control or CD209b blocking antibody. Experiment was performed twice, and representative data are shown (n=4 for isotype only (solid light grey) and CD209b block (solid black line), n=15-17 for S hIgG with iso (solid dark grey) or with CD209b block (dotted black line)). Statistics by log-rank Mantel–Cox tests against the Virus only group.

[0063] FIGS. 14A-14D. Sialylated hIgG reduces lung inflammation and protects lung function in influenza-infected mice. (FIG. 14A) Left: UMAP plot of the myeloid lineage assessed by flow cytometry from the whole lung tissue of FcγR humanized C57BL/6 mice post H1N1 infection, with the different clusters labelled in grey scale Middle: pseudocolor plot of the UMAPs from the virus only group, S hIgG and S0 hIgG receiving groups, clusters that are significantly different between groups (C3-alveolar macrophages and C7-neutrophils) are outlined (grey: higher density; black: lower density). Right: The percentage of cells in each cluster among the virus only (Vir), S and S0 groups. Clusters that are significantly different between groups (C3-alveolar macrophages, dark grey and C7-neutrophils, white) are shown in dark grey (C3) and white (C7). Statistics by two-way ANOVA with Bonferroni's correction. Experiment was performed once (n=5 per group). (FIG. 14B) Neutrophils and monocyte count in BAL fluid on day 4 and day 7 post H1N1 infection. Statistics by one-way ANOVA with Tukey's correction for day 4 analysis and two tailed student's T test for day 7 analysis: *P<0.05, **P<0.01. Experiments was performed twice and pooled data from two independent experiments are shown (n=9-12 mice per group for day 4, n= 6-8 mice per group). (FIG. 14C) Cytokine and chemokine levels in BAL fluid collected 4 days and 7 days post infection. Heatmaps represent the mean of log2 fold change for the cytokine level. Statistics by one-way ANOVA with Tukey's correction for day 4 analysis and two tailed student's T test for day 7 analysis: *P<0.05, **P<0.01, ***P<0.001; pink = S vs Vir, grey = S0 vs Vir, black = S vs S0. Experiments was performed twice and pooled data from two independent experiments are shown for day 4 (n=8 mice per group). Experiment was performed once for day 7 (n=4-5 per group). (FIG. 14D) The level of O2 and CO2 in the cardiac blood collected from H1N1-infected mice on Day 5. Statistics by one-way ANOVA with Tukey's correction: *P<0.05, **P<0.01. Experiments was performed twice and pooled data from two independent experiments are shown (n=8-9 mice per group).

[0064] FIGS. 15A-15D. The presence of sialylated IgG during influenza infection induces a unique transcriptomic signature in murine Amφ that stratifies disease severity in people with severe or mild influenza virus infections. (FIG. 15A) Volcano plots showing the differentially expressed genes (DEGs) of alveolar macrophages isolated from H1N1 challenged mice pretreated with S (n=5) or S0 (n=5) hIgG, or no treatment (Vir, n=3). (FIG. 15B) PCA plot showing the clustering of samples based on the transcriptomic analysis of alveolar macrophages isolated from H1N1 challenged mice pretreated with S (white circle) or S0 hIgG (black circle), or no treatment (Vir, grey circle). (FIG. 15C) Top 5 most downregulated pathways via pathway enrichment analysis on common DEGs from S vs

S0 and S vs Vir comparison. P values were determined by GSEA. (FIG. 15D) PCA depicting the stratification of influenza patients (n=328, 155 non-hospitalized, 173 hospitalized) into hospitalized (H, white open circles) and non-hospitalized (NH, dark grey circles) using the S hIgG associated gene signature.

[0065] FIGS. 16A-16I. Sialylated IgG blocks NF-κB and induces REST. (FIG. 16A) Expression of selected NF-κB genes by murine Amφ isolated from mice (n=4) that received sialylated (S, white) or asialylated (S0, light grey) immune complexes, or S IC after CD209b blockade (dark grey). Statistics by Kruskal-Wallis with Dunn's multiple comparisons test: **P<0.01, ***P<0.001, ****P<0.0001. N = 4. (FIG. 16B) GSEA of murine Amφ transcripts (left) and human CD209+ monocyte-derived macrophage (MDM) (right) revealed enrichment of REST/NRSF target genes after sialylated (S) immune complex administration compared to asialylated (S0).n = 4 (left) and 3 (right). (FIG. 16C) Representative images of REST expression (grey) in human MDMs stimulated with IgG with increasing abundance of Fc sialylation. 40x magnification; 10-micron scale bar; cell outline via phalloidin staining (light grey), nuclear outline via Hoechst staining (white). Representative pooled data of n = 3 from 2 independent experiments. (FIG. 16D) Quantified REST expression and nuclear localization of (FIG. 16B): median with 95% CI. Statistics by Kruskal-Wallis with Dunn's multiple comparisons test: *P<0.05, ****P<0.0001. Representative pooled data of n = 3 from 2 independent experiments. (FIG. 16E) THP1 NF-κB reporter cells were differentiated and polarized toward CD209+ macrophage and treated with asialylated IgG and DMSO (control; light gray), sialylated (S) IgG and DMSO (S IgG; white), or S IgG and the REST inhibitor, X5050 (S IgG + X5050; dark grey) prior to stimulation with well-characterized activators of NF-κB. Statistics by two-way ANOVA with Šidák correction: *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. (FIG. 16F) Human alveolar macrophage (hAmφ) were cultured overnight with sialylated (S) or asialylated (S0) IgG prior to stimulation with an inflammatory activator, afucosylated (F0, dark grey or white) immune complexes, or S0 IgG immune complexes (light grey). Data are from one experiment (n = 4-5). (FIG. 16G) Expression of selected NF-κB genes in hAmφ from (FIG. 16E). Statistics by two-way ANOVA with post-hoc Tukey's HSD test: *P<0.05. (FIG. 16H) GSEA revealed the positive enrichment of NRSF/REST target genes in hAmφ from (FIG. 16E) that were treated with sialylated IgG (S) compared to asialylated (S0) IgG. (FIG. 16I) Cytokine production by human Amφ from (FIG. 16E). Statistics by two-way ANOVA with post-hoc Tukey's HSD test: *P<0.05, **P<0.01, ***P<0.001.

[0066] FIGS. 17A-17E. REST depletion ablates sialylated IgG-mediated protection against influenza disease. (FIG. 17A) Neutrophils and cytokines within BALF of FcγR humanized C57BL/6 mice pretreated with either X5050 or DMSO followed by administration of sialylated IgG or PBS. Statistical significance for neutrophils was determined by one-way ANOVA with Tukey's correction and for cytokines by two-way ANOVA with Tukey's correction. Experiment was performed once (n=2-5 mice per group). (FIG. 17B) Neutrophils within BALF of FcγR humanized C57BL/6 mice pretreated with either X5050 or DMSO followed by administration of sialylated (S) IC or asialylated (S0) IC. Statistical significance for determined by one-way ANOVA with Tukey's correction. Experiment was performed once (n=5 mice per group). (FIG. 17C) FcγR humanized C57BL/6 mice received sialylated hIgG or no IgG prior to H1N1 infection, along with the REST inhibitor, X5050 or sham (DMSO alone). (FIG. 17D) Weight (top) and survival (bottom) of mice in (FIG. 17A) were monitored daily. Error bars depict SEM. Statistical significance for weight lost (top) was determined by two-way ANOVA with Bonferroni's correction. Body weight of sacrificed mice was defined as 85% for statistical analyses. Statistical significance for survival (bottom) was determined by log-rank Mantel–Cox tests against Vir group. For body weight, data are represented as mean ± SEM. Experiment was performed once (n=4 for X5050 (solid black), n=8 for DMSO (broken black), n=10 for S hIgG + DMSO (broken grey) and n=9 for S hIgG + X5050 (solid grey)). (FIG. 17E) Model figure demonstrating the induction of REST by sialylated IgG and associated repression of NF-κB mediated inflammatory responses.

[0067] FIGS. 18A-18D. Recombinant, sialylated Fc induces REST and protects against influenza disease. (FIG. 18A) Representative images showing REST induction in CD209+ human monocyte-derived macrophages stimulated with neutrally glycosylated ICs and either S Fc or S0 Fc. 40x magnification; 10-micron scale bar; REST (dark grey), cell outline via phalloidin staining (light grey), nuclear outline via Hoechst staining (white). Representative pooled data of N = 3 from 2 independent experiments. FIG. 18B) Quantified REST expression and nuclear localization of (FIG. 18A): median with 95% CI. Statistics by Mann-Whitney test: *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. Representative pooled data from 2 independent experiments (n=3). (FIG. 18C) FcγR humanized C57BL/6 mice received no treatment (Vir, solid grey), S0 Fc (broken black), or S Fc (solid black) on days 2, 4, and 6 post-lethal H1N1 challenge. (FIG. 18D) Weight (left) and survival (right) of mice in (FIG. 18B) were monitored daily. Statistical significance for weight loss (left) was

determined by two-way ANOVA with Bonferroni's correction. The body weight of sacrificed mice was defined as 85% for statistical analyses. Statistical significance for survival (right) was determined by log-rank Mantel–Cox tests against Vir group. The experiment was performed twice, and representative data are shown (n=5-10 mice per group).

[0068] FIGS. 19A-19D. Characterization of IgG glycosylation from influenza patients. (FIG. 19A) Schematic diagram of IgG1 Fc glycan. Left: Fc glycan present at N297 within the CH2 domain shown with all possible glycan modifications. Composition of the core Fc glycan (boxed) can be modified by addition of specific saccharide units (fucose [F], N-acetylglucosamine, galactose [G] and sialic acid [S]). Right: The various possible galactose and sialic acid residues that can be added to the core agalactosylated and fucosylated variant (G0F) of IgG1. (FIG. 19B) Anti-HA IgG were measured in bronchoalveolar lavage fluid (BALF), and sera collected from influenza patients (n=8). The median is plotted. (FIG. 19C) Level of anti-HA IgG1 Fc afucosylation (F0), bisection (N) and galactosylation (GS0) from influenza patients who developed symptoms requiring hospitalization (H) (n=10, open circles) or who maintained mild symptoms and were not hospitalized (NH) (n=16, solid grey circles). Median values are depicted with a solid black line and statistical significance were calculated using unpaired Student's test with Welch's correction. (FIG. 19D) Half-maximal neutralizing titers (pNT50) against a H1 pseudotyped virus (A/Hawaii/70/2019) in plasma of hospitalized and non-hospitalized influenza patients collected at acute and convalescent time points. p values were obtained using mixed effect analysis with Sidak's correction.

[0069] FIGS. 20A-20F. Characterization of enzymatically modified human IgG (hIgG). (FIG. 20A) Purified IgG pooled from thousands of donors (hIgG) was enzymatically treated to enhance sialylation by treatment with ST6Gal 1 (S hIgG) or was neuraminidase treated to remove existing sialic acids (S0 hIgG). The level of 2,6-sialic acid of the hIgG preparations was assessed by SNL lectin blot (left) and as loading control, the amount of protein loaded was shown with anti-human IgG antibody staining (right). (FIG. 20B) Age correlated negatively with sialic acid abundance on anti-HA IgG in healthy and influenza infection human cohorts. Pearson's correlation coefficient is shown. (FIG. 20C) Level of IgG1 sialylation of modified hIgG determined by mass spectroscopy. (FIG. 20D) Size exclusion chromatograms of unmodified, asialyated (S0) and sialylated (S) hIgG show overlap of all profiles. (FIG. 20E) Left panel: Neutralization curves of A/Netherlands/602/2009 H1N1 and A/X31 H3N2 viruses in MDCK cells with unmodified, S0 and S hIgG. Error bars indicate the range of technical replicates. Right panel: EC_{50} values

of unmodified, S0 and S hIgG against A/Netherlands/602/2009 H1N1 and A/X31 H3N2 viruses. (FIG. 20F) hIgG in BAL fluid collected 7 days post A/Netherlands/09 H1N1 infection from mice that received S or So hIgG or virus alone. Statistical analysis was performed by one-way ANOVA.

[0070] FIGS. 21A and 21B. Gating strategy for alveolar macrophages from whole lung and BAL fluid. (FIG. 21A) Bulk human myeloid cells were defined as viable CD45+ cells followed by downstream gating.Alveolar macrophage were defined as viable CD11b-CD11c+ Siglec-F+ MerTK+ leukocytes.Neutrophils were defined as viable Ly6G+ CD11b+ CD11c- CD3− B220− leukocytes. Monocytes were defined as viable CD11b+ CD11c-Ly6G− Ly6C+ CD3− B220− leukocytes. (FIG. 21B) Abundance (left), CD16 expression (middle) and CD209b expression (right) of populations in of various murine lung cells as determined by flow cytometry. Siglec-F+ MerTK+ CD11 blo alveolar macrophage (Amφ; dark), Siglec-F- MerTK- CD11 b+ interstitial macrophage (Imφ; light), Siglec-F- MerTK-Ly6G-Ly6C+ monocytes (mono; white), and CD24+ Ly6G- MHC-IIhi dendritic cells (DCs; black) were isolated from the whole lung of FcγR-humanized mice (n = 4). Statistics by one-way ANOVA with Dunnett's multiple comparisons test: **P<0.01, ***P<0.001, ****P<0.0001.

[0071] FIGS. 22A-22D. Transcriptomic analyses of alveolar macrophages (Amφ) from infected mouse. (FIG. 22A) Pathway enrichment analysis of differentially expressed genes (DEGs). The top 5 enriched upregulated (light) and downregulated (dark) Reactome pathways for DEGs between S hIgG versus S0 hIgG group (left) and between S hIgG versus Virus only group. P values were determined by GSEA. (FIG. 22B) Heatmap depicting the unsupervised clustering of common DEGs derived from S vs S0 and S vs Vir comparison. Each row depicts one DEG (in the order from top-down: Mapkapk2; Pi4k2a; Cited2; Rnf149; Fcgrt; Ext1; Btg3; Srsf9; Ube2m; Arf6; Hnrnpd; Whamm; Scn1b; Trp53i11; SdcJ; Ftl1; Nfkbib; Nupr1; Plekho1; B4galt5; Larp1; Basp1; Hras; Yrdc; Cdc34; Tent4a; Fbrsl1; Pou3f1; Chpt1; Rnf19b; Trim14; Mthfr; Ncoa7; Glrp1; Msrb2; Slc3a2; Apol9a; Smpdl3b; Tor3a; Lgals9; Il27; Tnf; Ccdc86; Batf2; Gch1; Ifi35; Usb1; Fbxw17; Cd69; Slc25a22; Junb; Parp12; Sertad1; Asns; Cyp2c69; Relb; Cdc42ep2; lcam1; Nfkbie; Slc2a6; Mcoln2; Bcl3; Adora2b; Fam20c; Akap11; Dkkl1; Cdk19; Pzp; Adamtsl4; Per2; Cytip; Kifap3; Pola1; Ift140; Pag1; Crot; Pdpr; Klhl24; Setx; Clasp2; Camk1d; lpo7; Arhgap5; Usp9x; Glce; Ablim1; Xpr1; Tnpo1; Dhx9; Siglecg; Zfp658; Slc2a3; Kcnj14; Slc6a16; Tead2; Dhdh; Itsn1) and each column depicts one mouse. The relative expression level of the DEGs. This list of DEGs is identified as the "sialylated hlgG gene signature" for subsequent analysis.

(n=3 for Vir, n=5 for S and S0 from one independent experiment). (FIG. 22C) Top 5 most up regulated pathways via pathway enrichment analysis on common DEGs from S vs S0 and S vs Vir comparison. P values were determined by GSEA. (FIG. 22D) Downregulated pathways under "Cytokine signaling in immune system" via pathway enrichment analysis on common DEGs from S vs S0 and S vs Vir comparison. P values were determined by GSEA.

[0072] FIGS. 23A and 23B. Gating strategy for alveolar macrophages from whole lung and BAL fluid. (FIG. 23A) Gating strategy of for alveolar macrophages for the sterile mouse model. (FIG. 23B) MerTK+ Amφ purity was >95% after magnetic separation as determined by flow cytometry.

[0073] FIGS. 24A-24F. Sialylated IgG elicits transcriptional changes in murine and human Amφ. (FIG. 24A) Differentially expressed genes (DEGs) expressed between mice (n =4) that received S immune complexes compared to S0 immune complexes, as determined by DESeq2. (FIG. 24B) Top five most down-regulated pathways by gene set enrichment analysis (GSEA) of murine Amφ transcripts. (FIG. 24C) Heatmap of DEGs related to the NF-κB signaling pathway in murine Amφ. (FIG. 24D) GSEA of NF-κB targets in murine alveolar macrophages. (FIG. 24E) Expression of selected NF-κB genes by human Amφ (n=5 donors). (FIG. 24F) GSEA of NF-κB targets in human alveolar macrophages.

[0074] FIGS. 25A-25G. CD209(b) is required for sialylated IgG-mediated induction of REST. (FIG. 25A) Inflammatory pathways enriched in murine Amφ receiving S immune complexes after CD209b blockade or S0 immune complexes compared to S immune complex treatment. NES by gene set enrichment analysis (GSEA). (FIG. 25B) Differentially expressed genes (DEGs) expressed by Amφ pretreated with CD209b blocking antibody compared to isotype control antibody. (FIG. 25C) GSEA revealed negative enrichment of REST/NRSF target genes with S immune complex administration after CD209b blockade compared to isotype control. (FIG. 25D) Frequency of CD209 positivity representative of polarization and knockdown efficiency in human MDMs was determined by flow cytometry. Cells were treated with Cd209-targeting siRNA (KD), non-targeting siRNA (NT), or unstained cells. Statistics by unpaired t-test: **P<0.01. (FIG. 25E) Inflammatory pathways enriched in $CD209^{KD}$ human MDM stimulated with neutrally glycosylated ICs and S Fc compared to $CD209^{WT}$ cells. NES by GSEA. (FIG. 25F) GSEA revealed negative enrichment of REST/NRSF target genes in $CD209^{KD}$ human MDM stimulated with neutrally glycosylated ICs and S Fc compared to $CD209^{WT}$ cells. (FIG. 25G) Quantified REST expression and nuclear localization of cells in (E): median with 95% CI. Statistics by Mann-Whitney test: *P<0.05, **P<0.01.

[0075] FIGS. 26A-26G. Sialylated IgG pre-treatment of human alveolar macrophage blunts NF-κB signaling and induces REST. Human alveolar macrophage (hAmφ) were cultured overnight with sialylated (S) or asialylated (S0) IgG prior to 4 hours of stimulation with afucosylated (F0) or S0 IgG immune complexes (n = 4-5). (FIG. 26A) DEGs in hAmφ stimulated with F0 IC after S0 pre-treatment compared to S0 stimulation after S0 pre-treatment, as determined by DESeq2. (FIG. 26B) GSEA revealed positive enrichment of TNFα signaling via NFκB pathway in hAmφ stimulated with F0 IC after S0 pre-treatment compared to S0 stimulation after S0 pre-treatment. (FIG. 26C) GSEA revealed negative enrichment of TNFα signaling via NFκB pathway in hAmφ stimulated with F0 IC after S pre-treatment compared to S0 pre-treatment. (FIG. 26D) DEGs in hAmφ stimulated with F0 IC after S pre-treatment compared to S0 pre-treatment, as determined by DESeq2. (FIG. 26E) Inflammatory pathways enriched in hAmφ stimulated with F0 IC after S pre-treatment compared to S0 pre-treatment, as determined by GSEA. (FIG. 26F) DEGs in hAmφ stimulated with F0 IC after S pre-treatment compared to S0 stimulation after S0 pre-treatment, as determined by DESeq2. (FIG. 26G) Quantified REST expression and nuclear localization of hAmφ following pre-treatment and stimulation: median with 95% CI. Statistics by Mann-Whitney test: *P<0.05.

[0076] FIG. 27. REST-binding RE-1 motifs within NF-KB-related and subunit genes. JASPAR sequence motif MA0138.2 was run against the hg19 human genome using the University of California at Santa Cruz (UCSC) Genome Browser. The table shown includes an inexhaustive collation of REST binding sites within and around the indicated gene as determined by JASPAR. *Grin1* is a known REST target gene and, as such, is included for statistical reference. Consensus nucleotides are depicted in bold, dark grey if consistent with the more conserved positions within the RE-1 motif. SEQ ID NOS:5-15.

5. DETAILED DESCRIPTION

5.1 Agents

[0077] In one aspect, provided herein are agents that may be used to treat and/or prevent respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*, a human subject), improve lung function or preserve lung function in a subject (*e.g.*, a human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*, a human subject), and/or reduce inflammation that associated with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*,

human subject). In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) has one or more (*e.g.*, 2, 3, 4, or more, or all) of the properties/characteristics of an agent described in Example 1 and/or Example 2, *infra*. In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) induces transcriptional factor REST/NRSF. In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) induces REST/NRSF expression in cells, such as, *e.g.*, monocytes and/or macrophages (*e.g.*, alveolar macrophages). In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) induces REST/NRSF nuclear expression in cells, such as, *e.g.*, monocytes and/or macrophages (*e.g.*, alveolar macrophages). In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) induces one or more differentially expressed genes correlated with transcription factor REST/NFSF. In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) suppresses the expression of one or more genes induced by the respiratory virus that are involved in the inflammatory response. In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) represses a virally-induced signaling pathway that triggers inflammation in a subject (*e.g.*, a human subject), such as, e.g., the NF-KB pathway. In some embodiments, an agent provided herein induces transcriptional factor REST/NRSF and suppresses virally-induced NF-KB signaling. In some embodiments, an agent provided herein (*e.g.*, one disclosed in Example 1 or Example 2) does not prevent the respiratory virus from binding to its host cell receptor in an in vitro assay (*e.g.*, an immunoassay, such as an ELISA). In some embodiments, the agent comprises one disclosed herein (*e.g.*, in Example 1 or Example 2). In some embodiments, the agent comprises sialylated intravenous immunoglobulin (IVIg). In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises sialylated IgG Fc region. In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises hypersialylated IgG Fc region. In some embodiments, the agent comprises one disclosed in Example 1 or Example 2, *infra*.

[0078] In some embodiments, provided herein is sialylated intravenous immunoglobulin (IVIg). In some embodiments, sialylated IVIg is produced by a technique to one of skill in the art. For example, techniques known in the art may be used to obtain IVIg from pooled plasma samples from subjects (*e.g.*, human subjects) and IVIg may be enriched for sialylated IgG using techniques known to one of skill in the art, such as, *e.g.*, *Sambucus nigra* agglutinin (SNA) lectin fractionation. Alternatively, the IVIg may be purchased (*e.g.*, from

Gammagard) and enriched for sialylated IgG using techniques known in the art. In specific embodiments, the sialylated IVIg is clinical-grade. In specific embodiments, the IVIg is enriched for sialylated IgG that contains α2,6-linked sialic acids.

[0079] In some embodiments, the sialylated IVIg contains about 12% to about 20% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IVIg contains about 12% to about 15% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IVIg contains about 12%, about 13%, about 14%, or about 15% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IVIg contains about 16%, about 17%, about 18%, about 19%, or about 20% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IVIg contains about 12% to about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IVIg contains about 12% to about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. For example, mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[0080] In some embodiments, the sialylated IVIg comprises α2,6-linked sialic acids. In some embodiments, the sialylated IVIg comprises α2,3-linked sialic acids. In some embodiments, the sialylated IVIg comprises α2,6-linked sialic acids and α2,3-linked sialic acids.

[0081] In some embodiments, the sialylated IVIg contains about 12%, about 13%, about 14%, or about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IVIg contains about 16%, about 17%, about 18%, about 19%, or about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. For example, mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[0082] In some embodiments, the sialylated IVIg binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the sialylated IVIg activates DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the sialylated IVIg induces DC-SIGN (CD209) signaling or signaling of a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the sialylated IVIg induces

and/or represses transcription of one or more genes dependent on DC-SIGN or a non-human homologue (*e.g.*, murine Cd209b). Techniques known to one of skill in the art may be used to assess the binding of sialylated IVIg binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b).

[0083] In some embodiments, the sialylated IVIg includes an antibody that binds to a respiratory virus antigen. In some embodiments, the sialylated IVIg includes two or more antibodies that bind to a respiratory virus antigen. In some embodiments, the sialylated IVIg includes an antibody that binds to an envelope protein or glycoprotein of a respiratory virus. For example, if the respiratory virus is an influenza virus (e.g., influenza A virus), the sialylated IVIg may contain an antibody that binds to influenza virus hemagglutinin (*e.g.*, H1 or H3). In another example, if the respiratory virus is SARS-CoV-1 or SARS-CoV-2, the sialylated IVIg may contain an antibody that binds to the spike protein of the virus. In some embodiments, the sialylated IVIg includes two or antibodies that bind to an envelope protein or glycoprotein of a respiratory virus. In some embodiments, the sialylated IVIg does not include a detectable antibody that binds to a respiratory virus antigen. In some embodiments, the sialylated IVIg does not include a detectable antibody that binds to an envelope protein or glycoprotein of a respiratory virus. Detection of an antibody may be assessed by techniques known in the art, such as, *e.g.*, ELISA or Western Blot.

[0084] In specific embodiments, the sialylated IVIg is obtained or derived from a human subject. In some embodiments, the sialylated IVIg is obtained or derived from a non-human subject capable of producing human IgG. In some embodiments, the sialylated IVIg is obtained or derived from a non-human subject.

[0085] In some embodiments, provided herein is hypersialyalated intravenous immunoglobulin (IVIg). In some embodiments, the hypersialylated IVIg has one or more (*e.g.*, 2, 3, 4, or more, or all) of the properties/characteristics of the hypersialylated IVIg described in Example 1 and/or Example 2, *infra*.

[0086] In some embodiments, hypersialylated IVIg is produced by a technique described herein (*see, e.g.*, Example 1 or Example 2) or known to one of skill in the art. For example, IVIg may be incubated with a sialyltransferase (*e.g.*, human ST6 beta-galactoside alpha-2,6-sialyltransferase 1 (ST6GAL1) or human ST3 beta-galactoside alpha-2,3-sialyltransferase 3 (STGAL3)) in the presence of CMP-sialic acid for a period of time, such as, *e.g.*, 48 hours at 37° C.

[0087] In some embodiments, hypersialylated IgG is produced by a method comprising: (a) incubating pooled IgG antibodies in a reaction mixture comprising b1,4-

Galactosyltransferase (B4GalT) or an enzymatically active portion thereof, UDP-Gal or salt thereof, Bis (2-hydroxyethyl) aminotris (hydroxymethyl)methane (BIS-TRIS) buffer, and $MnCl_2$, thereby producing galactosylated IgG antibodies; and (b) incubating the galactosylated IgG antibodies in a reaction mixture comprising ST6Gal or enzymatically active portion thereof, CMP -NANA or salt thereof, Bis (2-hydroxyethyl) aminotris (hydroxymethyl)methane (BIS-TRIS) buffer, and $MnCl_2$, In some embodiments, hypersialylated IgG is produced by a method comprising incubating pooled IgG antibodies in a reaction mixture comprising b1,4-Galactosyltransferase (B4GalT) or an enzymatically active portion thereof, UDP-Gal or salt thereof, ST6Gal or an enzymatically active portion thereof, CMP -NANA or salt thereof, Bis (2-hydroxyethyl) aminotris (hydroxymethyl)methane (BIS-TRIS) buffer, and $MnCl_2$ In some embodiments, hypersialylated IgG is produced by a method described in U.S. patent application publication No. 2023/0192814, which is incorporated by reference herein. In some embodiments, hypersialylated IgG is produced by a method described in U.S. patent application publication No. 2023/0193339, which is incorporated by reference herein.

[0088] In some embodiments, the hypersialylated IVIg contains about 21% to about 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 21% to about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 21%, about 22%, about 23%, about 24%, or about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 26%, about 27%, about 28%, about 29%, or about 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 21% to about 26% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 27% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialyated IVIg contains the percentage of Fc sialylation described in Example 1 or 2, as measured by a technique described herein or known to one of skill in the art.

[0089] In some embodiments, the hypersialylated IVIg contains about 25% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 30% to about 50% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In

some embodiments, the hypersialylated IVIg contains about 50% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 75% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 80% to about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 40%, about 45%, about 50%, about 55%, or about 60% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 70%, about 75%, or about 80% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 80%, about 85%, about 90%, about 95%, or about 98% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 85% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[0090] In some embodiments, the hypersialylated IVIg contains at least 21%, at least 22%, at least 23%, at least 24%, or at least 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least 26%, at least 27%, at least 28%, at least 29%, or at least 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least 35%, at least 40%, at least 50%, at least 55%, or at least 60 % Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least 65%, at least 70%, at least 75%, or at least 80% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least 85%, at least 90%, or at least 95% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[0091] In some embodiments, the hypersialylated IVIg contains about 30% to about 60% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 50% to about 75% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 30%, about 35%, about 40%, or about 45% sialylation as measured by a technique described herein or known to one of skill in the

art. In some embodiments, the hypersialylated IVIg contains about 50%, about 55%, about 60%, about 65%, or about 70% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 75% to about 90% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 75% to about 99% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 75%, about 80%, about 85%, about 90%, or about 95% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 96%, about 97%, about 98%, or about 99% sialylation as measured by a technique described herein or known to one of skill in the art.

[0092] In some embodiments, the hypersialylated IVIg contains at least about 15%, at least about 20% or at least about 25% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 30%, at least about 40%, at least about 50%, or at least about 60% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 70%, at least about 80%, at least about 90%, or at least about 90% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 96%, at least about 97%, at least about 98%, or at least about 99% sialylation as measured by a technique described herein or known to one of skill in the art.

[0093] In some embodiments, the hypersialylated IVIg comprises α2,6-linked sialic acids. In some embodiments, the hypersialylated IVIg comprises α2,3-linked sialic acids. In some embodiments, the hypersialylated IVIg comprises α2,6-linked sialic acids and α2,3-linked sialic acids.

[0094] In some embodiments, the hypersialylated IVIg contains about 21% to about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 21% to about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 21%, about 22%, about 23%, about 24%, or about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 26%, about 27%, about 28%, about 29%, or about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of

skill in the art. For example, mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[0095] In some embodiments, the hypersialylated IVIg contains about 21% to about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 30% to about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg c contains about 50% to about 75% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 27% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 30%, about 35%, about 40%, or about 45% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 50%, about 55%, about 60%, about 65%, or about 70% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 75% to about 90% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 75% to about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 75%, about 80%, about 85%, about 90%, or about 95% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains about 96%, about 97%, about 98%, or about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[0096] In some embodiments, the hypersialylated IVIg contains at least about 15%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, or at least about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, or at least about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 65%, at least about 70%, at

least about 80%, at least 85%, at least about 90%, or at least about 90% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 85% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IVIg contains at least about 96%, at least about 97%, at least about 98%, or at least about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[0097] In some embodiments, the hypersialylated IVIg binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the hypersialylated IVIg activates DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the hypersialylated IVIg induces DC-SIGN (CD209) signaling or signaling of a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the hypersialylated IVIg induces and/or represses transcription of one or more genes dependent on DC-SIGN or a non-human homologue (*e.g.*, murine Cd209b). Techniques known to one of skill in the art may be used to assess the binding of hypersialylated IVIg binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b).

[0098] In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of DC-SIGN (CD209) or a non-human homologue (e.g., murine Cd209b) in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is at the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess an upregulation of expression of DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b).

[0099] In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess an upregulation of expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG.

[00100] In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIG. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00101] In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00102] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of

one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the hypersialylated IVIg to the same type of subject (*e.g.*, a human subject or non-human subject) prior to infection with the same respiratory virus does not result in upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00103] In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg after infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00104] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the hypersialylated IVIg to the same type of subject (*e.g.*, a human subject or non-human subject)

after infection with the same respiratory virus does not result in upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00105] In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the subject relative to the gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the same type of subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in upregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be upregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be downregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00106] In some embodiments, culturing macrophages (*e.g.*, human macrophages) *in vitro*, such as described in Example 1 or Example 2, with the hypersialylated IVIg upregulates the

expression of one or more (*e.g.*, 2, 3, 4, or more, or all) of the M2 macrophage differentially expressed genes in Table 2. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of the one or more differentially expressed genes in Table 2.

[00107] In some embodiments, administration of hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of one or more transcripts of NF-KB-associated genes (*e.g.*, Relb, Junb, Nfkbie and Tnf) in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same one or more gene transcripts in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, administration of hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the administration of hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in transcriptional signature similar to that shown in FIG. 15A and/or FIG. 22A.

[00108] In some embodiments, administration of hypersialylated IVIg, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b) in alveolar macrophages. In some embodiments, administration of hypersialylated IVIg, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more neutrophil chemoattractants (*e.g.*,

Ccl3 and Ccl4) in alveolar macrophages. In some embodiments, administration of hypersialylated IVIg, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of hypersialylated IVIg, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b), one or more neutrophil chemoattractants (*e.g.*, Ccl3 and Ccl4), and one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of hypersialylated IVIg, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more of those identified in FIG. 24A.

[00109] In some embodiments, contacting alveolar macrophages with hypersialylated IVIg prior to stimulation with an inflammatory activator blocks NF-KB signaling. *See* Example 2. In some embodiments, contacting alveolar macrophages or THP-1 cells differentiated and polarized toward CD209+ macrophages with hypersialylated IVIg prior to stimulation with an inflammatory activator (*e.g.*, lipopolysaccharide (LPS) or TNFα) induces REST. *See* Example 2.

[00110] In some embodiments, administration of hypersialylated IVIg to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in the induction of REST, such as, *e.g.*, described in the Examples (*e.g.*, Example 2), a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection). *See* Example 2. In some embodiments, the induction of REST, such as, *e.g.*, described in the Examples (*e.g.*, Example 2), by the hypersialylated IVIg is necessary for the effectiveness of the hypersialyated IVIg in a subject (*e.g.*, a human or non-human subject) infected with a respiratory virus (*e.g.*, an influenza virus). *See* Example 2.

[00111] In some embodiments, the hypersialylated IVIg includes an antibody that binds to a respiratory virus antigen. In some embodiments, the hypersialylated IVIg includes two or more antibodies that bind to a respiratory virus antigen. In some embodiments, the hypersialylated IVIg includes an antibody that binds to an envelope protein or glycoprotein of a respiratory virus. For example, if the respiratory virus is an influenza virus (*e.g.*, influenza A virus), the hypersialylated IVIg may contain an antibody that binds to influenza virus hemagglutinin (*e.g.*, H1 or H3). In another example, if the respiratory virus is SARS-CoV-1

or SARS-CoV-2, the hypersialylated IVIg may contain an antibody that binds to the spike protein of the virus. In some embodiments, the hypersialylated IVIg includes two or antibodies that bind to an envelope protein or glycoprotein of a respiratory virus. In some embodiments, the hypersialylated IVIg does not include a detectable antibody that binds to a respiratory virus antigen. In some embodiments, the hypersialylated IVIg does not include a detectable antibody that binds to an envelope protein or glycoprotein of a respiratory virus. Detection of an antibody may be assessed by techniques known in the art, such as, *e.g.*, ELISA or Western Blot.

[00112] In specific embodiments, the hypersialylated IVIg is obtained or derived from a human subject. In some embodiments, the hypersialylated IVIg is obtained or derived from a non-human subject capable of producing human IgG. In some embodiments, the hypersialylated IVIg is obtained or derived from a non-human subject. In some embodiments, the hypersialylated IVIg is produced as described in Example 1.

[00113] In some embodiments, provided herein is sialyalated IgG Fc region. In some embodiments, sialyalated IgG Fc region is produced using techniques described herein or known to one of skill in the art. For example, an IgG Fc region may be produced from IVIg using an enzyme such as, *e.g.*, papain, or recombinantly produced. In some embodiments, an IgG Fc region is enriched for sialylation using techniques known to one of skill in the art, such as, *e.g.*, *Sambucus nigra* agglutinin (SNA) lectin fractionation.

[00114] In some embodiments, the sialylated IgG Fc region contains about 12% to about 20% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IgG Fc region contains about 12% to about 15% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IgG Fc region contains about 12%, about 13%, about 14%, or about 15% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IgG Fc region contains about 16%, about 17%, about 18%, about 19%, or about 20% sialylation as measured by a technique described herein or known to one of skill in the art. For example, mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[00115] In some embodiments, the sialylated IgG Fc region comprises α2,6-linked sialic acids. In some embodiments, the sialylated IgG Fc region comprises α2,3-linked sialic acids. In some embodiments, the sialylated IgG Fc region comprises α2,6-linked sialic acids and α2,3-linked sialic acids.

[00116] In some embodiments, the sialylated IgG Fc region comprises α2,6-linked sialic acids. In some embodiments, the sialylated IgG Fc region contains about 12% to about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IgG Fc region contains about 12% to about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IgG Fc contains about 12%, about 13%, about 14%, or about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the sialylated IgG Fc region contains about 16%, about 17%, about 18%, about 19%, or about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. For example, mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[00117] In some embodiments, the sialylated IgG Fc region is an IgG1 Fc region. In some embodiments, the sialylated IgG Fc region comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the sialylated IgG Fc region comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the sialylated IgG Fc region comprises an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the sialylated IgG Fc region comprises the amino acid sequence of SEQ ID NO:1.

[00118] In some embodiments, the sialylated IgG Fc region is obtained or derived from a human subject. In some embodiments, the sialylated IgG Fc region is obtained or derived from a non-human subject capable of producing human IgG. In some embodiments, the sialylated IgG Fc region is obtained or derived from a non-human subject.

[00119] In some embodiments, provided herein is hypersialylated IgG Fc region. In some embodiments, the hypersialylated IgG Fc region has one or more (e.g., 2, 3, 4, or more, or all) of the properties/characteristics of hypersialylated IVIg and/or sFc described in Example 1 and/or Example 2, *infra*.

[00120] In some embodiments, hypersialylated IgG Fc region is produced using techniques known or described herein. For example, an IgG Fc region may be produced from IVIg using an enzyme such as, *e.g.*, papain, or recombinantly produced and the IgG Fc region may be incubated with a sialyltransferase (*e.g.*, human ST6 beta-galactoside alpha-2,6-

sialyltransferase 1 (ST6GAL1) or human ST3 beta-galactoside alpha-2,3-sialyltransferase 3 (STGAL3)) in the presence of CMP-sialic acid for a period of time, such as, *e.g.*, 48 hours at 37° C. In some embodiments, the hypersialylated IgG Fc region is an IgG1 Fc region.

[00121] In some embodiments, the hypersialylated IgG Fc region contains about 21% to about 30% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 21% to about 25% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 21%, about 22%, about 23%, about 24%, or about 25% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 26%, about 27%, about 28%, about 29%, or about 30% sialylation as measured by a technique described herein or known to one of skill in the art. For example, mass spectrometry, lumniex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[00122] In some embodiments, the hypersialylated IgG Fc region contains about 30% to about 60% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 50% to about 75% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 30%, about 35%, about 40%, or about 45% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 50%, about 55%, about 60%, about 65%, or about 70% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 75% to about 90% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 75% to about 99% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 75%, about 80%, about 85%, about 90%, or about 95% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 96%, about 97%, about 98%, or about 99% sialylation as measured by a technique described herein or known to one of skill in the art.

[00123] In some embodiments, the hypersialylated IgG Fc contains at least about 15%, at least about 20% or at least about 25% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 30%, at least about 40%, at least about 50%, or at least about 60% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 70%, at least about 80%, at least about 90%, or at least about 90% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 96%, at least about 97%, at least about 98%, or at least about 99% sialylation as measured by a technique described herein or known to one of skill in the art.

[00124] In some embodiments, the hypersialylated IgG Fc contains about 21% to about 26% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 27% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialyated IgG Fc contains the percentage of sialylation described in Example 1 or 2, as measured by a technique described herein or known to one of skill in the art.

[00125] In some embodiments, the hypersialylated IgG Fc contains about 25% to about 90% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 30% to about 50% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 50% to about 90% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 75% to about 90% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 80% to about 99% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 40%, about 45%, about 50%, about 55%, or about 60% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 70%, about 75%, or about 80% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 80%, about 85%, about 90%, about 95%, or about 98% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the

hypersialylated IgG Fc contains about 85% sialylation as measured by a technique described herein or known to one of skill in the art.

[00126] In some embodiments, the hypersialylated IgG Fc contains at least 21%, at least 22%, at least 23%, at least 24%, or at least 25% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least 26%, at least 27%, at least 28%, at least 29%, or at least 30% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least 35%, at least 40%, at least 50%, at least 55%, or at least 60 % sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least 65%, at least 70%, at least 75%, or at least 80% sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least 85%, at least 90%, or at least 95% sialylation as measured by a technique described herein or known to one of skill in the art.

[00127] In some embodiments, the hypersialylated IgG Fc region comprises α2,6-linked sialic acids. In some embodiments, the hypersialylated IgG Fc region comprises α2,3-linked sialic acids. In some embodiments, the hypersialylated IgG Fc region comprises α2,6-linked sialic acids and α2,3-linked sialic acids.

[00128] In some embodiments, the hypersialylated IgG Fc region contains about 21% to about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 21% to about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 21%, about 22%, about 23%, about 24%, or about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc region contains about 26%, about 27%, about 28%, about 29%, or about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. Mass spectrometry, lumniex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may, *e.g.*, be used to measure sialylation.

[00129] In some embodiments, the hypersialylated IgG Fc contains about 30% to about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 50% to about 75% alpha 2,6-linked sialic acids as measured by a technique described herein or

known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 30%, about 35%, about 40%, or about 45% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 50%, about 55%, about 60%, about 65%, or about 70% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 75% to about 90% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 75% to about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 75%, about 80%, about 85%, about 90%, or about 95% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains about 96%, about 97%, about 98%, or about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[00130] In some embodiments, the hypersialylated IgG Fc contains at least about 15%, at least about 20%, or at least about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 21%, at least about 22%, at least about 22%, at least about 23%, or at least about 24% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 30% at least about 40%, at least about 50%, or at least about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 27%, at least about 28%, at least about 29%, at least about 30%, or at least about 35% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55%, or at least about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the hypersialylated IgG Fc contains at least about 96%, at least about 97%, at

least about 98%, or at least about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[00131] In some embodiments, the hypersialylated IgG Fc region binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the hypersialylated IgG Fc region activates DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the hypersialylated IgG Fc region induces DC-SIGN (CD209) signaling or signaling of a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the hypersialylated IgG Fc induces and/or represses transcription of one or more genes dependent on DC-SIGN or a non-human homologue (*e.g.*, murine Cd209b). Techniques known to one of skill in the art may be used to assess the binding of the hypersialylated IgG Fc region binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b).

[00132] In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of DC-SIGN (CD209) or a non-human homologue (e.g., murine Cd209b) in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is at the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess an upregulation of expression of DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b).

[00133] In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG.

[00134] In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb*

and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00135] In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (e.g., 1, 2, 3, 4, or more days post-infection) relative to the upregulation of the same one or more gene transcripts in the same type of subject (e.g., a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00136] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the hypersialylated IgG Fc region to the same type of subject (*e.g.*, a human subject or non-human subject) prior to infection with the same respiratory virus does not result in

upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1) may be used to assess the level of one or more gene transcripts.

[00137] In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg after infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00138] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the hypersialylated IgG Fc region to the same type of subject (*e.g.*, a human subject or non-human subject) after infection with the same respiratory virus does not result in upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included

two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00139] In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the subject relative to the gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the same type of subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in upregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be upregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the hypersialylated IgG Fc region to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be downregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00140] In some embodiments, administration of hypersialylated IgG Fc to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of one or more transcripts of NF-KB-associated genes (*e.g.*, Relb, Junb, Nfkbie and Tnf) in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same one or more gene transcripts in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human

subject or non-human subject) administered asialylated IgG Fc prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, administration of hypersialylated IgG Fc to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IgG Fc prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the administration of hypersialylated IgG Fc to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in transcriptional signature similar to that shown in FIG. 15A and/or FIG. 22A.

[00141] In some embodiments, administration of hypersialylated IgG Fc, relative to asialylated IgG Fc, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b) in alveolar macrophages. In some embodiments, administration of hypersialylated IgG Fc, relative to asialylated IgG Fc, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more neutrophil chemoattractants (*e.g.*, Ccl3 and Ccl4) in alveolar macrophages. In some embodiments, administration of hypersialylated IgG Fc, relative to asialylated IgG Fc, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of hypersialylated IgG Fc, relative to asialylated IgG Fc, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b), one or more neutrophil chemoattractants (*e.g.*, Ccl3 and Ccl4), and one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of hypersialylated IgG Fc, relative to asialylated IgG Fc, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more of those identified in FIG. 24A.

[00142] In some embodiments, contacting alveolar macrophages with hypersialylated IgG Fc prior to stimulation with an inflammatory activator blocks NF-KB signaling. *See* Example 2. In some embodiments, contacting alveolar macrophages or THP-1 cells differentiated and polarized toward CD209+ macrophages with hypersialylated IgG Fc prior to stimulation with an inflammatory activator (*e.g.*, lipopolysaccharide (LPS) or TNFα) induces REST. *See* Example 2.

[00143] In some embodiments, administration of hypersialylated IgG Fc to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in the induction of REST, such as, *e.g.*, described in the Examples (*e.g.*, Example 2), a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection). *See* Example 2. In some embodiments, administration of hypersialylated IgG Fc to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in the induction of REST, such as, *e.g.*, described in the Examples (*e.g.*, Example 2), a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection). In some embodiments, the induction of REST by the hypersialylated IgG Fc is necessary for the effectiveness of the hypersialyated IgG Fc in a subject (*e.g.*, a human or non-human subject) infected with a respiratory virus (*e.g.*, an influenza virus). *See* Example 2.

[00144] In some embodiments, culturing macrophages (*e.g.*, human macrophages) *in vitro* as described in Example 1 or Example 2 with the hypersialylated IgG Fc region upregulates the expression of one or more (*e.g.*, 2, 3, 4, or more, or all) of the M2 macrophage differentially expressed genes in Table 2. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of the one or more differentially expressed genes in Table 2.

[00145] In some embodiments, the hypersialylated IgG Fc region comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the hypersialylated IgG Fc region comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the hypersialylated IgG Fc region comprises an amino acid sequence that is at least 98% or at least 99% identical to

the amino acid sequence of SEQ ID NO:1. In some embodiments, the hypersialylated IgG Fc region comprises the amino acid sequence of SEQ ID NO:1.

[00146] In some embodiments, the hypersialylated IgG Fc region is obtained or derived from a human subject. In some embodiments, the hypersialylated IgG Fc region is obtained or derived from a non-human subject capable of producing human IgG. In some embodiments, the hypersialylated IgG Fc region is obtained or derived from a non-human subject.

[00147] In some embodiments, provided herein is an IgG Fc region-containing protein comprising a sialylated IgG Fc region. In some embodiments, the IgG Fc region-containing protein binds to a respiratory virus antigen. In some embodiments, the IgG Fc region-containing protein binds to an envelope protein or glycoprotein of a respiratory virus. For example, if the respiratory virus is an influenza virus (*e.g.*, influenza A virus), the IgG Fc region-containing protein may bind to an influenza virus hemagglutinin (*e.g.*, H1 or H3). In another example, if the respiratory virus is SARS-CoV-1 or SARS-CoV-2, the IgG Fc region-containing protein may bind to the spike protein of the virus. In some embodiments, the IgG Fc region-containing protein binds to two or more respiratory virus antigens.

[00148] In some embodiments, provided herein is an IgG Fc region-containing protein comprising a sialylated IgG Fc region. In some embodiments, the IgG Fc region-containing protein comprises more than one sialyalated IgG Fc region. For example, in some embodiments, the IgG Fc region-containing protein comprises two or more sialyalated IgG Fc regions. In some embodiments, the IgG Fc region-containing protein comprises three or more sialyalated IgG Fc regions. In some embodiments, the IgG Fc region-containing protein comprises multiple sialyalated IgG Fc regions. In some embodiments, the sialylated IgG Fc region comprises an IgG1 Fc region (*e.g.*, a human IgG Fc region). In some embodiments, the sialylated IgG Fc region consists of an IgG1 Fc region (*e.g.*, a human IgG Fc region).

[00149] In some embodiments, provided herein is an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region. In some embodiments, the IgG Fc region-containing protein comprises more than one hypersialyalated IgG Fc region. For example, in some embodiments, the IgG Fc region-containing protein comprises two or more hypersialyalated IgG Fc regions. In some embodiments, the IgG Fc region-containing protein comprises three or more hypersialyalated IgG Fc regions. In some embodiments, the IgG Fc region-containing protein comprises multiple hypersialyalated IgG Fc regions. In some embodiments, the hypersialylated IgG Fc region comprises an IgG1 Fc region (*e.g.*, a human

IgG Fc region). In some embodiments, the hypersialylated IgG Fc region consists of an IgG1 Fc region (*e.g.*, a human IgG Fc region).

[00150] In some embodiments, the IgG Fc-region-containing proteins has one or more (e.g., 2, 3, 4, or more, or all) of the properties/characteristics of hypersialylated IVIg and/or sFc described in Example 1 and/or Example 2, *infra*.

[00151] In some embodiments, the IgG Fc region-containing protein binds to a respiratory virus antigen. In some embodiments, the IgG Fc region-containing protein binds to an envelope protein or glycoprotein of a respiratory virus. For example, if the respiratory virus is an influenza virus (*e.g.*, influenza A virus), the IgG Fc region-containing protein may bind to an influenza virus hemagglutinin (*e.g.*, H1 or H3). In another example, if the respiratory virus is SARS-CoV-1 or SARS-CoV-2, the antibody may bind to the spike protein of the virus. In some embodiments, the IgG Fc region-containing protein binds to two or more respiratory virus antigens.

[00152] In some embodiments, the IgG Fc region-containing protein comprises an antibody or antigen-binding fragment thereof. In some embodiments, the IgG Fc region-containing protein consists of an antibody or antigen-binding fragment thereof. In some embodiments, the antibody binds to a respiratory virus antigen. In some embodiments, the antibody binds to an envelope protein or glycoprotein of a respiratory virus. For example, if the respiratory virus is an influenza virus (*e.g.*, influenza A virus), the antibody may bind to an influenza virus hemagglutinin (*e.g.*, H1 or H3). In another example, if the respiratory virus is SARS-CoV-1 or SARS-CoV-2, the antibody may bind to the spike protein of the virus. In some embodiments, the antibody binds to two or more respiratory virus antigens. In some embodiments, IgG Fc region-containing protein is not an antibody or antibody or antigen-binding fragment thereof that binds to a respiratory virus antigen.

[00153] In some embodiments, the IgG Fc region-containing protein contains about 12% to about 20% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12% to about 15% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12%, about 13%, about 14%, or about 15% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 16%, about 17%, about 18%, about 19%, or about 20% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to

about 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21%, about 22%, about 23%, about 24%, or about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 26%, about 27%, about 28%, about 29%, or about 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[00154] In some embodiments, the IgG Fc region-containing protein contains about 30% to about 60% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50% to about 75% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 30%, about 35%, about 40%, or about 45% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50%, about 55%, about 60%, about 65%, or about 70% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75%, about 80%, about 85%, about 90%, or about 95% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 96%, about 97%, about 98%, or about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[00155] In some embodiments, the IgG Fc region-containing protein contains at least about 15%, at least about 20% or at least about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 30%, at least about 40%, at least about 50%, or at least about 60% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 70%, at least about 80%, at least about 90%, or at least about 90% Fc

sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 96%, at least about 97%, at least about 98%, or at least about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[00156] In some embodiments, the IgG Fc region-containing protein comprises α2,6-linked sialic acids. In some embodiments, the IgG Fc region-containing protein comprises α2,3-linked sialic acids. In some embodiments, the IgG Fc region-containing protein comprises α2,6-linked sialic acids and α2,3-linked sialic acids.

[00157] In some embodiments, the IgG Fc region-containing protein contains about 12% to about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12% to about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12%, about 13%, about 14%, or about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 16%, about 17%, about 18%, about 19%, or about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21%, about 22%, about 23%, about 24%, or about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 26%, about 27%, about 28%, about 29%, or about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. Mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may, *e.g.*, be used to measure sialylation.

[00158] In some embodiments, the IgG Fc region-containing protein contains about 30% to about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50% to about 75% alpha 2,6-linked sialic acids as measured by a technique

described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 30%, about 35%, about 40%, or about 45% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50%, about 55%, about 60%, about 65%, or about 70% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 90% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75%, about 80%, about 85%, about 90%, or about 95% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 96%, about 97%, about 98%, or about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[00159] In some embodiments, the IgG Fc region-containing protein contains at least about 15%, at least about 20% or at least about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least 55%, or at least about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least 65%, at least about 70%, at least 75%, at least about 80%, at least 85%, at least about 90%, or at least about 90% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 96%, at least about 97%, at least about 98%, or at least about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[00160] In some embodiments, the IgG Fc region-containing protein binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the IgG Fc region-containing protein activates DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the IgG Fc region-containing protein induces DC-SIGN (CD209) signaling or signaling of a non-human homologue (*e.g.*, murine Cd209b). In

some embodiments, the IgG Fc region-containing protein induces and/or represses transcription of one or more genes dependent on DC-SIGN or a non-human homologue (*e.g.*, murine Cd209b).

[00161] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of DC-SIGN (CD209) or a non-human homologue (e.g., murine Cd209b) in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is at the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b).

[00162] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG.

[00163] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques

known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00164] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (e.g., 1, 2, 3, 4, or more days post-infection) relative the upregulation of the same one or more gene transcripts in the same type of subject (e.g., a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00165] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the IgG Fc region-containing protein to the same type of subject (*e.g.*, a human subject or non-human subject) prior to infection with the same respiratory virus does not result in upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00166] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg after infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00167] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the IgG Fc region-containing protein to the same type of subject (*e.g.*, a human subject or non-human subject) after infection with the same respiratory virus does not result in upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00168] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the

subject relative to the gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the same type of subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in upregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be upregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be downregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00169] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of one or more transcripts of NF-KB-associated genes (*e.g.*, Relb, Junb, Nfkbie and Tnf) in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same one or more gene transcripts in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human subject or non-human subject) administered the same type of IgG Fc region-containing protein but comprising asialylated IgG Fc region, or asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar

macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human subject or non-human subject) administered the same type of IgG Fc region-containing protein but comprising asialylated IgG Fc region, or asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in transcriptional signature similar to that shown in FIG. 15A and/or FIG. 22A.

[00170] In some embodiments, administration of the IgG Fc region-containing protein, relative to administration of the same type of IgG Fc region-containing protein but comprising an asialylated IgG Fc region, or asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b) in alveolar macrophages. In some embodiments, administration of the IgG Fc region-containing protein, relative to administration of the same type of IgG Fc region-containing protein but comprising an asialylated IgG Fc region, or asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more neutrophil chemoattractants (*e.g.*, Ccl3 and Ccl4) in alveolar macrophages. In some embodiments, administration of the IgG Fc region-containing protein, relative to administration of the same type of IgG Fc region-containing protein but comprising an asialylated IgG Fc region, or asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of the IgG Fc region-containing protein, relative to administration of the same type of IgG Fc region-containing protein but comprising an asialylated IgG Fc region, or asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b), one or more neutrophil chemoattractants (*e.g.*, Ccl3 and Ccl4), and one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of the IgG Fc region-containing protein, relative to administration of the same type of IgG Fc region-containing protein but comprising an asialylated IgG Fc region, or asialylated IVIg, to a subject (*e.g.*, a human

subject or non-human subject) suppresses expression of transcripts coding for one or more of those identified in FIG. 24A.

[00171] In some embodiments, contacting alveolar macrophages with the IgG Fc region-containing protein prior to stimulation with an inflammatory activator blocks NF-KB signaling. *See* Example 2. In some embodiments, contacting alveolar macrophages or THP-1 cells differentiated and polarized toward CD209+ macrophages with the IgG Fc region-containing protein prior to stimulation with an inflammatory activator (*e.g.*, lipopolysaccharide (LPS) or TNFα) induces REST. *See* Example 2.

[00172] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in the induction of REST, such as, *e.g.*, described in the Examples (*e.g.*, Example 2), a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection). *See* Example 2. In some embodiments, the induction of REST by the IgG Fc region-containing protein is necessary for the effectiveness of the IgG Fc region-containing protein in a subject (*e.g.*, a human or non-human subject) infected with a respiratory virus (*e.g.*, an influenza virus). *See* Example 2.

[00173] In some embodiments, culturing macrophages (*e.g.*, human macrophages) *in vitro* as described in Example 1 or Example 2 with the IgG Fc region-containing protein upregulates the expression of one or more (*e.g.*, 2, 3, 4, or more, or all) of the M2 macrophage differentially expressed genes in Table 2. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of the one or more differentially expressed genes in Table 2.

[00174] In specific embodiments, the IgG Fc region-containing protein is obtained or derived from a human subject. In some embodiments, the IgG Fc region-containing protein is obtained or derived from a non-human subject capable of producing human IgG. In some embodiments, the IgG Fc region-containing protein is obtained or derived from a non-human subject.

[00175] In some embodiments, the sialylated IgG Fc region or hypersialylated IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID

NO:1. In some embodiments, the sialylated IgG Fc region or hypersialylated IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the sialylated IgG Fc region or hypersialylated IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the sialylated IgG Fc region or hypersialylated IgG Fc region of the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:1. In some embodiments, the sialylated IgG Fc region or hypersialylated IgG Fc region of the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:1 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.*, the sugar molecule present on ASN297). In some embodiments, the sialylated IgG Fc region or hypersialylated IgG Fc region of the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:1. In some embodiments, the sialylated IgG Fc region or hypersialylated IgG Fc region of the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:1 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.*, the sugar molecule present on ASN297).

[00176] In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the IgG Fc region-containing protein comprises of the amino acid sequence of SEQ ID NO:1.

[00177] In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:1. In some embodiments, the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:1. In some

embodiments, the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:1 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297).

[00178] In some embodiments, provided herein is an IgG Fc region-containing protein comprising a modified IgG Fc region. In some embodiments, the IgG Fc region-containing protein comprises more than one modified IgG Fc region. For example, in some embodiments, the IgG Fc region-containing protein comprises two or more IgG Fc regions, including a modified IgG Fc region. In some embodiments, the IgG Fc region-containing protein comprises three or more IgG Fc regions, including a modified IgG Fc region. In some embodiments, the IgG Fc region-containing protein comprises multiple IgG Fc regions, including a modified IgG Fc region. In some embodiments, the modified IgG Fc region is derived from an IgG1 F region (*e.g.*, a human IgG1 Fc region). In some embodiments, the IgG Fc-region-containing proteins has one or more (e.g., 2, 3, 4, or more, or all) of the properties/characteristics of hypersialylated IVIg and/or sFc described in Example 1 and/or Example 2, *infra*.

[00179] In some embodiments, the IgG Fc region-containing protein binds to a respiratory virus antigen. In some embodiments, the IgG Fc region-containing protein binds to an envelope protein or glycoprotein of a respiratory virus. For example, if the respiratory virus is an influenza virus (*e.g.*, influenza A virus), the IgG Fc region-containing protein may bind to an influenza virus hemagglutinin (*e.g.*, H1 or H3). In another example, if the respiratory virus is SARS-CoV-1 or SARS-CoV-2, the antibody may bind to the spike protein of the virus. In some embodiments, the IgG Fc region-containing protein binds to two or more respiratory virus antigens.

[00180] In some embodiments, the IgG Fc region-containing protein comprises an antibody or antigen-binding fragment thereof. In some embodiments, the IgG Fc region-containing protein consists of an antibody or antigen-binding fragment thereof. In some embodiments, the antibody binds to a respiratory virus antigen. In some embodiments, the antibody binds to an envelope protein or glycoprotein of a respiratory virus. For example, if the respiratory virus is an influenza virus (e.g., influenza A virus), the antibody may bind to an influenza virus hemagglutinin (*e.g.*, H1 or H3). In another example, if the respiratory virus is SARS-CoV-1 or SARS-CoV-2, the antibody may bind to the spike protein of the virus. In some embodiments, IgG Fc region-containing protein is not an antibody or antibody or antigen-binding fragment thereof that binds to a respiratory virus antigen.

[00181] In some embodiments, the IgG Fc region-containing protein contains about 12% to about 20% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12% to about 15% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12%, about 13%, about 14%, or about 15% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 16%, about 17%, about 18%, about 19%, or about 20% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to about 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21%, about 22%, about 23%, about 24%, or about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 26%, about 27%, about 28%, about 29%, or about 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[00182] In some embodiments, the IgG Fc region-containing protein contains about 30% to about 60% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50% to about 75% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 30%, about 35%, about 40%, or about 45% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50%, about 55%, about 60%, about 65%, or about 70% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75%, about 80%, about 85%, about 90%, or about 95% Fc sialylation as measured by a

technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 96%, about 97%, about 98%, or about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[00183] In some embodiments, the IgG Fc region-containing protein contains at least about 15%, at least about 20% or at least about 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 30%, at least about 40%, at least about 50%, or at least about 60% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 70%, at least about 80%, at least about 90%, or at least about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 96%, at least about 97%, at least about 98%, or at least about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art. For example, mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[00184] In some embodiments, the IgG Fc region-containing protein contains about 21% to about 26% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 27% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains the percentage of Fc sialylation described in Example 1 or 2, as measured by a technique described herein or known to one of skill in the art.

[00185] In some embodiments, the IgG Fc region-containing protein contains about 25% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 30% to about 50% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 90% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 80% to about 99% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-

containing protein contains about 40%, about 45%, about 50%, about 55%, or about 60% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 70%, about 75%, or about 80% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 80%, about 85%, about 90%, about 95%, or about 98% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 85% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[00186] In some embodiments, the IgG Fc region-containing protein contains at least 21%, at least 22%, at least 23%, at least 24%, or at least 25% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least 26%, at least 27%, at least 28%, at least 29%, or at least 30% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least 35%, at least 40%, at least 50%, at least 55%, or at least 60 % Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least 65%, at least 70%, at least 75%, or at least 80% Fc sialylation as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least 85%, at least 90%, or at least 95% Fc sialylation as measured by a technique described herein or known to one of skill in the art.

[00187] In some embodiments, the IgG Fc region-containing protein comprises α2,6-linked sialic acids. In some embodiments, the IgG Fc region-containing protein comprises α2,3-linked sialic acids. In some embodiments, the IgG Fc region-containing protein comprises α2,6-linked sialic acids and α2,3-linked sialic acids.

[00188] In some embodiments, the IgG Fc region-containing protein contains about 12% to about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12% to about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 12%, about 13%, about 14%, or about 15% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 16%,

about 17%, about 18%, about 19%, or about 20% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21% to about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 21%, about 22%, about 23%, about 24%, or about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 26%, about 27%, about 28%, about 29%, or about 30% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. For example, mass spectrometry, luminex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[00189] In some embodiments, the IgG Fc region-containing protein contains about 30% to about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50% to about 75% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 30%, about 35%, about 40%, or about 45% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 50%, about 55%, about 60%, about 65%, or about 70% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 90% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75% to about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 75%, about 80%, about 85%, about 90%, or about 95% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains about 96%, about 97%, about 98%, or about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[00190] In some embodiments, the IgG Fc region-containing protein contains at least about 15%, at least about 20% or at least about 25% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least 55%, or at least about 60% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 65%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, or at least about 90% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art. In some embodiments, the IgG Fc region-containing protein contains at least about 96%, at least about 97%, at least about 98%, or at least about 99% alpha 2,6-linked sialic acids as measured by a technique described herein or known to one of skill in the art.

[00191] In some embodiments, the IgG Fc region-containing protein binds to DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the IgG Fc region-containing protein activates DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the IgG Fc region-containing protein induces DC-SIGN (CD209) signaling or signaling of a non-human homologue (*e.g.*, murine Cd209b). In some embodiments, the IgG Fc region-containing protein induces and/or represses transcription of one or more genes dependent on DC-SIGN or a non-human homologue (*e.g.*, murine Cd209b).

[00192] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b) in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is at the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of DC-SIGN (CD209) or a non-human homologue (*e.g.*, murine Cd209b).

[00193] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) upregulates the expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG in alveolar macrophages. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments,

the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess an upregulation of expression of the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin SiglecG.

[00194] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00195] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (e.g., 1, 2, 3, 4, or more days post-infection) relative the upregulation of the same one or more gene transcripts in the same type of subject (e.g., a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in

FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00196] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the IgG Fc region-containing protein to the same type of subject (*e.g.*, a human subject or non-human subject) prior to infection with the same respiratory virus does not result in upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00197] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) does not result in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs) relative the upregulation of the same one or more gene transcripts in the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg after infection with the same respiratory virus. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00198] In some embodiments, administration of asialylated IVIg a subject (*e.g.*, a human subject or non-human subject) after infection with a respiratory virus (*e.g.*, an influenza A

virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in upregulation of one or more gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway, such as, *e.g.*, *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in alveolar macrophages (AMs), whereas administration of the IgG Fc region-containing protein to the same type of subject (*e.g.*, a human subject or non-human subject) after infection with the same respiratory virus does not result in upregulation of those one or more gene transcripts. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12A. In some embodiments, the one or more (*e.g.*, 2, 3, 4, or more, or all) gene transcripts included one or more of those in FIG. 12B. In some embodiments, the one or more gene transcripts included two or more (*e.g.*, 3, 4, 5, 6, or more, or all) of those in FIGS. 12A and 12B. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00199] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the subject relative to the gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) influenza virus pathway differentially expressed genes shown in Table 3 in a BAL sample from the same type of subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in upregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be upregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) infected with a respiratory virus results in downregulation of gene transcripts of one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown to be downregulated in Table 4 in a BAL sample from the subject relative to gene transcripts of the same one or more (*e.g.*, 2, 3, 4, or more, or all) REST/NRSF differentially expressed genes shown in Table 4 in a BAL sample from the same

type subject infected with the same respiratory virus following administration of asialylated IVIg to that subject. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be used to assess the level of one or more gene transcripts.

[00200] In some embodiments, administration of the IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of one or more transcripts of NF-KB-associated genes (*e.g.*, Relb, Junb, Nfkbie and Tnf) in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same one or more gene transcripts in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, administration of IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in suppression of "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar macrophages (AMs) a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection) relative the same "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathway in alveolar macrophages (AMs) from the same type of subject (*e.g.*, a human subject or non-human subject) administered asialylated IVIg prior to infection with the same respiratory virus the same amount of time after infection. In some embodiments, the administration of IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in transcriptional signature similar to that shown in FIG. 15A and/or FIG. 22A.

[00201] In some embodiments, administration of IgG Fc region-containing protein, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b) in alveolar macrophages. In some embodiments, administration of IgG Fc region-containing protein, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more neutrophil chemoattractants (*e.g.*, Ccl3 and Ccl4) in alveolar macrophages. In some embodiments, administration of IgG Fc region-containing protein, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for

one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of IgG Fc region-containing protein relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more pro-inflammatory factors (*e.g.*, Tnf and Il1b), one or more neutrophil chemoattractants (*e.g.*, Ccl3 and Ccl4), and one or more macrophage activation genes (*e.g.*, Batf3, Serpina3g, Sdc4, and/or Cd74) in alveolar macrophages. In some embodiments, administration of IgG Fc region-containing protein, relative to asialylated IVIg, to a subject (*e.g.*, a human subject or non-human subject) suppresses expression of transcripts coding for one or more of those identified in FIG. 24A.

[00202] In some embodiments, contacting alveolar macrophages with IgG Fc region-containing protein prior to stimulation with an inflammatory activator blocks NF-KB signaling. *See* Example 2. In some embodiments, contacting alveolar macrophages or THP-1 cells differentiated and polarized toward CD209+ macrophages with IgG Fc region-containing protein prior to stimulation with an inflammatory activator (*e.g.*, lipopolysaccharide (LPS) or TNFα) induces REST, such as described in the Examples (*e.g.*, Example 2).

[00203] In some embodiments, administration of IgG Fc region-containing protein to a subject (*e.g.*, a human subject or non-human subject) prior to infection with a respiratory virus (*e.g.*, an influenza A virus, such as, *e.g.*, influenza virus A/Netherlands/10/2009 H1N1) results in the induction of REST, such as, *e.g.*, described in the Examples (*e.g.*, Example 2), a certain time after infection with the respiratory virus (*e.g.*, 1, 2, 3, 4, or more days post-infection). *See* Example 2. In some embodiments, the induction of REST, such as, *e.g.*, described in the Examples (*e.g.*, Example 2), by the IgG Fc region-containing protein is necessary for the effectiveness of the IgG Fc region-containing protein in a subject (*e.g.*, a human or non-human subject) infected with a respiratory virus (*e.g.*, an influenza virus). *See* Example 2.

[00204] In some embodiments, culturing macrophages (*e.g.*, human macrophages) *in vitro* as described in Example 1 or Example 2 with the IgG Fc region-containing protein upregulates the expression of one or more (*e.g.*, 2, 3, 4, or more, or all) of the M2 macrophage differentially expressed genes in Table 2. In some embodiments, the upregulation is at the RNA level. In some embodiments, the upregulation is at the protein level. In some embodiments, the upregulation is the RNA level and the protein level. Techniques known in the art or described herein (*e.g.*, in Example 1 or Example 2) may be

used to assess an upregulation of expression of the one or more differentially expressed genes in Table 2.

[00205] In specific embodiments, the IgG Fc region-containing protein is obtained or derived from a human subject. In some embodiments, the IgG Fc region-containing protein is obtained or derived from a non-human subject capable of producing human IgG. In some embodiments, the IgG Fc region-containing protein is obtained or derived from a non-human subject.

[00206] In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:2 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297). In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein consists of an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:2 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297).

[00207] In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:2 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297).

[00208] In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:2. In some embodiments, the IgG Fc region-containing protein consists the amino acid sequence of SEQ ID NO:2. In some embodiments, the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:2 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297).

[00209] In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:3 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297). In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:3. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:3. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:3 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (e.g., the sugar molecule present on ASN297).

[00210] In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-containing protein comprises an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-

containing protein comprises an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-containing protein comprises the amino acid sequence of SEQ ID NO:3 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297).

[00211] In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 80%, at least 85%, or at least 90% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 95%, at least 96%, or at least 97% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-containing protein consists of an amino acid sequence that is at least 98% or at least 99% identical to the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:3. In some embodiments, the IgG Fc region-containing protein consists of the amino acid sequence of SEQ ID NO:3 and is recombinantly produced in the presence of enzyme to facilitate alpha 2, 6-sialic acid linkage to a sugar molecule (*e.g.,* the sugar molecule present on ASN297).

[00212] In some embodiments, a modified IgG Fc region is one described in Example 1 or Example 2, *infra*.

[00213] In some embodiments, a modified IgG Fc region is one described in U.S. Patent No. 11,613,579, or International patent application No. WO 2016/141262, each of which is incorporated herein.

[00214] In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein mimics IgG sialylation (*e.g.*, alpha 2, 6-linked sialic acids and/or alpha 2, 3-linked sialic acids). In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein includes alpha 2, 6-linked sialic acids. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein mimics IgG sialylation and includes alpha 2, 6-linked sialic acids. In some embodiments, the modified IgG Fc region of the IgG Fc region-containing protein mimics IgG sialylation and includes alpha 2, 6-linked sialic acids and alpha 2, 3-linked sialic acids.

[00215] Techniques described herein (*e.g.*, in Example 1 or Example 2) known in the art may be used to produce an IgG Fc region-containing protein described herein. In some embodiments, the IgG Fc region-containing protein is recombinantly produced using techniques/methods described herein (*e.g.*, in Example 1 or Example 2) or known to one of

skill in the art. The IgG Fc region-containing protein may be recombinantly produced in, *e.g.*, Chinese hamster ovary (CHO) cells (*e.g.*, CHO-K1 cells), human embryonic kidney (HEK) 293T cells, or HEK 293-F cells. In some embodiments, the IgG Fc region-containing protein is obtained or derived from IVIg.

Fc of hIgG1 (starting from amino acid 210 in Kabat system)
KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 1; F241 and F243 are underlined)

Fc of hIgG1 FA241:
KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVALFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 2)

Fc of hIgG1 FA243
KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLAPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 3)

[00216] In some embodiments, an agent described herein (*e.g.,* one described in this section, Example 1, or Example 2) is used in a method described herein. In some embodiments, an agent described herein (*e.g.,* one described in this section, Example 1, or Example 2) is used are used to treat and/or prevent a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*, a human subject), improve lung function or preserve lung function in a subject (*e.g.*, a human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*, a human subject), and/or reduce inflammation that associated with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject).

5.2 Pharmaceutical Compositions

[00217] In one aspect, provided herein are pharmaceutical compositions comprising an agent described herein (*e.g.*, in Section 5.1, Example 1, or Example 2). In some embodiments, provided herein are pharmaceutical compositions comprising an agent described herein and a pharmaceutically acceptable carrier. In some embodiments, the agent comprises sialylated intravenous immunoglobulin (IVIg). In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises sialylated IgG Fc region. In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises hypersialylated IgG Fc region. In some embodiments, the agent comprises an IgG Fc region-containing protein. In some embodiments, the agent comprises one disclosed in Example 1 or Example 2, *infra*.

[00218] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances. Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include polysorbate 80 (TWEEN®80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[00219] In some embodiments, a pharmaceutical composition described herein is used in a method described herein. In some embodiments, the pharmaceutical compositions described herein are used to treat and/or prevent a respiratory virus disease (*e.g.*, moderate to severe

respiratory virus disease) in a subject (*e.g.*, a human subject), improve lung function or preserve lung function in a subject (*e.g.*, a human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*, a human subject), and/or reduce inflammation that associated with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject).

[00220] A pharmaceutical composition may be formulated for any route of administration to a subject. In some embodiments, the pharmaceutical composition is formulated for parenteral administration. In some embodiments, the pharmaceutical composition is formulated for subcutaneous administration. In some embodiments, the pharmaceutical composition is formulated for intramuscular administration. In some embodiments, the pharmaceutical composition is formulated for intravenous administration.

5.3 Methods of Preventing or Treating Respiratory Virus Diseases

[00221] In one aspect, provided herein is a method for treating a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject), comprising administering to the subject an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein. In another aspect, provided herein is a method for improving lung function or preserving lung function in a subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease), comprising administering to the subject an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein. In another aspect, provided herein is a method for reducing inflammation associated with a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject), comprising administering to the subject an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein. In some embodiments, the agent comprises sialylated IVIg. In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises sialylated IgG Fc region. In some embodiments, the agent comprises hypersialylated IgG Fc region. In some embodiments, the agent comprises an IgG

Fc region-containing protein. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is diagnosed with moderate to severe respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing one or more serious symptoms of the respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing one or more moderate to severe symptoms of the respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing dyspnoea, tachypnoea, and/or hypoxia. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has a sustained fever (e.g., a fever of about 102° F or higher, such as, *e.g.*, 102.5° F, 103° F, 103.5 ° F, 104 ° F, 104.5° F, 105 ° F, 105.5° F, or 106 ° F). In some embodiments, the sustained fever has lasted 24 hours, 36 hours, 48 hours, 72 hours, or more. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing chest pain (*e.g.*, moderate to severe chest). In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing stomach pain or muscle pain (*e.g.*, moderate to severe stomach pain or muscle pain). In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of one or more proinflammatory cytokines (*e.g.*, one or more of the proinflammatory cytokines described in Example 1 or Example 2) in a BAL sample or another sample (e.g., a blood sample) from the subject. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of one or more chemotactic factors (*e.g.*, one or more of the chemotactic factors described in Example 1 or Example 2) in a BAL sample or another sample (e.g., a blood sample) from the subject. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of one or more of the following, a combination of the following, or all of the following: TNF-alpha, TNF-beta, IL-6, IL-1 alpha, interferon (IFN)-gamma, GM-CSF, CXCL1, CXCL5, CXCL10, and/or CXCL11 in a BAL sample or another sample (e.g., a blood sample) from the subject. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of neutrophil and/or monocyte/macrophage infiltration in a BAL sample from the subject. In some embodiments, the evaluated levels are relative to a subject (*e.g.*, human subject) or population of subjects (*e.g.*, human subjects) with a mild case of the same respiratory virus disease. In some embodiments, the evaluated levels are relative to a subject (*e.g.*, human subject) or population of subjects (*e.g.*, human subjects) with the same respiratory virus disease that does not require hospitalization.

[00222] In another aspect, provided herein is use of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein in the manufacture of a medicament for use in treating a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject). In another aspect, provided herein is use of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein in the manufacture of a medicament for use in treating a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject). In another aspect, provided herein is a method for improving lung function or preserving lung function in a subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease), comprising administering to the subject an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein. In another aspect, provided herein is use of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein in the manufacture of a medicament for use in improving lung function or preserving lung function in a subject (*e.g.*, human subject). In another aspect, provided herein is a method for reducing inflammation associated with a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject (*e.g.*, human subject), comprising administering to the subject an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein. In another aspect, provided herein is use of an agent described herein (*e.g* an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein in the manufacture of a medicament for use in reducing inflammation associated with a respiratory virus disease (*e.g.*, a moderate to severe respiratory virus disease) in a subject

(*e.g.*, human subject). In some embodiments, the agent comprises sialylated IVIg. In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises sialylated IgG Fc region. In some embodiments, the agent comprises hypersialylated IgG Fc region. In some embodiments, the agent comprises an IgG Fc region-containing protein. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is diagnosed with moderate to severe respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing one or more serious symptoms of the respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing one or more moderate to severe symptoms of the respiratory virus disease. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing dyspnoea, tachypnoea, and/or hypoxia. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has a sustained fever (e.g., a fever of about 102° F or higher, such as, *e.g.*, 102.5° F, 103° F, 103.5 ° F, 104 ° F, 104.5° F, 105 ° F, 105.5° F, or 106 ° F). In some embodiments, the sustained fever has lasted 24 hours, 36 hours, 48 hours, 72 hours, or more. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing chest pain (*e.g.*, moderate to severe chest). In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent is experiencing stomach pain or muscle pain (*e.g.*, moderate to severe stomach pain or muscle pain). In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of one or more proinflammatory cytokines (*e.g.*, one or more of the proinflammatory cytokines described in Example 1 or Example 2) in a BAL sample or another sample (e.g., a blood sample) from the subject. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of one or more chemotactic factors (*e.g.*, one or more of the chemotactic factors described in Example 1 or Example 2) in a BAL sample or another sample (e.g., a blood sample) from the subject. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of one or more of the following, a combination of the following, or all of the following: TNF-alpha, TNF-beta, IL-6, IL-1 alpha, interferon (IFN)-gamma, GM-CSF, CXCL1, CXCL5, CXCL10, and/or CXCL11 in a BAL sample or another sample (*e.g.*, a blood sample) from the subject. In some embodiments, the subject (*e.g.*, human subject) prior to administration of the agent has elevated levels of neutrophil and/or monocyte/macrophage infiltration in a BAL sample from the subject. In some embodiments, the evaluated levels are relative to a subject (*e.g.*, human subject) or population of subjects

(*e.g.*, human subjects) with a mild case of the same respiratory virus disease. In some embodiments, the evaluated levels are relative to a subject (*e.g.*, human subject) or population of subjects (*e.g.*, human subjects) with the same respiratory virus disease that does not require hospitalization.

[00223] In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) parenterally. In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) subcutaneously. In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) intramuscularly. In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) intravenously.

[00224] In some embodiments, the agent is administered to the subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) at a concentration of 0.1 mg/kg to 2 mg/kg. In some embodiments, the subject is a human that weighs about 60 kg to about 75 kg. In some embodiments, the subject is a human that weighs about 5 kg to about 30 kg. In some embodiments, the subject is a human that weighs about 30 kg to about 50 kg.

[00225] In some embodiments, the administration of the agent or pharmaceutical composition to the subject (*e.g.*, human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) reduces the severity of symptoms of the respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) and/or number of symptoms of the respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease). In some embodiments, the administration of the agent or pharmaceutical composition to the subject (e.g., human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) improves lung function. An improvement in lung function may be assessed by an increase in blood (*e.g.*, arterial blood) oxygen levels and/or a decrease in blood (*e.g.*, arterial blood) CO_2 levels. An improvement in lung function may also be assessed by a decrease in difficulty breathing. For example, the subject (*e.g.*, human subject) may have improved lung function if they do not require oxygen supplementation or other breathing assistance. In some embodiments, the administration of the agent or pharmaceutical composition to the subject (*e.g.*, human subject) with a respiratory virus

disease (*e.g.*, moderate to severe respiratory virus disease) preserves lung function. For example, the ability of the subject (*e.g.*, human subject) to breathe does not decrease, or their blood (*e.g.*, arterial blood) oxygen levels and/or blood (*e.g.*, arterial blood) CO_2 levels do not worsen. In some embodiments, the administration of the agent or pharmaceutical composition to the subject (e.g., human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) reduces the need for hospitalization of the subject. In some embodiments, the administration of the agent or pharmaceutical composition to the subject (e.g., human subject) with a respiratory virus disease (*e.g.*, moderate to severe respiratory virus disease) reduces the length of time the subject needs to be hospitalized.

[00226] In another aspect, provided herein is a method for preventing moderate to severe respiratory virus disease in a subject (*e.g.*, human subject), comprising administering to the subject an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein. In some embodiments, the agent comprises sialylated IVIg. In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises sialylated IgG Fc region. In some embodiments, the agent comprises hypersialylated IgG Fc region. In some embodiments, the agent comprises an IgG Fc region-containing protein. In some embodiments, the subject is diagnosed with a respiratory virus disease (*e.g.*, mild respiratory virus disease). In some embodiments, the subject (*e.g.*, human subject) is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject less than 5 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 1 to about 5 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 1 to about 4 years old, about 1 to about 3 years old, or about 1 to about 2 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject 50 years old or older. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject 50 to 100 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject is about 55 years old or about 60 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 65 years old, about 70

years old, about 75 years old, or about 80 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 85 years old, about 90 years old, about 95 years old, or about 100 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject with diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject with a disorder that may cause breathing problems, such as, *e.g.*, a seizure, nerve or muscle disorder. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject that has a body mass index of 40 or higher. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject 6 months to 18 years old that is receiving long-term aspirin therapy.

[00227] In another aspect, provided herein is use of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) or a pharmaceutical composition described herein in the manufacture of a medicament for use in preventing moderate to severe respiratory virus disease in a subject (*e.g.*, human subject). In some embodiments, the agent comprises sialylated IVIg. In some embodiments, the agent comprises hypersialylated IVIg. In some embodiments, the agent comprises sialylated IgG Fc region. In some embodiments, the agent comprises hypersialylated IgG Fc region. In some embodiments, the agent comprises an IgG Fc region-containing protein. In some embodiments, the subject is diagnosed with a respiratory virus disease (*e.g.*, mild respiratory virus disease). In some embodiments, the subject (*e.g.*, human subject) is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject less than 5 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 1 to about 5 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 1 to about 4 years old, about 1 to about 3 years old, or about 1 to about 2 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject 50 years old or older. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject 50 to 100 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a

human subject is about 55 years old or about 60 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 65 years old, about 70 years old, about 75 years old, or about 80 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject about 85 years old, about 90 years old, about 95 years old, or about 100 years old. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject with diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject with a disorder that may cause breathing problems, such as, *e.g.*, a seizure, nerve or muscle disorder. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject that has a body mass index of 40 or higher. In some embodiments, the subject at high risk for moderate to severe respiratory virus disease is a human subject 6 months to 18 years old that is receiving long-term aspirin therapy.

[00228] In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) parenterally. In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) subcutaneously. In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) intramuscularly. In some embodiments, the agent or pharmaceutical composition is administered to the subject (*e.g.*, human subject) intravenously.

[00229] In some embodiments, the agent is administered to the subject (*e.g.*, human subject) at a concentration of 0.1 mg/kg to 2 mg/kg. In some embodiments, the subject is a human that weighs about 60 kg to about 75 kg. In some embodiments, the subject is a human that weighs about 5 kg to about 30 kg. In some embodiments, the subject is a human that weighs about 30 kg to about 50 kg.

[00230] In some embodiments, the methods of preventing moderate to severe respiratory virus disease disclosed herein reduce the severity of symptoms and/or reduce the number of moderate to severe symptoms of the respiratory virus disease. In some embodiments, the methods of preventing moderate to severe respiratory virus disease disclosed herein prevent the onset and/or progression of symptoms moderate to severe respiratory virus disease. In some embodiments, the methods of preventing moderate to severe respiratory virus disease disclosed herein prevent difficulty breathing. In some embodiments, the methods of

preventing moderate to severe respiratory virus disease disclosed herein prevent the onset and/or progression of dyspnoea. In some embodiments, the methods of preventing moderate to severe respiratory virus disease disclosed herein prevent the onset and/or progression of tachypnoea. In some embodiments, the methods of preventing moderate to severe respiratory virus disease disclosed herein prevent the onset and/or progression of hypoxia. In some embodiments, the methods of preventing moderate to severe respiratory virus disease disclosed herein prevent a decrease in blood (*e.g.*, arterial blood) oxygen levels and/or an increase in blood (*e.g.*, arterial blood) CO_2 levels. In some embodiments, the methods of preventing moderate to severe respiratory virus disease disclosed herein prevent the need to hospitalization of the subject (*e.g.*, human subject).

[00231] In some embodiments, the respiratory virus disease is influenza virus disease. In some embodiments, the respiratory virus disease caused by influenza virus. In some embodiments, the influenza virus is an influenza A virus. In some embodiments, the influenza A virus is an H1 or H3 subtype. Symptoms of moderate to severe influenza virus disease may include difficulty breathing or shortness of breath, persistent pain or pressure in the chest or abdomen, persistent dizziness, confusion, inability to arouse, seizures, not urinating, severe muscle pain, severe weakness or unsteadiness, a fever, and/or a cough.

[00232] In some embodiments, the respiratory virus disease is human respiratory syncytial (RSV) virus disease. In some embodiments, the respiratory virus disease is caused by a human respiratory syncytial virus. Symptoms of moderate to severe RSV disease may include wheezing, bluish color of skin due to lack of oxygen, rapid breathing or difficulty breathing, fever, and/or a severe cough.

[00233] In some embodiments, the respiratory virus disease is human metapneumovirus disease. In some embodiments, the respiratory virus disease is caused by a human metapneumovirus. Symptoms of moderate to severe human metapneumovirus disease may include wheezing, difficulty breathing, hoarseness, cough, pneumonia, and/or aggravation of asthma.

[00234] In some embodiments, the respiratory virus disease is a parainfluenza virus disease (*e.g.*, human parainfluenza virus disease). In some embodiments, the respiratory virus disease is caused by a parainfluenza virus (*e.g.*, human parainfluenza virus). In some embodiments, the respiratory virus disease is a coronavirus disease (*e.g.*, a human coronavirus disease). In some embodiments, the respiratory virus disease is caused by a coronavirus (*e.g.*, a human coronavirus).

[00235] In some embodiments, the respiratory virus disease is caused by a severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In some embodiments, the respiratory virus disease is COVID or COVID-19. Symptoms of moderate to severe COVID or COVID-19 may include trouble breathing, persistent pain or pressure in the chest, confusion, inability to wake or stay awake, pale, grey, or blue-colored skin, lips, or nail beds, dizziness, loss of speech or movement, fever, muscle aches, and/or persistent cough.

[00236] In some embodiments, the respiratory virus disease is an adenovirus disease. In some embodiments, the respiratory virus disease is caused by an adenovirus. In some embodiments, the respiratory virus disease is caused by a human bocavirus. In some embodiments, the respiratory virus disease is a human bocavirus disease.

5.4 Biological Assays

[00237] In some embodiments, an agent described herein is characterized/assessed using a technique or method described in Example 1 or Example 2, *infra*. In some embodiments, the sialylation (e.g., the alpha 2,6-linked sialic acids) of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) is assessed by a technique described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art. In some embodiments, the amount of alpha 2,6-linked sialic acids of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) is assessed by a technique described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art. For example, mass spectrometry, lumniex, ELISA, or a Western blot using a sialylated Fc-specific reagent or a sialic acid specific lectin may be used to measure sialylation.

[00238] In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to bind to DC-SIGN (CD209) or a non-human homologue of DC-SIGN is assessed by a technique known to one of skill in the art (*e.g.*, in an immunoassay). In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein)

to activate DC-SIGN (CD209) or a non-human homologue of DC-SIGN is assessed by a technique/method described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art. In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to activate DC-SIGN (CD209) or a non-human homologue of DC-SIGN is assessed in the presence and absence of an anti-DC-SIGN antibody or an isotype control, such as described in Example 1 or Example 2, *infra*. In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to induce DC-SIGN (CD209) signaling or signaling of a non-human homologue of DC-SIGN is assessed by a technique/method described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art. In some embodiments, the technique/method is *in vitro* or *ex vivo*.

[00239] In some embodiments, the ability of an agent described herein (*e.g.,* an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to induce REST expression may be assessed by a technique/method described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in art. In some embodiments, the technique/method is *in vitro* or *ex vivo*.

[00240] In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to reduce inflammation associated with respiratory virus disease in a subject or improve lung function or preserve lung function with a moderate to severe respiratory virus disease in a subject in is assessed by a technique/method described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art. In some embodiments, the reduction in inflammation associated with a respiratory virus disease is assessed by measuring one or more proinflammatory cytokines (*e.g.*, TNF-alpha, IL-6, IL-1 alpha, TNF-beta, interferon (IFN)-gamma, or GM-CSF) in a bronchoalveolar lavage (BAL) sample or other specimen (*e.g.*, a blood sample) from a subject before and a certain time after administration of an agent described herein. In some embodiments, the reduction in inflammation associated with a respiratory virus disease is assessed by measuring one or more monocyte/macrophage chemotactic factors (*e.g.*, CXCL1, CXCL2, CXCL5, CXCL10,

or CXCL11) in a BAL sample or other specimen (*e.g.*, a blood sample) from a subject before and a certain time after administration of an agent described herein. In some embodiments, the reduction in inflammation associated with a respiratory virus disease is assessed by measuring neutrophil and/or monocyte/macrophage levels in a BAL sample from a subject before and a certain time after administration of an agent described herein. The BAL sample (*e.g.*, BAL fluid) may be obtained from a subject (*e.g.*, a human subject) using techniques known to one of skill in the art. In some embodiments, an improvement or preservation of lung function is assessed by measuring the levels of blood (e.g., arterial) gases (*e.g.*, blood oxygen and/or blood CO_2 levels) in a subject before and a certain time after administration of an agent described herein. The subject may be human or non-human. The certain time after administration of an agent may be 24 hours, 36 hours, 48 hours, 72 hours, 1 week, or 2 weeks later.

[00241] In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to bind to a respiratory virus antigen (*e.g.*, an envelope protein or glycoprotein) is assessed using a technique known in the art (*e.g.*, an immunoassay, such as an ELISA). For example, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to bind to influenza virus (*e.g.*, influenza A virus) hemagglutinin (*e.g.*, an H1 or H3) may be assessed using a technique known in the art (*e.g.*, an immunoassay, such as an ELISA).

[00242] In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to neutralize a respiratory virus may be assessed using an *in vitro* neutralization assay described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art.

[00243] In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to reduce the titer of a respiratory virus is assessed using a technique/method described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art. In some embodiments, the respiratory virus titer is measured using a

technique described herein (*e.g.*, in Example 1 or Example 2) or known to one of skill in the art before and a certain time period after the administration of an agent described herein. The certain time after administration of an agent may be 24 hours, 36 hours, 48 hours, 72 hours, 1 week, or 2 weeks later.

[00244] In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to treat moderate to severe respiratory virus disease in a subject is assessed by assessing the lung capacity of the subject before and a certain time after administration of the agent using techniques/methods known to one of skill in the art. In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to treat moderate to severe respiratory virus disease in a subject is assessed by assessing the severity and/or number of symptoms the subject is experiencing before and a certain time after administration of the agent. The symptoms may include one or more, a combination of two or more, or all of the following: a fever (*e.g.*, a fever of about 102° F or higher), dyspnoea, tachypnoea, hypoxia, chest pain, and/or stomach pain. In some embodiments, the ability of an agent described herein (*e.g.*, an agent described in Section 5.1, Example 1, or Example 2, such as *e.g.*, sialylated IVIg, hypersialylated IVIg, sialylated IgG Fc region, hypersialylated IgG Fc region, or IgG Fc region-containing protein) to treat moderate to severe respiratory virus disease in a subject is assessed by the need for hospitalization before and a certain period of time after administration of the agent to the subject. The subject may be human or non-human. The certain time after administration of an agent may be 24 hours, 36 hours, 48 hours, 72 hours, 1 week, or 2 weeks later.

[00245] In some embodiments, a transcriptional profile in alveolar macrophages, such as described in Example 2 (*see*, *e.g.*, FIGs. 15A-15D and 22A-22D for different transcriptional profiles that may be used), is used to assess the severity of a respiratory virus disease (*e.g.*, influenza virus disease) in a subject (*e.g.*, a human subject). In some embodiments, a biological sample (*e.g.*, a blood sample, sputum sample, or Bronchoalveolar lavage (BAL)) may be obtained and used to analyze the transcriptional profile of immune cells (*e.g.*, macrophages such as, *e.g.*, alveolar macrophages), such as described in Example 2, to assess the severity of a respiratory virus disease (*e.g.*, influenza virus disease) in a subject (*e.g.*, a

human subject). Techniques/methods known to one of skill in the art or described herein may be used (*e.g.*, those described in Example 2).

6. EXAMPLES

6.1 EXAMPLE 1: IgG-Fc SIALYLATION SUPPRESSES INFLUENZA VIRUS-INDUCED LUNG INFLAMMATION AND DISEASE

[00246] This example provides data demonstrating that in mice expressing human Fc gamma receptors (hFcγR), sialylation of IgG Fc conferred broad protective activity against antigenically divergent H1N1 and H3N2 influenza virus strains, relative to asialylated IgG. This protection was independent of neutralizing activity, decoupled from lung viral titer, and mechanistically dependent on SIGN-R1. The presence of sialylated IgG during influenza virus infection limited the inflammatory response and protected lung function during infection.

6.1.1 Introduction

[00247] While most respiratory viral infections resolve with little harm to the host, severe symptoms arise when infection triggers an aberrant inflammatory response that damages lung tissue and compromises gas exchange[1-4]. Host regulators of virally-induced lung inflammation are not well defined. In addition to viral neutralization, IgG antibodies that are elicited in response to infection mediate pleiotropic immunomodulatory functions through engagement of Fcγ receptors (FcγRs). Although prior studies have defined the impact of Fc-FcγR interactions in antiviral immunity, the role of FcγR pathways in modulating the inflammatory response in the lung remains unknown. Using clinical cohorts with mild and severe influenza disease, protection from severe disease was found to be associated with elevated levels of Fc domain sialylation, a glycan modification that enables IgG to engage type II FcγRs[5-8]. Mechanistic studies in mice expressing human FcγRs[9] revealed that passive transfer of sialylated, but not asialylated, IgG conferred protection against lethal influenza infection with heterologous strains by limiting virus-induced lung inflammation and improving lung function. Protection by Fc sialylation was independent of IgG neutralizing activity, decoupled from lung viral titer, and was mechanistically dependent on the FcγR, SIGN-R1. These findings define a novel SIGN-R1-mediated mechanism, apart from virus neutralization, that may be harnessed to limit disease caused by antigenically diverse influenza strains.

6.1.2 Materials and Methods

[00248] Human IgG Fc glycan analysis

[00249] Methods for relative quantification of Fc glycans and IgG subclasses have been previously described[18, 49]. Briefly, IgG were isolated from serum of influenza patients by Protein G (GE Healthcare) purification. Antigen specific IgG were isolated on N-hydroxysuccinimide agarose resin (Thermo Fisher Scientific, cat. no. 26196) coupled to hemagglutinin (HA) produced in-house. After tryptic digestion of purified IgG bound to HA-coated beads, nanoscale liquid chromatography coupled to tandem mass spectrometry (nanoLC-MS/MS) analysis for characterization of glycosylation sites was performed on an UltiMate 3000 Nano LC (Dionex) coupled with a hybrid triple quadrupole linear ion trap mass spectrometer, the 4000 QTRAP (SCIEX). MS data acquisition were performed using Analyst 1.6.1 Software (SCIEX) for precursor ion scan–triggered information-dependent acquisition analysis for initial discovery-based identification.

[00250] For quantitative analysis of the glycoforms at the N297 site of IgG1, multiple-reaction monitoring (MRM) analysis for selected target glycopeptides and their glycoforms was applied using the nanoLC-4000 QTRAP platform to the samples, which had been digested with trypsin. The mass/charge ratio (m/z) of four-charged ions for all different glycoforms as Q1 and the fragment ion at m/z 366.1 as Q3 for each of transition pairs were used for the MRM assays. A native IgG tryptic peptide (131-GTLVTVSSASTK-142 (SEQ ID NO:4)) with Q1/Q3 transition pair of 575.9+2/780.4 was used as a reference peptide for normalization. All raw MRM data were processed using MultiQuant 2.1.1 (SCIEX). All MRM peak areas were automatically integrated and inspected manually. In the case where the automatic peak integration by MultiQuant failed, manual integration was performed using the MultiQuant Software.

[00251] Mice

[00252] This study used FcgR-humanized mice, which express all the human FcgRs but none of the mouse FcgRs, as previously described [9]. Mice at 8-10 weeks of age were used for all experiments and maintained at the Stanford animal facility. All *in vivo* studies were performed in compliance with the federal law and institutional guidelines approved by the Stanford University Institutional Animal Care and Use Committee.

[00253] IAV *in vivo* infection study

[00254] Mice at 8-10 weeks of age were used for IAV infection studies. 1 mg of either asialylated or sialylated IVIg were given to mice intraperitoneally at least 2 hours prior to

infection. For IAV infection, mice were anesthetized with 90 mg/kg Ketamine (Dechra) and 10 mg/kg Xylazine (Akorn) and inoculated with A/Netherlands/10/2009 H1N1 or X31 H3N2 virus intranasally. The mice were monitored for weight loss daily for 14 consecutive days. For the SIGNR1 blocking experiment, 100 μg SIGNR1 blocking antibody (BioxCell, BE0220) or isotype control antibody (BioxCell, BE0260) were given intraperitoneally to the infected mice every other day, starting from the day prior to the infection procedure to day 10 of the experiment. For the sFc experiment, 1 mg of sFc was administered to infected mice in 3 doses on day 2, 4, 6 post-infection.

[00255] Sialylation and asialylation of IVIg

[00256] IVIg (Gammagard) was enzymatically treated to either increase a2-6 sialic acid content (sialylation) or to remove sialic acid (asialylation). For sialylation, 22.2 mM IVIg was incubated in PBS with 1 mM recombinant ST6GAL1 (Sino Biological or produced in-house) in the presence of 2.5 mM CMP-Sialic Acid (Millipore Sigma) at 37° C for 48 hours. For asialylation, 150 mM IVIg was incubated in 1x GlycoBuffer with 150000 units of a 2-3,6,8 Neuraminidase (New England Biolabs) at 37° C for 24 hours. After the enzymatic treatments, the IVIg preparations were purified using Protein G beads (GE Healthcare) and dialyzed overnight in PBS.

[00257] Generation of sFc

[00258] Sialylated Fc-F241A was generated by co-expression of human IgG1 Fc-F241A and specific enzymes to facilitate terminal alpha 2,6 sialic acid linkage to the sugar molecule present on ASN297. sFc was confirmed to be ~85% 2,6 sialylated at ASN297 by HILIC-HPLC-FLD glycan analysis.

[00259] Releasing and Labelling N-glycans of sFc

[00260] N-glycan analysis of sFc was performed by ATUM using standard methodology. N-glycans were released and labeled using the InstantPC kit (Agilent). In brief, 20 mg of intact mAB or fragments and 2 ml of Gly-x denaturant was added. The samples were incubated at 90°C for 3 minutes, and then the samples were allowed to cool at room temperature for 2 minutes. 2 ml of N-glycanase was added to each sample, mixed and then incubated at 50° C for 5 minutes. 5 ml of InstantPC Dye solution was mixed with the samples and incubated for a further 1 minute at 50° C. To each sample, 150 ml of load/wash solution was applied. The samples were transferred to a cleanup plate and vacuum applied. The samples were washed three times with load/wash buffer before the released labeled N-glycans were eluted with 100 ml of Gly-X Instant PC. The samples were run immediately on the HILIC-HPLC-FLD.

[00261] HILIC-HPLC-FLD Glycan Analysis

[00262] InstantPC labeled glycans were analyzed by HPLC-FLD on an Agilent 1290 HPLC system with a fluorescence detector (Agilent, USA) using an AdvanceBio Glycan mapping 300A column (1.8 mm, 2.1 x 150 mm, Agilent) with an increasing ammonium formate linear-gradient (mobile phase A: 100 mM ammonium formate pH 4.5 in water; mobile phase B: Acetonitrile) at a flow rate of 0.6mL/min. An injection volume of 2 ml and a column temperature of 40° C were used. Glycans were detected at a wavelength of 345 nm with an excitation wavelength of 285nm. Peaks were integrated using OpenLabs CDS software (Agilent), and the relative glycan compositions were calculated. In conjunction with the samples being run, a dextran ladder (AdvanceBio InstantPC Maltodextrin ladder; Agilent) was run before and after the samples. A ladder was used to calibrate the LC runs and to plot a curve to allocate GU values from retention times. Calculated GU values were compared to a database of reference structures (InstantPC Labeled Glycans, Agilent), allowing N-Glycan to be assigned to each peak. The relative abundance (%Area) of each glycan is expressed as the average of the percentage of the total peak area.

[00263] Pseudovirus neutralization assay

[00264] Vesicular stomatitis virus (VSV)–based green fluorescent protein (GFP)/nanoluciferase-expressing influenza H1 pseudovirus was produced following a protocol described previously[50]. VSV-ΔG-GFP/nanoluciferase was a gift from Dr. G. S. Tan (J. Craig Venter Institute). Plasmid encoding the hemagglutinin gene of A/Hawaii/70/2019 were produced in-house by cloning mammalian codon-optimized gene fragments (Integrated DNA Technologies) using Gibson Assembly (New England BioLabs). To perform the neutralization assay, MDCK cells were seeded at a density of 1×10^4 per well in half-area 96-well black opaque plates (Greiner Bio-One) and were grown overnight at 37°C in a 5% CO2 atmosphere. Serum samples were serially diluted using infection medium [Minimum essential medium (MEM, Gibco; 11430-030) supplemented with 0.5% bovine serum albumin (Sigma; A8412), 0.1% sodium bicarbonate (Gibco; 25080-094), 10 mM HEPES (Gibco; 15630-080), 1% penicillin-streptomycin-glutamine solution, (Gibco, 10378016), and 1 μg/mL TPCK trypsin in duplicates with a starting concentration of 1:100. Diluted serum samples were then mixed with an equal volume of A/Hawaii/70/2019 pseudovirus particles diluted in infection medium at an amount of 200 to 400 focus-forming units per well, followed by incubation at 37° C for 1 hour. Subsequently, pseudovirus and diluted sera were added onto the monolayers of PBS-washed MDCK cells and incubated at 37° C. 18 hours after incubation, supernatants were removed, cells were washed once with PBS, and

nanoluciferase enzymatic activities were measured using the Nano-Glo Luciferase Assay System (Promega, #N1120) and a SpectraMax iD3 multimode microplate reader. Nonlinear curves and IC50 values were determined using GraphPad Prism.

[00265] Lectin-blot and Western-blot

[00266] Unmodified, sialylated and asialylated IVIg were diluted with sample buffer (Boster), boiled at 95° C for 10 mins, then loaded to and resolved with any-KDa polyacrylamide gel (Bio-rad). The proteins were transferred to 0.45 mm PVDF membrane (Thermo Fisher Scientific) followed by blocking with 1% BSA/TBST. For the a2-6 sialylation level, the PVDF was subsequently incubated with biotinylated SNL (Vector Laboratories, B-1305), followed by incubation with IRDye 800CW streptavidin (Li-cor, 926-32230). For the human IgG level, as the loading control, the PVDF was incubated with IRDye 800CW Goat anti-Human IgG Antibody (Li-cor, 926-32232). The signal intensity was captured with LICOR machine (Li-cor).

[00267] Homogenization of lungs

[00268] Whole lungs from IAV infected mice were collected in BeadBug homogenizer tubes with 3 mm Zirconium beads (Sigma-Aldrich) in 1 ml of cold DMEM un-supplemented media, followed by homogenization using BeadBug microtube homogenizer (Millipore-Sigma) with 05 cycle, 2500 rpm, 90 seconds settings until homogenized. Homogenates were then spun down at maximum speed for 5 minutes at 4° C, and supernatants were collected and frozen at -80 degrees for further characterization.

[00269] Plaque assay

[00270] MDCK cells were purchased from ATCC and maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum and 1% Penicillin-Streptomycin at 37°C/5% CO_2. For plaque assay or neutralization assay, MDCK cells were seeded at 90% confluency in 6-well plates the day prior to infection. For neutralization assays, virus was incubated with a dilution series of IVIg preparations prior to addition to cells. For plaque assays, dilutions of virus stocks or lung homogenates prepared in infection media (Gibco Minimum Essential Media, 0.6% BSA, 1% Penicillin-Streptomycin-Glutamine, 0.02 M HEPES, 0.2% sodium bicarbonate, 1 mg/ml TPCK trypsin) were added directly to cells. MDCK cells were incubated with virus or virus in the presence of antibody for 1 hour at 37° C/5% CO_2. After infection, media was removed and MDCK cells were rinsed with PBS, followed by addition of overlay containing 1.2% methylcellulose in infection media. Plates were left undisturbed at 37° C/5% CO_2 for 48-72 hours. 4% PFA was then added to the MDCK cells to fix the cells for 30 minutes, followed by removal of overlay media and rinsed

with PBST. IAV nucleoprotein antibody (H16) (GeneTex) was diluted in staining buffer (0.1% BSA, 0.1% Saponin in PBS) and added to the MDCK cells for 2 hours, followed by rinsing with PBST. Finally, a secondary HRP-anti-mouse IgG antibody (Southern Biotech) was added for 1 hour, followed by rinsing with PBST. TrueBlue Peroxidase substrate (Sera Care) was used to visualize plaques.

[00271] Bronchoalveolar fluid IVIg ELISA

[00272] Bronchoalveolar lavage was performed on mice euthanized at day 4 and day 7 post infection. Immune cells were isolated from the BAL fluid and profiled, while the cell free BAL fluid was used to characterize chemokines, cytokines and IVIg content. For probing the levels of S and S0 IVIg in BAL fluids of mice, total IVIg in the BAL fluid was captured on ELISA plates (Immulon 2 HB, Thermo Fisher Scientific) with human anti-kappa and anti-lambda antibodies (Southern Biotech, cat. no. 9230-01 and 9180-01) and probed 1:5000 diluted horseradish peroxidase–conjugated anti-human IgG secondary antibody (Southern Biotech, cat. no. 2040-05). ELISA plates were developed using 3,3′,5,5′-tetramethylbenzidine substrate solution (MilliporeSigma). The reaction was stopped with 0.2 N sulfuric acid (Sigma-Aldrich), and absorbance was measured at 450 nm (SpectraMax iD3, Molecular Devices). The plates were washed five times with PBST between each step, and an additional wash with PBS was done before developing the plates.

[00273] Cardiac blood collection and blood gas analysis

[00274] Mice were anaesthetized with 90 mg/kg Ketamine (Dechra) and 10 mg/kg Xylazine (Akorn) and positioned in dorsal recumbency. Syringe with a 25-gauge needle was inserted into the thoracic cavity up into the left ventricle of the heart at a slight angle. Cardiac blood was collected by slowly and steady withdrawal of the plunger of the syringe, and blood was transferred into K2EDTA-coated tubes (BD). Blood oxygen and carbon dioxide level were then measured with RAPIDPoint 500 Systems (Siemens-Healthineers).

[00275] BAL immune cells profiling

[00276] Cells isolated from BAL fluid, blocked with Human TruStain FcX (BioLegend, cat. no. 422302) to reduce nonspecific binding, and stained with combinations of the following cell staining antibodies for 20 min at 4° C: LIVE/DEAD Blue Fixable Dye (Thermo Fisher Scientific, cat. no. L34962), PerCP-Cy5.5 anti-CD3 (clone 17A2; cat. no. 100218), BV650 anti-CD11b (clone M1/70; cat. no. 101259), BV605 anti-CD11c (clone N418; cat. no. 117334), AF700 anti-CD45 (clone I3/2.3; cat. no. 147716), PerCP-Cy5.5 anti-B220 (clone RA3-682; cat. no. 103236), AF488 anti-Ly6C (clone HK1.4; cat. no. 128022), BV711 anti-Ly6G (clone 1A8; cat. no. 127643), BV785 anti-F4/80 (clone BM8; cat. no.

123141) PE anti-Siglec-F (clone X; cat. no. X), BV421 anti-MerTK (clone 2B10C42; cat. no. 151510), and APC/Fire-750 anti–major histocompatibility complex (MHC) II (clone M5/114.15.2; cat. no. 107652), APC/Fire-750 anti-CD44 (clone NIM-R8; cat. no. 156004), BUV615 anti-CD62L (BD, clone MEL-14; cat. no. 752311), BUV805 anti-CD8a (BD, clone 53-6.7; cat. no. 612898), BV421 anti-CXCR5 (clone L138D7; cat. no. 145512), BV605 anti-CD19 (clone 6D5; cat. no. 115540), BV650 anti-NK-1.1 (clone PK136; cat. no. 108736), BV711 anti-IgD (clone 11-26c-2a; cat. no. 405731), BV785 anti-CD4 (clone RM4-5; cat. no. 100552), PE anti-CD3 (clone 17A2; cat. no. 100206), PE-Cy7 anti-γδ-TCR (clone GL3; cat. no. 118124), and PerCP-Cy5.5 anti-CD25 (clone 3C7; cat. no. 101912). Antibodies were purchased from BioLegend unless otherwise noted. Once stained, cells were washed, resuspended in fixation buffer (BioLegend, cat. no. 420801), and acquired using a Cytek Aurora flow cytometer (Cytek). Neutrophils were defined as viable Ly6G+ CD11b+ CD11c- CD3− B220− leukocytes. Monocytes were defined as viable CD11b+ CD11c- Ly6G− Ly6C+ CD3− B220− leukocytes. Alveolar macrophages were defined as viable CD11b- CD11c+ Siglec-F+ MerTK+ leukocytes. T cells were defined as viable CD3+ NK-1.1- CD19- leukocytes. T cells were further subdivided based on CD4 and CD8a expression. Central memory T cells (CM) were defined CD44+ CD62L+ T cells. Effector memory (EM) T cells were defined as CD44+ CD62L- T cells. Γδ T cells were defined as CD4- CD8- γδTCR+ T cells. B cells were defined as viable CD3- NK-1.1- CD19+ leukocytes. NK cells were defined as viable CD3- NK-1.1+ CD19- leukocytes. NKT cells were defined as viable CD3+ NK-1-1+ CD19- leukocytes.

[00277] BAL cytokine profiling

[00278] Cell-free BAL fluid was processed within 24 hours of collection to measure cytokine and chemokine content using LEGENDplex bead array kits (BioLegend, cat. nos. 740390 and 740451).

[00279] IgG immune complex formation

[00280] Polyclonal IgG was isolated from SARS-CoV-2 immune individuals with and was characterized for anti-RBD Fc glycoforms including afucosylation and sialylation of anti-RBD IgG1 using established mass spectrometry methods. A portion of the sialylated (FS) IgG pool was subsequently incubated with α-2-3,6,8 neuraminidase (New England Biolabs; cat. no. P0720L) per manufacturer's instruction to remove sialic acid and form the asialylated product (FS0). 100 μg of pooled, purified IgG were incubated with SARS-CoV-2 spike trimer at a 20:1 molar ratio overnight at 4° C to form immune complexes.

[00281] ***In vivo*** **lung inflammation model**

[00282] All *in vivo* experiments were performed in compliance with the federal laws and institutional guidelines and have been approved by the Stanford University Institutional Animal Care and Use Committee (IACUC). Immune complexes were intratracheally or intranasally administered to 8- to 12-week-old, sex-matched, fully FcγR-humanized C57BL/6 mice (FcγR mice reference). Experimental groups were consistently matched for sex and age but otherwise randomized. 4 or 24 hours after immune complex administration, mice were euthanized and BAL fluid was collected or whole lung was harvested. Immune cells were isolated from within the BAL fluid or whole lung suspension, blocked with Human TruStain FcX (BioLegend, cat. no. 422302) to reduce nonspecific binding, and stained with combinations of the following fluorescent antibodies and reagents for 20 min at 4° C: LIVE/DEAD Aqua Fixable Dye (Thermo Fisher Scientific, cat. no. L34957), PerCP-Cy5.5 anti-CD3 (clone 17A2; cat. no. 100218), PerCP-Cy5.5 anti-B220 (clone RA3-682; cat. no. 103236), APC-Fire750 anti-NK-1.1 (clone S17017D; cat. no. 156516), BV650 anti-CD11b (clone M1/70; cat. no. 101259), PE anti-CD11b (clone M1/70; cat. no. 101207), BV605 anti-CD11c (clone N418; cat. no. 117334), AF700 anti-CD45 (clone I3/2.3; cat. no. 147716), APC anti-Ly6C (clone HK1.4; cat. no. 128016), APC-Fire750 anti-Ly6C (clone HK1.4; cat. no. 128046), BV785 anti-Ly6G (clone 1A8; cat. no. 127645), PE anti-myeloid-epithelial-reproductive tyrosine kinase (MerTK) (clone 2B10C42; cat. no. 151506), BV421 anti-MERTK (clone 2B10C42; cat. no. 151510), PE anti-Siglec-F (clone S17007L; cat. no. 1555506), BV650 anti-human CD16 (clone 3G8; cat. no. 302042), APC anti-SIGN-R1 (Invitrogen, clone 22D1; cat. no. 50-112-3106), APC/Fire 750 anti–I-A/I-E (clone M5/114.15.2; cat. no. 107652), and/or BV785 anti–I-A/I-E (clone M5/114.15.2; cat. no. 107645) purchased from BioLegend unless otherwise noted. Once stained, cells were washed, resuspended in fixation buffer (BioLegend, cat. no. 420801), and acquired using an Attune NxT flow cytometer (Invitrogen). Neutrophils were defined as viable $Ly6G^+$ $CD11b^+$ leukocytes. Monocytes were defined as viable $CD11b^+$ $Ly6C^+$ $Ly6G^-$ leukocytes. Alveolar macrophage were defined as viable $CD11b^{lo}$ $CD11c^+$ I-A/I-E^{lo} $MerTK^+$ Siglec-F^+ leukocytes. Interstitial macrophage were defined as viable $CD11b^+$ $CD11c^+$ I-A/I-E^+ Siglec-F^- leukocytes. Dendritic cells were defined as viable $CD11c^+$ I-A/I-E^+ $CD24^+$ Siglec-F^- leukocytes. T cells were defined as viable $CD3^+$ $B220^-$ $CD11b^-$ I-A/I-E^- leukocytes. B cells were defined as viable $B220^+$ $CD3^-$ $CD11b^-$ I-A/I-E^+ leukocytes. NK cells were defined as viable NK-1.1^+ $CD3^-$ $B220^-$ leukocytes. Cell-free BAL fluid was stored at 4° C and processed within 24 hours to measure cytokine and chemokine content using

LEGENDplex bead array kits (BioLegend, cat. nos. 740390 and 740451). In SIGN-R1 blockade experiments, 100 μg of anti-SIGN-R1 mAb (Invitrogen, clone 22D1; cat. no. 50-129-87) or isotype control mAb (Invitrogen, clone eBio299Arm; cat. no. 50-112-9491) was intranasally pre-administered 24 hours prior to immune complex administration, and immune complex administration and BAL were performed as described above. Researchers were blinded to experimental groups and agents throughout these *in vivo* studies.

[00283] RNA-seq library preparation, sequencing, and analysis

[00284] Alveolar macrophage (Amφ) were purified from BAL fluid by positive magnetic separation based on MerTK expression (STEMCELL; cat. no. 17684). Amφ purity post-separation was observed to be >95% (FIGS. 9C-9F). Cells were promptly resuspended in lysis buffer (Takara; cat. no. 635013) supplemented with RNase inhibitor (Takara; cat. no. 2313B) and stored at -80° C until further processing. First-strand cDNA synthesis directly from cells was primed by the 3' SMART-Seq CDS Primer II A and used SMART-Seq v4 Oligonucleotide for template switching at the 5' end of the transcript. Full length cDNA was synthesized and amplified by LD PCR for 14 cycles using a SMART-Seq v4 Ultra Low Input RNA kit (Takara; cat. no. 634888) followed by the Illumina Nextera XT library preparation kit (cat. no. FC-131-1096) per the manufacturer's protocol. An equal molar amount of tagmented cDNA library from each sample was pooled for sequencing on the Illumina HiSeq 4000 platform at Stanford University Genomics Center. FASTQ files were generated using the bcl2fastq2 Conversion v2.19 tool. Each set of sample sequence data was aligned and normalized using STAR aligner to assemble the mapped reads into mouse transcriptome (mm10). Differential gene expression analysis was conducted using DEseq2. Pathway analysis was conducted using Gene Set Enrichment Analysis (GSEA; UC San Diego & Broad) and Enrichr (Ma'ayan Lab, ISMMS). DEG analysis, secondary analysis, and visualization was performed using R Statistical Software (v.4.2.0; R Core Team 2022) with the additional utilization of factoextra (v.1.0.7; Kassambra and Mundt 2020), EnhancedVolcano (v.1.14.0; Blighe, Rana, and Lewis 2022), and pheatmap (v.1.0.12; Kolde 2019) R packages.

[00285] Transcriptomic Analysis

[00286] Monocytes purified from the peripheral blood of healthy blood donors were cultured for 120 hours in complete media (RPMI 1640 base media, 10% FBS, penicillin-streptomycin, sodium pyruvate, non-essential amino acids) supplemented with 20 ng/mL recombinant human M-CSF. Resulting macrophage were treated with 200 nM small interfering RNA targeting CD209 or an untargeted control siRNA complexed with

DharmaFect 3 transfection reagent. After an overnight rest, cells were re-cultured for an additional 48 hours in complete media supplemented with 10 ng/mL recombinant human M-CSF and 20 ng/mL recombinant human IL-4. After 48 hours, the resulting M2 macrophage were stimulated with 10 nM sFc for 24 hours. After 24 hours, cells were lysed, RNA was purified, and bulk RNA-seq was performed. Transcriptomic analysis was performed using DESeq2 and Gene Set Enrichment Analysis (GSEA). Il4i1 – IL-4 induced gene. A checkpoint molecule (PMID: 32818467); Mmp25 – matrix metalloproteinase involved in CD16 downregulation (PMID: 23851692); Qpct – enzymatic modifier of the CD47 – SIRPα checkpoint axis (PMID: 30833751); Lilrb1 – CD85j. Checkpoint molecule containing ITIM domains (PMID: 26636629); Ly75 – CD205. Myeloid cell receptor that induces tolerance toward ligand/binding partners (PMID: 33679806); and Ccl17 – One of two ligand of CCR4, present on regulatory T cells (PMID: 28723576).

[00287] All *in vivo* experiments were performed in compliance with the federal laws and institutional guidelines and have been approved by the Stanford University Institutional Animal Care and Use Committee (IACUC). Immune complexes were intratracheally or intranasally administered to 8- to 12-week-old, sex-matched, fully FcγR-humanized C57BL/6 mice. Experimental groups were consistently matched for sex and age but otherwise randomized. 4 hours after sialylated, asialylated, or no immune complex administration, mice were euthanized and BAL fluid was collected. Immune cells were isolated from within the BAL fluid and alveolar macrophage were purified based on MerTK expression. Alveolar macrophage were subsequently lysed, RNA was purified, and bulk RNA-seq was performed. Transcriptomic analysis was performed using DESeq2 and Gene Set Enrichment Analysis (GSEA).

[00288] **Flu RNAseq Analysis.**

[00289] Mice were given 1 mg of either asialylated or sialylated IVIg through intraperitoneal route 2 hours prior to A/Netherlands/10/2009 H1N1 infection. On day 4 post infection, bronchoalveolar lavage was performed to isolate BAL fluid for FACS sorting of alveolar macrophages (CD11c+SIGLEC-F+) followed by RNA extraction using RNeasy Micro Kit (Qiagen) for downstream transcriptomic analysis. For alveolar macrophages transcriptomic analysis, messenger RNA was purified from the total RNA using poly-T oligo-attached magnetic beads. After fragmentation, cDNA was synthesized for library construction involving end repair, A-tailing, adapter ligation, size selection, amplification, and purification. The library was checked with Qubit and real-time PCR for quantification and bioanalyzer for size distribution detection. Quantified libraries were pooled and

sequenced on Illumina platforms, according to effective library concentration and data amount. For bioinformatic analysis, raw reads of fastq format were firstly processed through in-house perl scripts. Clean reads were obtained by removing reads containing adapter, poly-N and low quality reads. At the same time, Q20, Q30 and GC content of the clean data were calculated for downstream analysis. For reads mapping to the reference genome, index of the reference genome was built using Hisat2 v2.0.5 and paired-end clean 1 reads were aligned to the reference genome using Hisat2 v2.0.5. featureCounts v1.5.0-p3 was used to count the reads numbers mapped to each gene. DESeq2Rpackage (1.20.0) was used to determine differential gene expression. Metascape was used to conduct pathway analysis.

6.1.3 Results

[00290] Antibodies are central mediators of immunity against respiratory viral pathogens and can protect by direct neutralization or through Fc mediated effector functions. Glycosylation of the IgG Fc domain is one mechanism for regulating the precise effector functions that IgG can engage and whether the outcome is pro- or anti-inflammatory[10-13]. The composition of the core Fc glycan can be altered by addition of specific saccharide units (fucose, N-acetylglucosamine, galactose and sialic acid) and these modifications directly affect the biological activity of IgG (FIGS. 1A and 1B)[14]. An absence of core fucose (afucosylation), confers a specific high affinity interaction with the activating Fc receptor CD16a to enhance effector functions such as cytotoxicity and pro-inflammatory cytokine and chemokine production[15-20]. In contrast, the presence of terminal sialic acid and core fucose on the Fc glycan converts IgG1 to anti-inflammatory molecules that can counterbalance some autoantibody- and T cell-mediated diseases[5-8,21,22]. As humans produce highly variable Fc glycans, the hypothesis that Fc glycosylation might modulate the lung immune response during influenza virus infection, a setting in which disease is driven by a dysregulated inflammatory response to the virus, was tested.

[00291] First, it was assessed whether any anti-HA IgG Fc glycoforms correlated with clinical outcome in a cohort of 26 patients with influenza virus infections. Study participants had laboratory confirmed H1N1 infections in 2019 (2009 pandemic-like strain) and varying disease severities during infection. Ten patients in the cohort required hospitalization, whereas the others had mild symptoms, enabling a comparison of antibody glycosylation and disease severity (**Table 1**). Overall, only sialylated Fc glycoforms distinguished patients with severe (hospitalized) and mild (outpatient) disease; sialylated forms of IgG were reduced in people who developed severe influenza disease (FIG. 2A). Sialylated forms were further

assessed based on whether the biantennary glycan contained one (G1FS) or two (G2FS) galactose residues (FIGS. 1A, 1B and FIG. 2B). The abundance of G2FS glycans on anti-HA IgG was a strong predictor of disease severity with an area under the receiver-operating-characteristic curve (AUC) of 0.89 with 95% confidence interval of (0.75-1) (FIG. 2C). The distribution of all other glycans profiled was similar (FIG. 2A). Notably, Fc afucosylation, a pro-inflammatory modification that is associated with more severe COVID-19 and dengue virus infections[18,19,23-26], was not significantly different between patients with mild and severe influenza disease; this result is consistent with severe influenza disease being driven by a hyperinflammatory response to the virus rather than a pathogenesis involving activating immune complexes. Neutralizing titers against a contemporary HA from A/Hawaii/70/2019 (pandemic-like H1N1) were equivalent between people with mild and severe influenza disease (FIG. 2D). Of the features profiled, protection against severe disease correlated best with the abundance of Fc sialylation.

[00292] Next, it was probed whether sialylation of IgG might impact influenza virus infection or disease in an *in vivo* experimental model. IgG reagents were generated from a clinical-grade source that is readily available, intravenous immunoglobulin (IVIg), which consists of pooled IgG from thousands of donors. IVIg was enzymatically modified to remove sialic acids (asialylated IVIg) or to enrich for α2-6 sialylation (sialylated IVIg), the predominant sialic acid linkage in humans (FIG. 3A). Sialylated IVIg preparations contained 21-26% Fc sialylation, whereas no sialylation was detected in asialylated preparations by mass spectrometry (FIG. 3B). All preparations had similar size exclusion profiles (FIG. 3C). Because sialoglycans are receptors for influenza viruses, it was assessed whether modifying IVIg sialylation impacted neutralizing potency. IVIg had neutralizing activity against two antigenically distinct influenza virus strains, A/Netherlands/10/2009 (H1N1) and X31 (H3N2), but this activity was equivalent among sialylated, asialyalted and unmodified IVIg preparations (FIGS. 3D, 3E), demonstrating an absence of competitive inhibition by the sialylated IVIg.

[00293] To test whether sialylation of IgG impacted immunity against influenza viruses *in vivo*, a humanized FcγR mice (hFcγR), which is a physiologically relevant model for studying Fc effector functions of human IgG, was used[9]. hFcγR mice were administered a single dose of IVIg (sialylated or asialylated) that was determined to be subneutralizing in concentration against the A/Netherlands/10/2009 (H1N1) virus strain *in vivo*. Two hours later, mice were challenged with five times the lethal dose (5LD) of A/Netherlands/10/2009

(FIG. 4A). Mice that received sialylated IVIg exhibited delayed weight loss and enhanced survival compared to mice that received asialylated IVIg (FIGS. 4B and 4C). All control mice that received PBS and virus only succumbed to infection by day 8.

[00294] To assess whether the protective activity of sialylated IgG could be applied to another influenza virus, the experiment using the A/X-31 (H3N2) challenge strain was performed next. As before, hFcγR mice were administered a single, subneutralizing, dose of sialylated or asialyalted IVIg or PBS two hours prior to challenge with 5LD of A/X-31. Consistent with results from the H1N1 challenge, mice that received sialylated IVIg lost less weight and were more likely to survive relative to mice that received asialyalted IVIg or virus alone (FIGS. 4D, 4E). These studies demonstrated that asialylated IgG did not have any pathogenic activity during infection, whereas increasing the sialic acid content of IVIg was sufficient to confer protective activity against antigenically distinct influenza viruses.

[00295] Several assessments were performed to probe the mechanism by which sialylated antibodies protected against influenza disease (FIG. 5A). To test whether protection was associated with a difference in transfer to the lung mucosa based on sialylation status of IVIg, levels of IVIg in bronchoalveolar lavage (BAL) fluid on day 7 post infection were measured and were equivalent between groups (FIG. 5B). Next, to ascertain whether sialylation of IVIg was associated with a difference in virus replication, lung titers were measured on day 4 (A/Netherlands/10/2009 and X31) and day 7 post infection (H1N1) and were not different between groups (FIG. 5C). These data supported an antibody-based mechanism of protection against disease that was decoupled from virus infection.

[00296] Severe influenza disease is marked by excessive inflammation that ultimately compromises lung function[1-3]. As such, it was next probed whether sialylated IgG might protect by tempering lung inflammation during infection. To test this idea, measurements of cells and soluble factors in BAL fluid following infection were performed. Mice receiving sialylated IVIg had reduced neutrophil accumulation in BAL fluid on day 4 relative to those infected in the absence of any IVIg, demonstrating a suppression of the virally-induced inflammatory response by sialylated IVIg (FIG. 5D and FIG. 6). On day 7, BAL fluid from mice that received sialylated IVIg had reduced levels of cytokines including TNFα, IL-6, IL-1α and GM-CSF, and TGFβ (FIG. 5E) along with lower levels of neutrophil and monocyte/macrophage chemotactic factors such as GM-CSF, CXCL1, CXCL11, CXCL2 and CXCL10. This was coupled with lower neutrophil and monocyte infiltration detected in BAL fluid on day 7 post infection (FIG. 5F) [27-30].

[00297] Next, the FcγR requirement for this activity was determined. It was hypothesized that SIGN-R1 might be a relevant receptor since it has anti-inflammatory activity in some autoimmune settings, although it has not been shown to protect against an infectious disease or a disease that is not immune-complex or T cell mediated. To test the requirement of SIGN-R1, mice were administered sialylated IVIg prior to A/Netherlands/10/2009 challenge in addition to receiving a SIGNR1 blocking antibody or an isotype control. Blocking SIGN-R1 abrogated the protective effect of sialylated IVIg, whereas blocking SIGN-R1 alone or administration of an isotype control did not affect survival (FIG. 5G). As disease is a function of tissue health, it was determined whether the protection mediated by SIGN-R1 was associated with improved lung function. To do this, arterial blood gas on day 5 post infection was measured. Mice that received sialylated IVIg prior to infection had increased blood oxygen levels along with decreased CO2, supporting improved gas exchange relative to mice that received virus alone or asialylated IVIg followed by infection (FIG. 5H). Together, these data demonstrated that sialylation of IgG provided SIGN-R1-dependent protection against influenza disease through a mechanism that did not impact virus titers but reduced inflammatory activity within the lung and preserved lung function.

[00298] To determine whether influenza-reactive Fab domains contributed to the protection mediated by sialylated IVIg, it was next evaluated whether a sialylated Fc domain alone could mediate protection in the hFcγR challenge system. To test this, a recombinant human IgG1 Fc was utilized which contains ~85% α2-6 sialic acid on the asparagine 297-linked N-glycan in addition to a protein mutation, F241A, that mimics the activity of sialylated Fc (sFc)[22] and is in development for a variety of non-infectious disease indications. Mice were administered three doses of the clinical grade sFc molecule on days 2, 4 and 6 post-infection with A/Netherlands/10/2009 (FIG. 7A). Notably, administration of sFc alone conferred protection against weight loss (FIG. 7B) and survival (FIG. 7C). These data show that sFc protected when administered as a therapeutic treatment and that protection by sFc did not require Type I FcγR-mediated effector function, which are only engaged upon immune complex formation[31].

[00299] **Activity of sialylated IgG immune complexes in the lung**

[00300] IgG immune complexes formed with viral particles, proteins, or infected cells accumulate within the lung during respiratory viral infection, but the resulting Fc-mediated effector functions of immune complexes within the lung are largely undefined. To this end, a model system was developed in which human immune complexes of defined composition are

administered into the airway of FcγR-humanized mice (FIG. 8A). Bronchoalveolar lavage (BAL) fluid can then be collected and analyzed for cell composition, as well as cytokine and chemokine concentrations. As this model uses non-infectious immune complexes, it is useful for decoupling effects of viral replication and activity mediated through different antibody signaling pathways. Using this model, it was established that afucosylated immune complexes trigger an acute inflammatory lung response[51], but the activity of sialylated immune complexes in the lung required further elucidation. To study this, immune complexes containing IgG enriched for Fc sialylation (FS) or IgG that was neuraminidase-treated to remove sialic acids (F) were administered. While sialylated immune complexes were essentially inert, promoting immune activity indistinguishable from mock control, removal of sialic acid from IgG converted previously sialylated immune complexes to a more inflammatory stimulus as demonstrated by increases in innate immune recruitment and pro-inflammatory factors, including tumor necrosis factor (TNF)-α and C-C motif chemokine ligand (CCL)-3 (FIGS. 8B, 8C). As the anti-inflammatory activity of sialylated IgG outside of the lung relies on SIGN-R1 signaling, it was tested whether SIGN-R1 had a role in mediating similar anti-inflammatory activity in the lung. Indeed, SIGN-R1 blockade de-suppressed the lung immune response to sialylated IgG to a similar degree as the removal of sialic acid (FIGS. 8A, 8C). Together, these data demonstrate that sialylated IgG are not immunogenically inert but actively anti-inflammatory through interactions with SIGN-R1$^+$ immune cells in the lung.

[00301] Transcriptional profiling of alveolar macrophage after immune complex stimulation *in vivo*.

[00302] To further investigate how sialylated immune complexes impact effector cells within the lung, it was next asked whether they induce distinct transcriptional programs in sentinel cells of the lung, specifically alveolar macrophage (Amφ). Amφ are the predominant resident immune cell within the lung and human Amφ express receptors for sialylated and afucosylated immune complexes, DC-SIGN and CD16, respectively[52-54]. It was confirmed that Amφ from humanized FcγR mice also express both receptors (SIGN-R1 and CD16 in mice) (FIGS. 9A, 9B). Due to their abundance and FcγR expression profile, it was hypothesized that Amφ are one of, if not the principal effector cell capable of responding to immune complex formation in the airway. To characterize the transcriptional response to afucosylated or sialylated immune complexes, Amφ were isolated from BAL fluid 4 hours after administration of immune complexes to the airway. Transcriptomic analysis by bulk

RNA sequencing revealed that differentially glycosylated immune complexes induced distinct transcriptional changes in Amφ by principal component analysis (PCA) (FIG. 9C).

[00303] Further analysis revealed that several key genes related to macrophage function and survival (*Amica1*, *Osm*, and *Ier3*) were upregulated in response to afucosylated immune complexes, whereas genes related to proteasomal and metabolic processes (*Alas1*, *Psme2*, *Wfdc21*, and *Ch25h*) were downregulated in response to sialylated immune complexes (FIG. 9D). Amφ expression of *Tnf* and *Il1b*, as well as the neutrophil chemoattractants *Ccl3* and *Ccl4* were increased in response to afucosylated immune complexes and decreased in response to sialylated immune complexes (FIGS. 9D, 9E). The inverse expression of these pro-inflammatory soluble factors was consistent with proteomic data where TNFα, CCL3, and CCL4 were detected at high and low concentrations in respective response to afucosylated and sialylated immune complexes (FIG. 8C, *see* also reference 53). Overall, sialylated immune complexes suppressed genes involved in general cellular metabolic activity and the expression of proinflammatory soluble factors (FIG. 9D). Amφ isolated from mice that received SIGN-R1 blockade prior to sialylated immune complexes did not downregulate these most differentially expressed and proinflammatory genes (FIG. 9F). The symmetry in DEGs between Amφ treated with sialylated immune complexes under SIGN-R1-blocked or unblocked conditions demonstrates the SIGN-R1-dependent transcriptional regulation that sialylated immune complexes have on Amφ. Together, these data demonstrate that CD16a and SIGN-R1 signaling elicit dramatic yet opposing changes in Amφ gene expression *in vivo*, with sialylated immune complexes repressing transcription of several inflammatory mediators in a SIGN-R1 dependent manner.

[00304] **Transcriptomic Analysis**

[00305] As shown in FIGS. 10A-10C, genes specifically in the upper-right quadrant indicate significantly upregulated DEGs, whereas genes in the upper-left quadrant indicate significantly downregulated DEGs. *See* Table 2 for the genes upregulated by sFc treatment of human macrophage. FIGS. 11A-11B provide enrichment plots, which represent the spectrum of all genes arranged from most upregulated to most downregulated, left to right. Each vertical line represents a DEG predetermined to be involved in a particular pathway. Higher ranked DEGs within the upregulated (left-most) portion of genes support positive pathway enrichment, whereas lower ranked DEGs within the downregulated (right-most) portion of genes support negative pathway enrichment. *See* Table 3 for murine influenza virus DEGS and Table 4 for the murine REST/NRSF DEGs.

Table 2 Genes upregulated by sFc treatment of human macrophage (*see* FIG. 10A)

Gene	log2FC (sFc/PBS)	p-value (sFc/PBS)
GGT5	2.389215367	9.31409E-05
MMP25	1.976058731	0.004622307
IL4I1	1.551039369	0.009938545
CCL17	1.414806687	0.029708404
LY75	1.31806223	0.012398561
MT2A	1.153577598	5.1118E-06
QPCT	1.008147659	0.006673418
LILRB1	0.852086653	0.007704804

Table 3 Murine influenza virus DEGS (DEGs associated with enrichment plot in FIG. 11A)

Gene	log2FC (S IVIg/S0 IVIg)	p-value (S IVIg/S0 IVIg)
Rps11	-4.978494659	0.014578409
Rpl34	-4.584697951	0.025538536
Rps27l	-4.563166711	0.012022545
Rps3	-4.50648323	0.006419309
Rps25	-4.410069621	0.000428992
Rpl35	-4.339619967	0.011261474
Rpl18	-4.277090283	0.005616992
Polr2f	-4.263876742	0.013261356
Rps19	-4.236528878	0.008299716
Uba52	-4.185298805	0.015389514
Rpl11	-4.095523372	1.75047E-08
Rpl14	-4.092949015	0.00220529
Rps16	-4.09094552	0.020585694
Rps18	-4.074949911	2.11955E-05
Rps2	-4.058147269	0.006749516
Rpl10a	-4.057008598	0.003469181
Rps23	-4.046430983	0.000216624
Rpl19	-4.043289167	0.012295372
Rpl32	-4.016613937	0.00119796
Rps13	-3.98769996	4.03027E-06
Rpl13	-3.957347089	0.000805316
Rpl15	-3.944778465	0.000511763
Rpl36	-3.93831528	0.007397417
Rps27	-3.933561748	0.000126495
Rpl37	-3.877777448	0.000178872
Rplp0	-3.855128751	2.42206E-05

Gene	log2FC (S IVIg/S0 IVIg)	p-value (S IVIg/S0 IVIg)
Polr2j	-3.852579277	0.002216746
Rpl22l1	-3.84936443	3.76128E-06
Rpl10	-3.843057854	0.013039204
Rpl23	-3.834831225	1.26026E-05

Table 4 Murine REST/SRSF DEGs (DEGs associated with enrichment plot in FIG. 11B)

Gene	log2FC (S IVIg/S0 IVIg)	p-value (S IVIg/S0 IVIg)
Ncan	3.558384915	0.010733987
Sarm1	3.349217916	0.001681
Hcn1	3.10705594	0.004867264
Celf3	2.529771428	0.002175754
Grm1	2.501030696	0.003806902
Nrsn1	2.417912287	0.003508301
Lhfpl5	2.40410152	0.001462475
Srrm4	2.278739194	0.00067801
Drd2	2.151287551	0.002056026
Syt6	2.13362341	5.88547E-05
Gprin1	2.132998017	0.003245738
Slc12a5	2.057111554	0.000406134
Pcsk2	2.0167257	0.006959133
Elavl3	1.891714256	0.000371996
Pdzd7	1.883895561	0.009837523
Col5a3	1.872861131	0.007828155
Scamp5	1.839539998	1.15047E-05
Ghsr	1.796075088	0.00271536
Cdk5r1	1.727467909	0.001747553
Prg3	1.614844914	0.002026181
Kcnip2	1.514467035	0.001180917
Drd3	1.478069205	0.000308079
Phyhipl	1.394315943	0.007015097
Rph3a	1.301096526	7.79935E-05
Prlhr	1.280964347	0.007271719
Glra1	1.097864403	0.002034278
Atp6v0a1	-1.666151677	0.002122444
Chka	-2.403279879	0.000551933
Rnf13	-2.548665145	2.10674E-05
Hes1	-3.968011254	0.010883177

[00306] Flu RNAseq.

[00307] To further probe how sialylated IVIg protected mice from disease following infection, RNA sequencing was performed of purified alveolar macrophages (AM) isolated from BAL fluid 4 days post-infection from mice that were pretreated with either hypersialylated IVIg, or asialylated IVIg or PBS 2 hours before challenge with 5LD of A/Netherlands/10/2009. Differential gene expression analyses revealed 73 genes that were commonly upregulated in mice that received no pretreatment or mice that received asialylated IVIg as compared to sialylated IVIg followed by a virus challenge. Reactome pathway analyses of the differentially expressed genes revealed upregulation of multiple gene transcripts associated with the inflammatory non-canonical NF-kappa B signaling pathway such as *Nfkbib* and *Relb* and their downstream effectors like *Tnf*, *Junb* and *Icam1* in AMs of mice that were exposed to a virus and those that received asialylated IVIg but not sialylated IVIg (FIGS. 12A, 12B). Mice that received sialylated IVIg had higher expression of *Cd209b* as compared to asialylated IVIg, the gene that codes for SIGN-R1, the type 2 Fc-gamma receptor that has been shown to preferentially engage sialylated IgG and mediate their anti-inflammatory activity (FIG. 12C). Another gene transcript upregulated in the sialylated IVIg receiving mice was the inhibitory ITIM domain containing sialic acid-binding immunoglobulin (Ig)-like lectin *SiglecG* (FIG. 12C). Together, these data demonstrated that mice that receive sialylated IVIg but not asialylated IVIg had a generally blunted inflammatory response to influenza virus infection by actively targeting inflammatory signaling pathways and soluble effectors.

6.1.4 Discussion

[00308] Historically, strategies to combat influenza disease have focused on preventing or reducing viral replication. The present findings highlight the potential for strategies that aim to limit disease by harnessing anti-inflammatory mechanisms. Strict regulation of inflammation is critical to the proper functioning of the lung, and especially during the resolution phase of influenza virus infection. Herein it is shown that humans who maintain mild symptoms during influenza virus infection produce anti-HA IgGs with higher levels sialylated Fc relative to people who progress to severe disease. Sialylated IgG Fc acted *in vivo* in mice in a SIGN-R1-dependent manner to limit virally-induced lung inflammation. SIGN-R1, the murine homolog of human DC-SIGN, is expressed on several $CD45^+$ innate immune cells such as dendritic and macrophages and $Epcam1^+$ lung epithelial cells[32]. It is likely that the observed effects in this study are the outcome of SIGN-R1 engagement on

multiple cell types however, depletion studies to further dissect the role of SIGN-R1 on specific cellular populations may not be informative as these cells are also directly involved in antiviral control and immunity against influenza viruses[33]. Despite the conflicting reports on sialylation on the impact of complement activation, the observed effect by sFc is not expected to be related to complement activity since monomeric Fc fails to promote the complement system[34-38].

[00309] Much remains to be learned about the *in vivo* functions that can be mediated by FcγRs, particularly Type II FcγRs. As influenza disease is not mediated by formation of pathogenic immune complexes, the SIGN-R1-mediated mechanism defined here is distinct from mechanisms previously described in which SIGN receptor activity counterbalances pathogenic activating FcγR signaling in immune-complex mediated diseases by triggering upregulation of the inhibitory FcγRIIb on effector cells[5,6]. In the context of influenza virus infection, protection by sialylated IgG was coupled to reduced expression of cytokines on day 7 after infection that are associated with influenza disease pathology and tissue damage including TNFα, IL-6, IL-1α/IL-1R1, and TGFβ[39, 40, 41, 42, 43, 44]. In conjunction with lower levels of inflammatory cytokines and chemokines, mice receiving sialylated IgG also had lower infiltration of neutrophils and monocytes which produce factors that increase morbidity in murine models of influenza disease[45-48]. The suppressed lung inflammatory response was coupled to increased arterial blood oxygenation and decreased blood CO_2. Overall, these data show that sialylation of IgG has a role in resolving inflammation induced by influenza virus infection by blunting production of proinflammatory cytokines, immune cell infiltration and preserving lung function. This mechanism has potential to be harnessed for reduction of disease in antigenically variable influenza virus infections.

[00310] **Table 1: Influenza Patient Cohort Clinical Characteristics**

	Influenza Patients (N = 26)
Age [Median (IQR)]	50.5 (44.5 – 60.75)
Sex [Percent; (N)]	
Female	38.5% (10)
Male	61.5% (16)
Hospitalizations [Percent; (N)]	38.5% (10)
Vaccinated for Influenza [Percent; (N)]	34.6 (9)
Comorbidities [Percent; (N)]	
Diabetes	7.7% (2)
Chronic neurological disease	3.8% (1)
Chronic renal failure	0% (0), NA = 1
Ischemic heart disease	11.5% (3)
COPD	19.2% (5)
Previous Stroke	0% (0)
Smoker	
Current	42.3% (11)
Ex	11.5% (3)
Never	42.3% (11)
E-cigarettes	3.9% (1)
Fever [Percent; (N)]	100% (26)
Fever Temperature [Median (IQR)]	101.84°F (100.76°F – 102.2°F)
Nose Symptoms [Percent; (N)]	50.0% (13)
Throat Symptoms [Percent; (N)]	46.2% (12)
Headache [Percent; (N)]	61.5% (16)
Nausea/Vomiting [Percent; (N)]	23.1% (6)
Weakness [Percent; (N)]	96.2% (25)
Arthralgia [Percent; (N)]	61.5% (16)
Myalgia [Percent; (N)]	57.7% (15)

6.1.5 References Cited in the Example

1 Kalil, A. C. & Thomas, P. G. Influenza virus-related critical illness: pathophysiology and epidemiology. Crit Care 23, 258 (2019). https://doi.org:10.1186/s13054-019-2539-x

2 Fukuyama, S. & Kawaoka, Y. The pathogenesis of influenza virus infections: the contributions of virus and host factors. Current opinion in immunology 23, 481-486 (2011). https://doi.org:10.1016/j.coi.2011.07.016

3 Gill, J. R. et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Arch Pathol Lab Med 134, 235-243 (2010). https://doi.org:10.5858/134.2.235

4 Heaton, N. S. et al. Long-term survival of influenza virus infected club cells drives immunopathology. J Exp Med 211, 1707-1714 (2014). https://doi.org:10.1084/jem.20140488

5 Anthony, R. M., Kobayashi, T., Wermeling, F. & Ravetch, J. V. Intravenous gammaglobulin suppresses inflammation through a novel T(H)2 pathway. Nature 475, 110-113 (2011). https://doi.org:10.1038/nature10134

6 Anthony, R. M. et al. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. Science 320, 373-376 (2008). https://doi.org:10.1126/science.1154315

7 Archer, E. J., Gonzalez, J. C., Ghosh, D., Mellins, E. D. & Wang, T. T. Harnessing IgG Fc glycosylation for clinical benefit. Current opinion in immunology 77, 102231 (2022). https://doi.org:10.1016/j.coi.2022.102231

8 Kaneko, Y., Nimmerjahn, F. & Ravetch, J. V. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science 313, 670-673 (2006). https://doi.org:10.1126/science.1129594

9 Smith, P., DiLillo, D. J., Bournazos, S., Li, F. & Ravetch, J. V. Mouse model recapitulating human Fcgamma receptor structural and functional diversity. Proceedings of the National Academy of Sciences of the United States of America 109, 6181-6186 (2012). https://doi.org:10.1073/pnas.1203954109

10 Li, T. et al. Modulating IgG effector function by Fc glycan engineering. Proceedings of the National Academy of Sciences of the United States of America 114, 3485-3490 (2017). https://doi.org:10.1073/pnas.1702173114

11 Krapp, S., Mimura, Y., Jefferis, R., Huber, R. & Sondermann, P. Structural analysis of human IgG-Fc glycoforms reveals a correlation between glycosylation and

structural integrity. Journal of molecular biology 325, 979-989 (2003). https://doi.org:10.1016/s0022-2836(02)01250-0

12 Mimura, Y. et al. Role of oligosaccharide residues of IgG1-Fc in Fc gamma RIIb binding. The Journal of biological chemistry 276, 45539-45547 (2001). https://doi.org:10.1074/jbc.M107478200

13 Ferrara, C., Stuart, F., Sondermann, P., Brunker, P. & Umana, P. The carbohydrate at FcgammaRIIIa Asn-162. An element required for high affinity binding to non-fucosylated IgG glycoforms. The Journal of biological chemistry 281, 5032-5036 (2006). https://doi.org:10.1074/jbc.M510171200

14 Wang, T. T. IgG Fc Glycosylation in Human Immunity. Curr Top Microbiol Immunol 423, 63-75 (2019). https://doi.org:10.1007/82_2019_152

15 Okazaki, A. et al. Fucose depletion from human IgG1 oligosaccharide enhances binding enthalpy and association rate between IgG1 and FcgammaRIIIa. Journal of molecular biology 336, 1239-1249 (2004). https://doi.org:10.1016/j.jmb.2004.01.007

16 Shields, R. L. et al. Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. The Journal of biological chemistry 277, 26733-26740 (2002). https://doi.org:10.1074/jbc.M202069200

17 Umana, P., Jean-Mairet, J., Moudry, R., Amstutz, H. & Bailey, J. E. Engineered glycoforms of an antineuroblastoma IgG1 with optimized antibody-dependent cellular cytotoxic activity. Nature biotechnology 17, 176-180 (1999). https://doi.org:10.1038/6179

18 Chakraborty, S. et al. Proinflammatory IgG Fc structures in patients with severe COVID-19. Nature immunology 22, 67-73 (2021). https://doi.org:10.1038/s41590-020-00828-7

19 Chakraborty, S. et al. Early non-neutralizing, afucosylated antibody responses are associated with COVID-19 severity. Sci Transl Med, eabm7853 (2022). https://doi.org:10.1126/scitranslmed.abm7853

20 Gonzalez, J. C., Chakraborty, S., Thulin, N. K. & Wang, T. T. Heterogeneity in IgG-CD16 signaling in infectious disease outcomes. Immunol Rev 309, 64-74 (2022). https://doi.org:10.1111/imr.13109

21 Sondermann, P., Pincetic, A., Maamary, J., Lammens, K. & Ravetch, J. V. General mechanism for modulating immunoglobulin effector function. Proceedings of

the National Academy of Sciences of the United States of America 110, 9868-9872 (2013). https://doi.org:10.1073/pnas.1307864110

22 Fiebiger, B. M., Maamary, J., Pincetic, A. & Ravetch, J. V. Protection in antibody- and T cell-mediated autoimmune diseases by antiinflammatory IgG Fcs requires type II FcRs. Proc Natl Acad Sci U S A 112, E2385-2394 (2015). https://doi.org:10.1073/pnas.1505292112

23 Bournazos, S. et al. Antibody fucosylation predicts disease severity in secondary dengue infection. Science 372, 1102-1105 (2021). https://doi.org:10.1126/science.abc7303

24 Larsen, M. D. et al. Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Science 371 (2021). https://doi.org:10.1126/science.abc8378

25 Thulin, N. K. et al. Maternal Anti-Dengue IgG Fucosylation Predicts Susceptibility to Dengue Disease in Infants. Cell Rep 31, 107642 (2020). https://doi.org:10.1016/j.celrep.2020.107642

26 Wang, T. T. et al. IgG antibodies to dengue enhanced for FcgammaRIIIA binding determine disease severity. Science 355, 395-398 (2017). https://doi.org:10.1126/science.aai8128

27 McCormick, T. S., Hejal, R. B., Leal, L. O. & Ghannoum, M. A. GM-CSF: Orchestrating the Pulmonary Response to Infection. Front Pharmacol 12, 735443 (2021). https://doi.org:10.3389/fphar.2021.735443

28 Antoniak, S. et al. PAR1 regulation of CXCL1 expression and neutrophil recruitment to the lung in mice infected with influenza A virus. J Thromb Haemost 19, 1103-1111 (2021). https://doi.org:10.1111/jth.15221

29 De Filippo, K. et al. Mast cell and macrophage chemokines CXCL1/CXCL2 control the early stage of neutrophil recruitment during tissue inflammation. Blood 121, 4930-4937 (2013). https://doi.org:10.1182/blood-2013-02-486217

30 Ichikawa, A. et al. CXCL10-CXCR3 enhances the development of neutrophil-mediated fulminant lung injury of viral and nonviral origin. Am J Respir Crit Care Med 187, 65-77 (2013). https://doi.org:10.1164/rccm.201203-0508OC

31 Pincetic, A. et al. Type I and type II Fc receptors regulate innate and adaptive immunity. Nature immunology 15, 707-716 (2014). https://doi.org:10.1038/ni.2939

32 Cox, N., Pilling, D. & Gomer, R. H. DC-SIGN activation mediates the differential effects of SAP and CRP on the innate immune system and inhibits fibrosis

in mice. Proc Natl Acad Sci U S A 112, 8385-8390 (2015). https://doi.org:10.1073/pnas.1500956112

33 Iwasaki, A. & Pillai, P. S. Innate immunity to influenza virus infection. Nat Rev Immunol 14, 315-328 (2014). https://doi.org:10.1038/nri3665

34 van Osch, T. L. J. et al. Fc Galactosylation Promotes Hexamerization of Human IgG1, Leading to Enhanced Classical Complement Activation. J Immunol 207, 1545-1554 (2021). https://doi.org:10.4049/jimmunol.2100399

35 Quast, I. et al. Sialylation of IgG Fc domain impairs complement-dependent cytotoxicity. J Clin Invest 125, 4160-4170 (2015). https://doi.org:10.1172/JCI82695

36 Dekkers, G. et al. Decoding the Human Immunoglobulin G-Glycan Repertoire Reveals a Spectrum of Fc-Receptor- and Complement-Mediated-Effector Activities. Front Immunol 8, 877 (2017). https://doi.org:10.3389/fimmu.2017.00877

37 Monsalvo, A. C. et al. Severe pandemic 2009 H1N1 influenza disease due to pathogenic immune complexes. Nat Med 17, 195-199 (2011). https://doi.org:10.1038/nm.2262

38 Diebolder, C. A. et al. Complement is activated by IgG hexamers assembled at the cell surface. Science 343, 1260-1263 (2014). https://doi.org:10.1126/science.1248943

39 Shi, X. et al. Inhibition of the inflammatory cytokine tumor necrosis factor-alpha with etanercept provides protection against lethal H1N1 influenza infection in mice. Crit Care 17, R301 (2013). https://doi.org:10.1186/cc13171

40 Yamaya, M. et al. Magnitude of influenza virus replication and cell damage is associated with interleukin-6 production in primary cultures of human tracheal epithelium. Respir Physiol Neurobiol 202, 16-23 (2014). https://doi.org:10.1016/j.resp.2014.07.010

41 Zhang, J. et al. Interleukin-6 and granulocyte colony-stimulating factor as predictors of the prognosis of influenza-associated pneumonia. BMC Infect Dis 22, 343 (2022). https://doi.org:10.1186/s12879-022-07321-6

42 Sever-Chroneos, Z. et al. GM-CSF modulates pulmonary resistance to influenza A infection. Antiviral Res 92, 319-328 (2011). https://doi.org:10.1016/j.antiviral.2011.08.022

43 Botelho, F. M. et al. IL-1alpha/IL-1R1 expression in chronic obstructive pulmonary disease and mechanistic relevance to smoke-induced neutrophilia in mice. PLoS One 6, e28457 (2011). https://doi.org:10.1371/journal.pone.0028457

44 Denney, L., Branchett, W., Gregory, L. G., Oliver, R. A. & Lloyd, C. M. Epithelial-derived TGF-beta1 acts as a pro-viral factor in the lung during influenza A infection. Mucosal Immunol 11, 523-535 (2018). https://doi.org:10.1038/mi.2017.77

45 Bradley, L. M., Douglass, M. F., Chatterjee, D., Akira, S. & Baaten, B. J. Matrix metalloprotease 9 mediates neutrophil migration into the airways in response to influenza virus-induced toll-like receptor signaling. PLoS Pathog 8, e1002641 (2012). https://doi.org:10.1371/journal.ppat.1002641

46 Narayana Moorthy, A. et al. In vivo and in vitro studies on the roles of neutrophil extracellular traps during secondary pneumococcal pneumonia after primary pulmonary influenza infection. Front Immunol 4, 56 (2013). https://doi.org:10.3389/fimmu.2013.00056

47 Kulkarni, U. et al. Excessive neutrophil levels in the lung underlie the age-associated increase in influenza mortality. Mucosal Immunol 12, 545-554 (2019). https://doi.org:10.1038/s41385-018-0115-3

48 Bendib, I. et al. Neutrophil Extracellular Traps Are Elevated in Patients with Pneumonia-related Acute Respiratory Distress Syndrome. Anesthesiology 130, 581-591 (2019). https://doi.org:10.1097/ALN.0000000000002619

49 Wang, T. T. et al. Anti-HA Glycoforms Drive B Cell Affinity Selection and Determine Influenza Vaccine Efficacy. Cell 162, 160-169 (2015). https://doi.org:10.1016/j.cell.2015.06.026

50 Sievers, B. L. et al. Antibodies elicited by SARS-CoV-2 infection or mRNA vaccines have reduced neutralizing activity against Beta and Omicron pseudoviruses. Sci Transl Med 14, eabn7842 (2022). https://doi.org:10.1126/scitranslmed.abn7842

51 Chakraborty, S., et al., Early non-neutralizing, afucosylated antibody responses are associated with COVID-19 severity. Sci Transl Med, 2022: p. eabm7853.

52 Soilleux, E.J., et al., Constitutive and induced expression of DC-SIGN on dendritic cell and macrophage subpopulations in situ and in vitro. J Leukoc Biol, 2002. **71**(3): p. 445-57.

53 Bruggeman, C.W., et al., Tissue-specific expression of IgG receptors by human macrophages ex vivo. PLoS One, 2019. **14**(10): p. e0223264.

54 Cox, N., D. Pilling, and R.H. Gomer, DC-SIGN activation mediates the differential effects of SAP and CRP on the innate immune system and inhibits fibrosis in mice. Proc Natl Acad Sci U S A, 2015. **112**(27): p. 8385-90.

6.2 EXAMPLE 2: SIALYLATED IGG-INDUCED RE1-SILENCING TRANSCRIPTION FACTOR (REST) PROTECTS AGAINST LUNG INFLAMMATION AND SEVERE INFLUENZA DISEASE

[00311] While most respiratory viral infections resolve with little harm to the host, severe symptoms arise when infection triggers an aberrant inflammatory response that damages lung tissue. Host regulators of virally-induced lung inflammation have not been well defined. This Example shows that enrichment for sialylated, but not asialylated IgG, predicts mild influenza disease in humans and is broadly protective against heterologous influenza viruses in a murine challenge model. Mechanistic studies show that sialylated IgG protects by inducing REST which represses NF-κB -driven responses, preventing severe lung inflammation and protecting lung function during influenza infection. Therapeutic administration of a recombinant, sialylated Fc molecule in clinical development similarly activates REST and protects against severe influenza disease demonstrating that this pathway can be clinically harnessed. Overall, induction of REST through sialylated IgG signaling is a strategy to limit inflammatory disease sequelae in infections caused by antigenically distinct influenza strains.

6.2.1 Introduction

[00312] Influenza viruses are important human pathogens that cause annual epidemics as well as pandemic-scale disease with some regularity. Seasonal influenza virus epidemics are estimated to cause 2–5 million cases of severe illness and up to 650,000 deaths per year worldwide[1]. Humans and some avian species are the major reservoirs for influenza A viruses which generally exhibit restriction to either human or avian hosts. Yet additional mammalian hosts such as swine and cattle can act as intermediate hosts, able to be infected by strains that come from both humans and avian species[2,3]. Co-infection events are particularly high risk for emergence of new virus strains that are immunologically novel to humans, with potential to cause pandemic disease. Thus, influenza viruses represent a serious public health concern with a substantial seasonal impact on the global economy and they pose an ongoing threat for pandemic human disease. New prophylactic and therapeutic treatment strategies are needed to combat influenza disease, especially broad strategies that are unimpacted by antigenic change and viral escape.

[00313] IgG antibodies are produced upon influenza virus infection or vaccination and titers of neutralizing anti-influenza IgGs are a principal correlate of protection[4,5]. Aside from neutralizing activity of IgG, anti-influenza Fc effector functions exhibit considerable heterogeneity among people[6]. How naturally produced anti-influenza Fc domain repertoires

impact protection against influenza disease is not well understood[7]. A central mechanism for regulating IgG effector functions is through Fc glycosylation which determines binding to different Type I or Type II Fc gamma receptors (FcγRs) (FIG. 19A)[8,9]. For example, an absence of core fucose (afucosylation), confers a specific high affinity interaction with the activating Fc receptor CD16a to enhance effector functions such as cytotoxicity and pro-inflammatory cytokine and chemokine production[10-12]. In contrast, the presence of terminal sialic acid and core fucose on the Fc glycan converts IgG1 to anti-inflammatory molecules with therapeutic activity established in some autoimmune diseases[13-15].

[00314] While the role of endogenously produced anti-influenza IgG effector functions has not been fully defined in influenza immunity, prior work has shown an important role for activating IgG-FcγR interactions in limiting virus replication during infection[16,17]. Yet severe influenza disease is driven by both unchecked virus replication together with an aberrant host inflammatory response that damages lung tissue[18-21]. Whether FcγR pathways can be harnessed to prevent a detrimental inflammatory response, independent of targeting viral replication, is not known[22].

[00315] How Fc glycosylation on endogenously produced anti-influenza IgG impacts influenza immunity is addressed in this Example. To do this, Fc glycans on anti-hemagglutinin (HA) IgGs from people with mild or severe influenza virus infections were initially profiled and it was found that patients with mild disease had a specific enrichment for sialylated Fc domains. In a murine model expressing human, but not murine, FcγRs[23], it was found that enrichment for sialylated human IgG protects against influenza disease by limiting virus-induced lung inflammation without impacting virus replication. Subsequent experiments led to the identification of the mechanism by which sialylated IgG Fc domains mediate protection during influenza infection. Specifically, enrichment of sialylated Fc induces REST in alveolar macrophage, which are sentinel cells for sensing both IgG and influenza viruses in the airways and lung[17]. REST, also known as neuron-restrictive silencing factor (NRSF), has been investigated principally within the context of neurogenesis[24-28]; regulation of REST by antibody signaling or a function in controlling lung inflammation have not been previously established. This Example shows that induction of REST represses NF-κB-mediated inflammatory responses and is required for sialylated IgG-mediated protection against influenza disease *in vivo*. These findings point to a novel strategy that can be harnessed therapeutically to treat influenza disease by targeting the inflammatory response via sialylated IgG Fc. Finally, therapeutic treatment with a sialylated Fc molecule that is

currently in clinical development was protective against influenza disease in a murine model, highlighting its potential as a virus strain-agnostic therapeutic.

6.2.2 Results

[00316] Level of IgG sialylation predicts the severity of influenza disease

[00317] Bronchoalveolar lavage fluid (BALF) from subjects hospitalized with influenza virus infection (n=8) contains anti-HA IgG, supporting the role of airway IgG in regulating lung inflammation during infection (FIG. 19B). Whether any anti-HA IgG Fc glycoforms correlated with clinical outcomes in a cohort of 26 patients with influenza virus infections was first assessed. Study participants had laboratory-confirmed H1N1 infections in 2019 (2009 pandemic-like strain) and varying disease severities during infection. Ten patients in the cohort required hospitalization, whereas the others had mild symptoms, enabling a comparison of antibody glycosylation and disease severity (Table 5). Overall, only di-galactosylated, sialylated Fc (G2FS) glycoforms distinguished patients with severe (hospitalized) and mild (outpatient) disease on anti-HA IgG purified from patient sera with these sialylated glycans being reduced in people who developed severe influenza disease (FIG. 13A). The abundance of G2FS glycans on anti-HA IgG was a strong predictor of disease severity (AUC) of 0.89 [95% confidence interval of (0.75-1)] (FIG. 13B). The distribution of all other glycans profiled and neutralizing titers against a contemporary HA from A/Hawaii/70/2019 (pandemic-like H1N1) were equivalent between people with mild and severe disease (FIG. 19C). As sialylation was the only glycoform that separated severe and mild cases of influenza infection, it was hypothesized that IgG sialylation has protective activity against influenza disease.

Table 5: Influenza patient cohort clinical characteristics

	Influenza Patients (N = 26)
Age [Median (IQR)]	50.5 (44.5- 60.75)
Sex [Percent; (N)]	
Female	38.5% (10)
Male	61.5% (16)
Hospitalizations [Percent; (N)]	38.5% (10)
Vaccinated for Influenza [Percent; (N)]	34.6 (9)
Comorbidities [Percent; (N)]	
Diabetes	7.7% (2)
Chronic neurological disease	3.8% (1)
Chronic renal failure	0% (0), NA= 1
Ischemic heart disease	11.5% (3)

COPD	19.2% (5)
Previous Stroke	0% (0)
Smoker	
Current	42.3% (11)
Ex	11.5% (3)
Never	42.3% (11)
E-cigarettes	3.9% (1)
Fever [Percent; (N)]	100% (26)
Fever Temperature [Median (IQR)]	101.84° F (100. 76° F - 102.2° F)
Nose Symptoms [Percent; (N)]	50.0% (13)
Throat Symptoms [Percent; (N)]	46.2% (12)
Headache [Percent; (N)]	61.5% (16)
Nausea/Vomiting [Percent; (N)]	23.1% (6)
Weakness [Percent; (N)]	96.2% (25)
Arthralgia [Percent; (N)]	61.5% (16)
Myalgia [Percent; (N)]	57.7% (15)

[00318] Sialylated IgG is protective against lethal influenza infection with antigenically divergent strains

[00319] Whether sialylation of IgG might impact influenza virus infection or disease was probed next. To do this, an experimental model was developed that evaluated the effect of the preexisting IgG with low or high Fc sialylation on influenza virus infection outcomes. To prepare sialylated and asialylated IgG, purified, pooled human IgG (hIgG) was enzymatically modified to remove sialic acids (asialylated hIgG) or to enrich for a2-6 sialylation (sialylated hIgG), the predominant sialic acid linkage in humans (FIG. 20A). Sialylated hIgG preparations contained 21-26% Fc sialylation, a physiologic level of IgG1 sialylation that is found in younger adults and that declined with age in two independent cohorts studied (FIG. 20B). No sialylation was detected in asialylated preparations by mass spectrometry (FIG. 20C). All preparations had similar size exclusion profiles (FIG. 20D) demonstrating that Fc sialylation did not impact aggregation of IgG. Because sialoglycans are receptors for influenza viruses, it was assessed whether modifying hIgG sialylation impacted its neutralizing potency. While the hIgG contained neutralizing activity against two antigenically distinct influenza virus strains, A/Netherlands/10/2009 (H1N1) and A/X-31 (H3N2), the inhibitory potency was not impacted by the level of Fc sialyation (FIG. 20E).

[00320] To test whether sialylation of IgG impacted influenza virus disease, hFcγR mice were administered a single dose of hIgG (sialylated or asialylated) prior to challenge with five times the 50% lethal dose ($5LD_{50}$) of A/Netherlands/10/2009 (H1N1) or A/X-31 (H3N2)

virus strains (FIG. 13C). Mice that received sialylated hIgG exhibited delayed weight loss and enhanced survival compared to those given asialylated hIgG in both the H1N1 and H3N2 challenge systems (FIGS. 13D and 13E). To test whether protection was associated with a difference in transfer efficiency of the IgG to the lung mucosa based on sialylation status, levels of hIgG in BALF on day 7 post infection were measured; equivalent levels of sialylated and asialylated IgG were observed between groups (FIG. 20F). Next, to ascertain whether sialylation of hIgG was associated with a difference in virus replication, lung titers were measured on day 4 and/or 7 post infection; these also were similar between the two groups at both timepoints (FIGS. 13F and 13G). These data support a mechanism of protection against diverse strains of influenza disease that is decoupled from viral load.

[00321] While antibody signaling via CD209b has not been shown to protect against any infectious disease, it was hypothesized that CD209b might be a relevant receptor since it can preferentially bind sialylated IgG and has anti-inflammatory activity in some autoimmune settings. To test for a requirement of CD209b, mice were administered sialylated hIgG in addition to receiving a CD209b blocking antibody or an isotype control in the H1N1 challenge model. Blocking CD209b significantly reduced the protective effect of sialylated hIgG, whereas blocking CD209b alone or administration of an isotype control did not affect survival (FIG. 13H).

[00322] **Sialylated IgG reduces lung inflammation and protects lung function**

[00323] Severe influenza disease is marked by excessive inflammation that ultimately compromises lung function [18-20,29]. To investigate whether sialylated IgG may protect against severe influenza disease by modulating lung inflammation, measurements of cells were performed in the whole lung and cells and soluble factors in BAL fluid from influenza-infected mice. On day 4 after infection, mice that received sialylated hIgG had reduced neutrophils and increased alveolar macrophage relative to those that received the virus alone (FIG. 14A). The abundances of other cell types studied from whole lung were not different between groups. Neutrophils were also suppressed in the BAL fluid of mice that received sialylated hIgG relative to the virus alone group (FIG. 14B, left panel; FIG. 21A). Numerous inflammatory cytokines and chemokines were also significantly suppressed by sialylated hIgG relative to virus infection alone demonstrating suppression of the virally-induced inflammatory lung response (FIG. 14C, top panel). By day 7, nearly all mice that received virus alone had succumbed to infection but those that received sialylated hIgG had significantly lower neutrophil and monocyte counts (FIG. 14B, right panel) and suppressed production of inflammatory factors in BAL fluid relative to mice that received asialylated

hIgG (FIG. 14C, bottom panel). As disease is a function of tissue health, whether suppression of the inflammatory pathways by sialylated hIgG was associated with improved lung function was determined. Blood gas measurements on day 5 showed that the sialylated hIgG treatment, but not asialylated hIgG, was associated with increased blood O_2 levels and decreased CO_2 levels, supporting a role for sialylated hIgG in preserving tissue function and gas exchange during infection (FIG. 14D). Based on these observations, sialylated IgG appeared to protect against severe influenza disease by blocking the inflammatory response to the virus and protecting lung function.

[00324] Sialylated hIgG remodels the transcriptional signature of Amφ and predicts disease severity of influenza patients

[00325] To begin to probe the mechanism by which sialylated IgG protects against influenza disease, it was studied how the presence of sialylated IgG during infection impacted the transcriptional program of alveolar macrophage (Amφ), sentinel cells in the airway that are sensors for both influenza viruses and they express FcγRs to detect IgGs. Amφ were harvested from mice on day 4 post-infection (FIG. 21A). Amφ were one of the dominant FcγR-expressing immune cells in the lungs of hFcγR mice and expressed both CD16 and CD209b, the receptors for afucosylated and sialylated IgGs, respectively (FIG. 21B)[30,31]. Amφ from the sialylated IgG receiving group showed a unique transcriptional signature relative to Amφ from mice that received asialylated IgG or the virus alone group. Notably, the presence of sialylated IgG during infection led to suppression of transcription of several NF-κB associated genes (Relb, Junb, Nfkbie and Tnf) and of the "TNFa signaling via NF-κB" and "Cytokine signaling in immune system" pathways. No significant differentially expressed genes (DEGs) were observed between the asialylated IgG and virus alone groups (FIGS. 15A and 22A). Principal component analysis confirmed distinct transcriptional profiles in Amφ from mice that received sialylated hIgG, as compared to mice that received asialylated IgG or virus alone which showed overlapping transcriptional profiles (FIGS. 15A-15C, 22C-22D).

[00326] DEGs associated with the presence of sialylated IgG when compared to asialylated IgG and the virus only group were defined as the "sialylated IgG gene signature" (FIG. 22B). Whether this signature was relevant to human influenza disease was next assessed. Twelve (12) publicly available datasets from human PBMC composed of 328 samples (155 non-hospitalized, 173 hospitalized) from patients across 8 countries infected with influenza virus were identified (see Methods). The sialylated IgG gene signature identified from hFcγR mice separated hospitalized from non-hospitalized patients with

influenza infections (FIG. 15D). This demonstrated that a common set of genes differentiates mild and severe influenza disease in humans and mild disease associated with sialylated IgG signaling in the humanized mouse model.

[00327] Sialylated IgG blocks NF-κB signaling and induces nuclear REST expression

[00328] Having established that sialylated IgG signaling was associated with blocked transcription of NF-κB-associated genes during influenza infection, it was next assessed how sialylated IgG impacts Amφ in the absence of confounding effects of infection (FIG. 23A and 23B). Using a newly established model that defines the signaling outcomes by distinct human IgG forms in the airway of mice that express humanized FcγRs[32], it was observed that sialylated IgG, relative to asialylated IgG, suppressed expression of transcripts coding for multiple pro-inflammatory factors (*Tnf* and *Il1b*, as well as the neutrophil chemoattractants *Ccl3* and *Ccl4)* and other macrophage activation genes (*e.g.*, *Batf3, Serpina3g, Sdc4, Cd74*) (FIG. 24A). Pathway enrichment analysis revealed that the presence of sialylated IgGs suppressed multiple pathways commonly associated with both innate and adaptive immune functions, with "TNFa signaling via NF-κB" pathway being one of the most significant, consistent with the activity of sialylated IgG in influenza infection system (FIGS. 15C and 24B). In addition, multiple NF-κB regulated genes (FIGS. 24C, 24D and 24F) and NF-κB components themselves were suppressed by Fc sialylation in both murine and human Amφ (FIGS. 16A and 24E), in a CD209b-dependent manner (FIGS. 25A-25G). The CD209b block alone did not have any transcriptional effect on murine AM (FIG. 25B).

[00329] Aside from suppressing NF-κB, sialylated IgGs induced enrichment of REST-associated pathways in murine Amφ and in human monocyte-derived macrophage (MDM). Notably, REST induction was dependent on CD209 expression (FIGS. 16B, 25D-25G). REST has been defined as a transcriptional repressor that suppresses inflammation in neural tissue, among other functions, but a role for REST in the regulation of antibody effector functions or in the regulation of lung inflammation has not been established[33]. Therefore, it was hypothesized that sialylated IgG signaling might inhibit NF-κB-mediated inflammation via induction of REST. In support of this hypothesis, canonical REST-targeting RE-1 transcription factor binding sites were identified within or near multiple NF-κB subunit genes *in silico*[34] (FIG. 27). To test this, it was first assessed whether sialylated IgG modulates REST expression. $CD209^+$ human MDMs were stimulated with IgGs containing 3-27% Fc sialylation. REST was induced by IgG with 27% sialylated Fc but was not appreciably induced at the lower levels of sialylated IgG that were tested. Expression and nuclear localization of REST were positively correlated with the abundance of IgG Fc sialylation

(FIGS. 16C and 16D). Together, these data demonstrate that REST is induced by sialylated IgG Fc in human MDM.

[00330] REST induction by sialylated IgG blocks NF-κB

[00331] To directly test the effect of sialylated IgG and REST on NF-κB, a human NF-κB reporter cell line (THP-1 Blue) was used[35]. THP-1 cells were differentiated and polarized toward $CD209^+$ macrophages and were then treated with sialylated IgG or asialylated control IgG [36]. Sialylated IgG treatment decreased NF-κB reporter activity in response to subsequent stimulation with the common activators of NF-κB, lipopolysaccharide (LPS), TNFα, and IgG immune complexes (FIG. 16E). Decreased NF-κB responsiveness after sialylated IgG treatment was reversed if cells were pretreated with the well-characterized small molecule inhibitor of REST activity, X5050 (FIG. 16E) [37-40]. Together these data showed that sialylated IgG represses NF-κB activity in a REST-dependent manner.

[00332] Next, it was reasoned that induction of REST by sialylated IgG might change the phenotype of Amφ, rendering them less sensitive to activation by triggers of NF-κB. Primary human Amφ were incubated with sialylated or asialylated IgG prior to stimulation with a well-characterized activator of NF-κB responses, afucosylated immune complexes (FIG. 16F). Treatment with sialylated IgG prior to the inflammatory stimulus blocked expression of NF-κB subunit genes (FIG. 16G), reversed multiple DEGs, and induced a negative enrichment of genes associated with the Hallmark pathway "TNFα signaling via NF-κB" (FIGS. 16H, 26A-26E). Notably, treatment of cells with sialylated IgG prior to the inflammatory stimulus rendered their transcriptomes indistinguishable from cells that were stimulated with asialylated IgGs only, demonstrating a complete blunting of the inflammatory response by the presence of sialylated IgG (FIG. 26F). Sialylated IgG further elicited an enrichment of REST target genes and increased whole cell and nuclear REST expression in primary human Amφ, despite subsequent stimulation with afucosylated immune complexes (FIGS. 16H and 26G). Additionally, pretreatment of human Amφ with sialylated IgG suppressed production of NF-κB-regulated factors, including TNFα, IL-6, and IL-1β (FIG. 16I). Collectively, sialylated IgG induced REST in human Amφ and a change in cellular phenotype to one with repressed sensitivity to NF-κB activation.

[00333] The protective activity of sialylated IgG against influenza disease is dependent on REST

[00334] Next, it was hypothesized that depleting REST *in vivo* would diminish the anti-inflammatory activity of sialylated IgG. To test this, the sterile lung model described above was first used. hFcγR mice were administered the REST inhibitor, X5050 or carrier alone

(DMSO), 24 hours before administration of preformed sialylated hIgG immune complexes, or PBS. BALF was collected 4 hours after IgG immune complex administration. This experiment revealed that depletion of REST de-repressed the anti-inflammatory activity of sialylated IgG in the airway evidenced by increased neutrophil recruitment and TNFa levels in X5050-treated animals (FIG. 17A). It was then further assessed whether this REST-dependent phenotype was specific to sialylated IgG signaling by comparing the activity associated with REST depletion after treatment with sialylated or asialylated IgG immune complexes. It was observed that depletion of REST via X5050 administration derepressed the activity of sialylated IgG but not asialylated IgG immune complexes demonstrating specificity of the phenotype (FIG. 17B).

[00335] Finally, the hypothesis that depleting REST *in vivo* would diminish the protective activity of sialylated IgG against influenza disease was tested. To test this, hFcγR mice were administered the REST inhibitor, X5050, along with sialylated hIgG, or X5050 alone in the H1N1 challenge model (FIG. 17C). Administration of X5050 significantly diminished the protective effect of sialylated hIgG whereas inhibiting REST alone during infection did not affect weight loss or survival (FIG. 17D). Together, these data support a model wherein REST induction via CD209 engagement by sialylated IgG renders cells refractory to triggers of NF-κB signaling, resulting in a decreased inflammatory response and protection from sequelae during influenza virus infection (FIG. 17E).

[00336] Recombinant, sialylated Fc molecules induce REST and protect against influenza

[00337] Finally, whether activation of REST by Fc signaling in the absence of any neutralizing activity might be harnessed therapeutically to treat influenza disease was assessed. It was hypothesized that the sialylated Fc domain, alone, might have anti-inflammatory activity. To test this, a Fc molecule that is in clinical development for treatment of some autoimmune diseases was used. The recombinant IgG1 Fc contains ~85% a2-6 sialic acid on the asparagine 297-linked N-glycan in addition to a protein mutation, F241A, which mimics the activity of Fc sialylation[15]. Using this Fc molecule in the human MDM system, an induction and nuclear localization of REST was observed (FIGS. 18A and 18B). Notably, the induction of REST did not require IgG Fab domains or the presence of virus. The activity of the sialylated Fc (S Fc) was next tested *in vivo*. Mice were challenged with A/Netherlands/10/2009, followed by administration of S Fc on days 2, 4 and 6 post-infection (FIG. 18C). Administration of S Fc improved survival and protection was dependent on sialylation of the Fc as asialylated IgG1 Fc did not impact survival following challenge (FIG.

18D). These data show that IgG Fab domains were not required for the sialylated IgG-mediated protection against influenza disease and that sFc alone confers protection via REST induction when administered therapeutically following infection.

[00338] Discussion

[00339] Historically, strategies to combat influenza disease have focused on preventing or reducing viral replication. Described herein is a mechanism for targeting influenza virus disease that is decoupled from virus replication by harnessing an anti-inflammatory IgG-FcγR signaling pathway. The data of this Example show that the presence of IgG enriched in sialylation prior to infection blunted a damaging lung response to influenza viruses, raising the hypothesis that the level of endogenous sialylation on IgG contributes to protection against influenza viruses in humans. Overall, these studies support the induction of REST by antibody signaling as an important parallel strategy to combat influenza viruses, together with approaches aimed at limiting viral replication. This strategy may be particularly important given that it is not impacted by the antigenic evolution of influenza viruses which is a central hurdle in eliciting broad immunity via IgG activities that depend on Fab specificity.

[00340] In prior landmark studies, sialylation of the IgG Fc was identified as the glycoform that confers the anti-inflammatory activity of IVIg. These studies defined a cellular mechanism whereby production of soluble factors by distinct cell populations in response to sialylated IgG results in increased effector macrophage activation thresholds that protect from some autoinflammatory diseases [13,14,42]. The study herein identifies a separate and novel mechanism by which sialylated IgG mediates anti-inflammatory activity that is upstream of this established pathway. How sentinel IgG effector cells integrate signals through the Type II Fc receptor, CD209, to initiate an anti-inflammatory response through induction of REST is described herein. Further, identified herein is a previously unknown function of REST as a transcription factor that blunts responsiveness to activators of NF-κB, such as LPS, afucosylated immune complexes and influenza viruses, exerting broad suppression on NF-κB-mediated activities. These data support a key regulatory role for sialylated IgG in determining inflammatory thresholds of sentinel effector cells.

[00341] Though factors that regulate IgG glycosylation are still not well understood, aging is associated with specific changes including a progressive loss in Fc sialylation[43,44]. In this study, levels of IgG sialylation commonly found in young adults (~25%) were shown to induce REST in innate sentinel cells that orchestrate inflammatory responses and to protect the airways from the inflammatory response triggered during influenza infection. By contrast, low levels of IgG sialylation commonly found in elderly people, did not induce REST. These

observations raise the hypothesis that loss of IgG sialylation may contribute to the persistent, mild inflammation that occurs with age, termed "inflammaging"[45-47] and may contribute to the increased risk for more severe influenza disease that occurs with aging [48-50].

[00342] Finally, this Example demonstrates that the anti-inflammatory pathway described in this study can be harnessed by administering sialylated Fc as a therapeutic treatment for influenza infections. Since recombinant Fc provides protection from disease independent of the infecting influenza virus strain in the murine model, this may be an attractive tool for pandemic preparedness against novel future influenza strains whose identities cannot be predicted ahead of time.

[00343] Materials and Methods

[00344] Healthy and influenza-infected human samples

[00345] Purified IgG were characterized from healthy adults. These samples were collected under a study was conducted at the Rockefeller University Hospital in New York City in accordance with a protocol approved by the Institutional Review Board of Rockefeller University (protocol #TWA-0804), in compliance with guidelines of the International Conference on Harmonization Good Clinical Practice guidelines and was registered on www.clinicaltrials.gov (NCT01967238).

[00346] Samples from influenza virus-infected adults were collected as part of a controlled influenza A virus challenge study have been previously described[51].The study (ClinicalTrials.gov identifier NCT01646138) was approved by the National Institute of Allergy and Infectious Diseases institutional review board and underwent an ethics review by the NIH Department of Bioethics prior to being conducted. Samples from influenza virus-infected adults were also collected from a cohort of patients with confirmed H1N1 influenza A virus infection that were recruited at the 'Sotiria' General Chest Diseases Hospital, University of Athens Medical School, Athens, Greece[52] The study was approved by the institutional review board under protocol number 16707/10-7-18. All participants provided written informed consent. Both studies were conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

[00347] Human IgG Fc glycan analysis

[00348] Methods for relative quantification of Fc glycans and IgG subclasses have been previously described[6]. Briefly, IgG were isolated from serum of influenza patients by Protein G (GE Healthcare) purification. Antigen specific IgG were isolated on N-hydroxysuccinimide agarose resin (Thermo Fisher Scientific, cat. no. 26196) coupled to hemagglutinin (HA) produced in-house. After tryptic digestion of purified IgG bound to HA-

coated beads, nanoscale liquid chromatography coupled to tandem mass spectrometry (nanoLC-MS/MS) analysis for characterization of glycosylation sites was performed on an UltiMate 3000 Nano LC (Dionex) coupled with a hybrid triple quadrupole linear ion trap mass spectrometer, the 4000 QTRAP (SCIEX). MS data acquisition was performed using Analyst 1.6.1 Software (SCIEX) for precursor ion scan–triggered information-dependent acquisition analysis for initial discovery-based identification.

[00349] For quantitative analysis of the glycoforms at the N297 site of IgG1, multiple-reaction monitoring (MRM) analysis for selected target glycopeptides and their glycoforms was applied using the nanoLC-4000 QTRAP platform to the samples, which had been digested with trypsin. The mass/charge ratio (m/z) of four-charged ions for all different glycoforms as Q1 and the fragment ion at m/z 366.1 as Q3 for each of transition pairs were used for the MRM assays. A native IgG tryptic peptide (131-GTLVTVSSASTK-142 (SEQ ID NO:4)) with Q1/Q3 transition pair of 575.9+2/780.4 was used as a reference peptide for normalization. All raw MRM data were processed using MultiQuant 2.1.1 (SCIEX). All MRM peak areas were automatically integrated and inspected manually. In the case where the automatic peak integration by MultiQuant failed, manual integration was performed using the MultiQuant Software.

[00350] **ELISA of bronchoalveolar fluid (BALF) samples from influenza patients**

[00351] Immunolon 2HB round-bottom 96-well plates (Thermo Scientific, cat. no. 3655) were coated with 50 µl of full-length Cal09/HA (produced in-house) at 2 µg ml^{-1} in PBS for 1 h at room temperature (RT) per well followed by blocking for 1 h with 3% non-fat milk in PBS with 0.1% Tween 20 (PBST). BALF were diluted 1:2, and 50 µl of the diluted sample was added to each well and incubated for 2 h at RT. Following primary incubation, 50 µl of horseradish peroxidase (HRP)-conjugated goat anti-human IgG Fab (SouthernBiotech, cat. no. 2048-05) at a dilution of 1:5,000 was added and incubated for 1 h at RT. The plates were developed by adding 50 µl per well of the chromogenic substrate 3,3′,5,5′-tetramethylbenzidine (TMB) solution (Millipore Sigma, cat. no. T8665) and the reaction was stopped with 0.2 N sulfuric acid (Millipore Sigma, cat. no. 30743), and absorbance was measured at 450 nm (SpectraMax iD3, Molecular Devices). The plates were washed five times with PBST between each step, and an additional wash with PBS was completed before developing the plates. Area under curve (AUC) calculation were performed using GraphPad Prism.

[00352] Pseudovirus neutralization assay for influenza patient sera samples

[00353] Vesicular stomatitis virus (VSV)–based green fluorescent protein (GFP)/nanoluciferase-expressing influenza H1 pseudovirus was produced following a protocol described previously[53] VSV-ΔG-GFP/nanoluciferase was a gift from Dr. G. S. Tan (J. Craig Venter Institute). Plasmid encoding the hemagglutinin gene of A/Hawaii/70/2019 were produced in-house by cloning mammalian codon-optimized gene fragments (Integrated DNA Technologies) using Gibson Assembly (New England BioLabs). To perform the neutralization assay, MDCK cells were seeded at a density of 1×10^4 per well in half-area 96-well black opaque plates (Greiner Bio-One) and were grown overnight at 37°C in a 5% CO2 atmosphere. Serum samples were serially diluted using infection medium [Minimum essential medium (MEM, Gibco; cat. no. 11430-030) supplemented with 0.5% bovine serum albumin (Sigma; cat. no. A8412), 0.1% sodium bicarbonate (Gibco; cat. no. 25080-094), 10 mM HEPES (Gibco; cat. no.15630-080), 1% penicillin-streptomycin-glutamine solution, (Gibco, cat. no.10378016), and 1 ug/mL TPCK trypsin in duplicates with a starting concentration of 1:100. Diluted serum samples were then mixed with an equal volume of A/Hawaii/70/2019 pseudovirus particles diluted in infection medium at an amount of 200 to 400 focus-forming units per well, followed by incubation at 37°C for 1 hour. Subsequently, pseudovirus and diluted sera were added onto the monolayers of PBS-washed MDCK cells and incubated at 37°C. 18 hours after incubation, supernatants were removed, cells were washed once with PBS, and nanoluciferase enzymatic activities were measured using the Nano-Glo Luciferase Assay System (Promega, cat. no. N1120) and a SpectraMax iD3 multimode microplate reader. Nonlinear curves and IC50 values were determined using GraphPad Prism.

[00354] Enzymatic modification of hIgG to modulate sialylation

[00355] hIgG (Gammagard) was enzymatically treated to either increase α2-6 sialic acid content (sialylation) or to remove sialic acid (asialylation). For sialylation, 22.2 mM hIgG was incubated in PBS with 1 mM recombinant ST6GAL1 (Sino Biological, cat. no. 11590-H07H or produced in-house) in the presence of 2.5 mM CMP-Sialic Acid (Millipore Sigma, cat. no. 505223) at 37 °C for 48 hours. For asialylation, 150 mM hIgG was incubated in 1x GlycoBuffer with 150000 units of α2-3,6,8 Neuraminidase (New England Biolabs, cat. no. P0722L) at 37 °C for 24 hours. After the enzymatic treatments, the hIgG preparations were purified using Protein G beads (GE Healthcare, cat. no. 17061802) and dialyzed overnight in PBS.

[00356] Lectin-blot and Western-blot

[00357] Unmodified (not treated to enrich or reduce the sialic acid content), sialylated and asialylated hIgG were diluted with sample buffer (Boster, cat. no. AR1112), boiled at 95°C for 10 mins, then loaded to and resolved with any-KDa polyacrylamide gel (Bio-rad, cat. no. 4569033). The proteins were transferred to 0.45 mm PVDF membrane (Thermo Fisher Scientific, cat. no. 88518) followed by blocking with 5% BSA/TBST. For the α2-6 sialylation level, the PVDF was subsequently incubated with biotinylated SNL (Vector Laboratories, B-1305), followed by incubation with IRDye 800CW streptavidin (Li-cor, cat. no. 926-32230). For the human IgG level, as the loading control, the PVDF was incubated with IRDye 800CW Goat anti-Human IgG Antibody (Li-cor, cat. no. 926-32232). The signal intensity was captured with LICOR machine (Li-cor).

[00358] Size exclusion chromatography

[00359] Size exclusion chromatography was performed on AKTA pure 25 (Cytiva Life Sciences) to determine the oligomeric state of the enzymatically modified and wild-type hIgG preparations under non-denaturing conditions at 4° C on a Superdex-200 analytical gel filtration column (Cytiva Life Sciences). For molecular weight estimations, the column was calibrated using broad range molecular weight markers (Bio Rad).

[00360] Virus neutralization assay for hIgG_preparations

[00361] MDCK cells were purchased from ATCC and maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum and 1% Penicillin-Streptomycin at 37° C/5% CO_2. MDCK cells were seeded at 90% confluency in 6-well plates the day prior to infection. Dilutions of virus stocks (A/Netherlands/602/2009 H1N1 and A/X31 H3N2) were prepared in infection media (Gibco Minimum Essential Media, 0.6% BSA, 1% Penicillin-Streptomycin-Glutamine, 0.02 M HEPES, 0.2% sodium bicarbonate, 1mg/ml TPCK trypsin) and were incubated with a dilution series of hIgG preparations (unmodified, S and S0 hIgG) prior to addition to cells. MDCK cells were subsequently incubated with virus or virus in the presence of antibody for 1 hour at 37° C/5% CO_2. After infection, media was removed and MDCK cells were rinsed with PBS, followed by addition of overlay containing 1.2% methylcellulose in infection media. Plates were left undisturbed for 48-72 hours. 4% PFA was then added to the MDCK cells to fix the cells for 30 minutes, followed by removal of overlay media and rinsed with PBST. IAV nucleoprotein antibody (H16) (GeneTex, cat. no. GTX14213) was diluted in staining buffer (0.1% BSA, 0.1% Saponin in PBS) and added to the MDCK cells for 2 hours, followed by rinsing with PBST. Finally, a secondary HRP-anti-mouse IgG antibody (Southern Biotech, cat. no. 1036-05) was

added for 1 hour, followed by rinsing with PBST. TrueBlue Peroxidase substrate (Sera Care, cat. no. 5510-0030) was used to visualize plaques.

[00362] IAV *in vivo* infection study

[00363] Mice at 8-10 weeks of age were used for IAV infection studies. 1 mg of either asialylated or sialylated hIgG were given to mice intraperitoneally at least 2 hours prior to infection. For IAV infection, mice were anesthetized with 90 mg/kg Ketamine (Dechra) and 10 mg/kg Xylazine (Akorn) and inoculated with A/Netherlands/10/2009 H1N1 virus intranasally. The mice were monitored for weight loss daily for 14 consecutive days. Mice that lost more than 15% of their starting body weight were euthanized. For the CD209b blocking experiment, 100 µg CD209b blocking antibody (BioxCell, cat. no. BE0220) or isotype control antibody (BioxCell, cat. no. BE0260) were given intraperitoneally to the infected mice every other day, starting from the day prior to the infection procedure to day 10 of the experiment. For the REST blocking experiment, 10 mg/kg of X5050 (Sigma, stock concentration of 80 mM) or DMSO were given intraperitoneally to the infected mice every other day, starting from the day prior to the infection procedure to day 10 of the experiment.

[00364] Measurement of lung viral titers

[00365] Whole lungs from IAV infected mice were collected in BeadBug homogenizer tubes with 3 mm Zirconium beads (Sigma-Aldrich) in 1 ml of cold DMEM un-supplemented media, followed by homogenization using BeadBug microtube homogenizer (Millipore-Sigma) with 05 cycle, 2500 rpm, 90 seconds settings until homogenized. Homogenates were then spun down at maximum speed for 5 minutes at 4°C, and supernatants were collected and frozen at -80 degrees for assessing viral titers.

[00366] MDCK cells were seeded at 90% confluency in 6-well plates the day prior to infection. Dilution of lung homogenates was prepared in infection media (Gibco Minimum Essential Media, 0.6% BSA, 1% Penicillin-Streptomycin-Glutamine, 0.02 M HEPES, 0.2% sodium bicarbonate, 1 mg/ml TPCK trypsin) and were added directly to cells. MDCK cells were incubated with the homogenates for 1 hour at 37°C/5% CO_2. After infection, media was removed and MDCK cells were rinsed with PBS, followed by addition of overlay containing 1.2% methylcellulose in infection media. Plates were left undisturbed for 48-72 hours. 4% PFA was then added to the MDCK cells to fix the cells for 30 minutes, followed by removal of overlay media and rinsed with PBST. IAV nucleoprotein antibody (H16) (GeneTex) was diluted in staining buffer (0.1% BSA, 0.1% Saponin in PBS) and added to the MDCK cells for 2 hours, followed by rinsing with PBST. Finally, a secondary HRP-anti-mouse IgG

antibody (Southern Biotech) was added for 1 hour, followed by rinsing with PBST. TrueBlue Peroxidase substrate (Sera Care) was used to visualize plaques.

[00367] Immune cells profiling from whole lung or BALF of infected mice

[00368] Mice were euthanized on day 4 and day 7 post-infection and BAL fluid was collected or whole lung was harvested day 4 post-infection. Cells were isolated from whole lung using GentleMACS Tissue Dissociator (Miltenyi Biotech) using manufacturer's protocol or from BAL fluid by centrifugation and were blocked with Human TruStain FcX (BioLegend, cat. no. 422302) to reduce nonspecific binding. Cells from BAL fluid was subsequently stained with combinations of the following cell staining antibodies for 30 min at room temperature: LIVE/DEAD Blue Fixable Dye (Thermo Fisher Scientific, cat. no. L34962), BV650 anti-CD11b (clone M1/70; cat. no. 101259), BV605 anti-CD11c (clone N418; cat. no. 117334), AF700 anti-CD45 (clone I3/2.3; cat. no. 147716), AF488 anti-Ly6C (clone HK1.4; cat. no. 128022), BV711 anti-Ly6G (clone 1A8; cat. no. 127643), BV785 anti-F4/80 (clone BM8; cat. no. 123141) PE anti-Siglec-F (clone S17007L; cat. no. 1555506), BV421 anti-MerTK (clone 2B10C42; cat. no. 151510), and APC/Fire-750 anti–major histocompatibility complex (MHC) II (clone M5/114.15.2; cat. no. 107652). Cells from whole lung subsequently stained with combinations of the following cell staining antibodies for 30 min at room temperature: LIVE/DEAD Aqua Fixable Dye (Thermo Fisher Scientific, cat. no. L34957), BV650 anti-CD11b (clone M1/70; cat. no. 101259), BV605 anti-CD11c (clone N418; cat. no. 117334), AF700 anti-CD45 (clone I3/2.3; cat. no. 147716), AF488 anti-Ly6C (clone HK1.4; cat. no. 128022), BV711 anti-Ly6G (clone 1A8; cat. no. 127643), BV785 anti-F4/80 (clone BM8; cat. no. 123141) PE anti-Siglec-F (clone S17007L; cat. no. 1555506), BV421 anti-MerTK (clone 2B10C42; cat. no. 151510), and APC/Fire-750 anti–major histocompatibility complex (MHC) II (clone M5/114.15.2; cat. no. 107652), APC anti-CD209b (Invitrogen, clone 22D1; cat. no. 50-112-3106), BUV395 anti-CD24 (BD Horizon, clone ML5; cat. no. 566221), BUV805 anti-CD103 (BD Horizon, clone M290; cat. no. 741948), PE-Cy7 anti-CD32b (clone FUN2; cat. no. 303213), PE-Dazzle 594 anti-CD64 (clone 10.1; cat. no. 305031), and BUV615 anti-CD16 (BD Horizon, clone 3G8; cat. no. 751572). Antibodies were purchased from BioLegend unless otherwise noted. Once stained, cells were washed, resuspended in fixation buffer (BioLegend, cat. no. 420801), and acquired using a Cytek Aurora flow cytometer (Cytek). Neutrophils were defined as viable CD45+ Ly6G+ CD11b+ CD11c- leukocytes. Monocytes were defined as viable CD45+ CD11b+ CD11c- Ly6G− Ly6C+ CD3− B220− leukocytes. Alveolar macrophages were defined as viable CD45+ CD11b- CD11c+ Siglec-F+ MerTK+ leukocytes. The FlowJo plugin uniform

manifold approximation and projection (UMAP) was used for dimensionality reduction to visualize Flowjo high-parameter data sets in 2-dimensional space, and the plugin PhenoGraph was used to group data into different unsupervised clusters.

[00369] Quantification of hIgG from BALF by ELISA

[00370] Bronchoalveolar lavage was performed on mice euthanized at day 4 and day 7 post infection. Cell free BAL fluid was used to characterize chemokines, cytokines and hIgG content. For probing the levels of S and S0 hIgG in BAL fluids of mice, total hIgG in the BAL fluid was captured on ELISA plates (Immulon 2 HB, Thermo Fisher Scientific) with human anti-kappa and anti-lambda antibodies (Southern Biotech, cat. no. 9230-01 and 9180-01) and probed 1:5000 diluted horseradish peroxidase–conjugated anti-human IgG secondary antibody (Southern Biotech, cat. no. 2040-05). ELISA plates were developed using 3,3′,5,5′-tetramethylbenzidine substrate solution (MilliporeSigma). The reaction was stopped with 0.2 N sulfuric acid (Sigma-Aldrich), and absorbance was measured at 450 nm (SpectraMax iD3, Molecular Devices). The plates were washed five times with PBST between each step, and an additional wash with PBS was done before developing the plates.

[00371] Cardiac blood collection and blood gas analysis

[00372] Mice were anaesthetized with 90 mg/kg Ketamine (Dechra) and 10 mg/kg Xylazine (Akorn) and positioned in dorsal recumbency. Syringe with a 25-gauge needle was inserted into the thoracic cavity up into the left ventricle of the heart at a slight angle. Cardiac blood was collected by slowly and steady withdrawal of the plunger of the syringe, and blood was transferred into K2EDTA-coated tubes (BD). Blood oxygen and carbon dioxide level were then measured with RAPIDPoint 500 Systems (Siemens-Healthineers).

[00373] BAL cytokine profiling from mouse lung post-infection

[00374] Cell-free BAL fluid was processed within 24 hours of collection to measure cytokine and chemokine content using LEGENDplex bead array kits (BioLegend, cat. nos. 740390 and 740451).

[00375] RNA-seq library preparation, sequencing, and analysis

[00376] Alveolar macrophage were purified from BAL fluid of immune complex-administered FcγR-humanized mice by positive magnetic separation based on MerTK expression (STEMCELL; cat. no. 17684). Amφ purity post-separation was observed to be >95% (FIGS. 23A and 23B). Cells were promptly resuspended in lysis buffer (Takara; cat. no. 635013) supplemented with RNase inhibitor (Takara; cat. no. 2313B) and stored at -80°C until further processing. First-strand cDNA synthesis directly from cells was primed by the 3' SMART-Seq CDS Primer II A and used SMART-Seq v4 Oligonucleotide for template

switching at the 5' end of the transcript. Full length cDNA was synthesized and amplified by LD PCR for 14 cycles using a SMART-Seq v4 Ultra Low Input RNA kit (Takara; cat. no. 634888) followed by the Illumina Nextera XT library preparation kit (cat. no. FC-131-1096) per the manufacturer's protocol. An equal molar amount of tagmented cDNA library from each sample was pooled for sequencing on the Illumina HiSeq 4000 platform at Stanford University Genomics Center. FASTQ files were generated using the bcl2fastq2 Conversion v2.19 tool. Each set of sample sequence data was aligned and normalized using STAR aligner to assemble the mapped reads into mouse transcriptome (mm10). Differential gene expression analysis was conducted using DEseq2[54]. Pathway analysis was conducted using Gene Set Enrichment Analysis (GSEA; UC San Diego & Broad[55]) DEG analysis, secondary analysis, and visualization was performed using R Statistical Software (v.4.2.0; R Core Team 2022) with the additional utilization of factoextra (v.1.0.7; Kassambra and Mundt 2020), EnhancedVolcano (v.1.14.0; Blighe, Rana, and Lewis 2022), and pheatmap (v.1.0.12; Kolde 2019) R packages.

[00377] For the transcriptomic analysis from the influenza disease model, mice were given 1mg of either asialylated or sialylated hIgG through intraperitoneal route 2 hours prior to A/Netherlands/10/2009 H1N1 infection. On day 4 post infection, bronchoalveolar lavage was performed to isolate BAL fluid for FACS of alveolar macrophages (CD11c+SIGLEC-F+MerTK+, FIG. 21A) followed by RNA extraction using RNeasy Micro Kit (Qiagen, cat. no. 74004). For alveolar macrophages transcriptomic analysis, library preparation and sequencing were performed by Novogen company (France). Messenger RNA was purified from the total RNA using poly-T oligo-attached magnetic beads. After fragmentation, cDNA was synthesized for library construction involving end repair, A-tailing, adapter ligation, size selection, amplification, and purification. The library was checked with Qubit and real-time PCR for quantification and bioanalyzer for size distribution detection. Quantified libraries were pooled and sequenced on Illumina platforms, according to effective library concentration and data amount. For bioinformatic analysis, raw reads of fastq format were firstly processed through in-house perl scripts. Clean reads were obtained by removing reads containing adapter, poly-N and low-quality reads. At the same time, Q20, Q30 and GC content of the clean data were calculated for downstream analysis. For reads mapping to the reference genome, index of the reference genome was built using Hisat2 v2.0.5 and paired-end clean 1 reads were aligned to the reference genome using Hisat2 v2.0.5. featureCounts v1.5.0-p3 was used to count the reads numbers mapped to each gene. The expression values were reported in FPKM (Fragments per kilobase per million) units for each gene. Differential

gene expression analysis was performed using DESeq2 Counts were transformed and normalized using a regularized log transformation. Principal component analysis (PCA) was performed using the R statistics package and the PCA plots were calculated using all genes differentially expressed between the samples. Volcano plots were generated using ggplot2. Differentially expressed genes were defined as genes with an adjusted p-value < 0.05 and |fold change| > 1.5. Heatmaps were generated using the heatmap2 package, which clusters based upon Euclidean distances. Gene set enrichment analysis (GSEA) was performed using GSEA v4.3 software. Pathway enrichment analysis and cell type analysis were performed using Metascape analysis.

[00378] Human influenza patient datasets

[00379] Data collection, curation, and co-normalization were performed as previously described[56]. Briefly, the public repository Gene Expression Omnibus (GEO) was searched for transcriptome profiles of peripheral blood samples from patients with viral infection. Twelve datasets were identified, composed of 328 samples (155 non-hospitalized, 173 hospitalized), from patients across 8 countries who were infected with influenza. Overall, these cohorts included a broad spectrum of biological, clinical, and technical heterogeneity represented by blood samples using either microarray or RNA sequencing.

[00380] Microarray datasets were renormalized using standard methods when raw data were available from the GEO database. GC robust multiarray average (gcRMA) were applied to arrays with mismatch probes for Affymetrix arrays. Normal-exponential background correction was used followed by quantile normalization for Illumina, Agilent, GE, and other commercial arrays. Custom arrays were not renormalized and used preprocessed data as made publicly available by the study authors. Microarray probes were mapped in each dataset to Entrez Gene identifiers (IDs) to facilitate integrated analysis. If a probe matched more than one gene, the expression data for that probe was expanded to add one record for each gene. When multiple probes mapped to the same gene within a dataset, a fixed-effect model was applied. Principle component analysis was performed using the sialylated hIgG gene signature identified from hFcγR mice.

[00381] IgG immune complex formation

[00382] Polyclonal IgG was isolated from human serum and pooled based on the individual abundances of afucosylated and sialylated anti-RBD IgG1 as previously described [57]. A portion of the sialylated (S) IgG pool was subsequently incubated with α-2-3,6,8 neuraminidase (New England Biolabs; cat. no. P0720L) per manufacturer's instruction to remove sialic acid and form the asialylated product (S0). 100μg of pooled, purified IgG were

incubated with SARS-CoV-2 spike trimer at a 20:1 molar ratio overnight at 4°C to form immune complexes.

[00383] ***In vivo*** **lung inflammation model**

[00384] All *in vivo* experiments were performed in compliance with federal laws and institutional guidelines and have been approved by the Stanford University Institutional Animal Care and Use Committee (IACUC). Immune complexes were intratracheally or intranasally administered to 8- to 12-week-old, sex-matched, fully FcγR-humanized C57BL/6 mice. In experiments using X5050, X5050 (80mM stock) was diluted in DMSO and was dosed one time at 10 mg/kg 24 hours prior to immune complex administration. Experimental groups were consistently matched for sex and age but otherwise randomized. 4 or 24 hours after immune complex administration, mice were euthanized, and BAL fluid was collected or whole lung was harvested. Immune cells were isolated from within the BAL fluid or whole lung suspension, blocked with Human TruStain FcX (BioLegend, cat. no. 422302) to reduce nonspecific binding and stained with combinations of the following fluorescent antibodies and reagents for 20 min at 4°C: LIVE/DEAD Aqua Fixable Dye (Thermo Fisher Scientific, cat. no. L34957), PerCP-Cy5.5 anti-CD3 (clone 17A2; cat. no. 100218), PerCP-Cy5.5 anti-B220 (clone RA3-682; cat. no. 103236), APC-Fire750 anti-NK-1.1 (clone S17017D; cat. no. 156516), BV650 anti-CD11b (clone M1/70; cat. no. 101259), PE anti-CD11b (clone M1/70; cat. no. 101207), BV605 anti-CD11c (clone N418; cat. no. 117334), AF700 anti-CD45 (clone I3/2.3; cat. no. 147716), APC anti-Ly6C (clone HK1.4; cat. no. 128016), APC-Fire750 anti-Ly6C (clone HK1.4; cat. no. 128046), BV785 anti-Ly6G (clone 1A8; cat. no. 127645), PE anti-myeloid-epithelial-reproductive tyrosine kinase (MerTK) (clone 2B10C42; cat. no. 151506), BV421 anti-MERTK (clone 2B10C42; cat. no. 151510), PE anti-Siglec-F (clone S17007L; cat. no. 1555506), BV650 anti-human CD16 (clone 3G8; cat. no. 302042), APC anti-CD209b (Invitrogen, clone 22D1; cat. no. 50-112-3106), APC/Fire 750 anti–I-A/I-E (clone M5/114.15.2; cat. no. 107652), and/or BV785 anti–I-A/I-E (clone M5/114.15.2; cat. no. 107645) purchased from BioLegend unless otherwise noted. Once stained, cells were washed, resuspended in fixation buffer (BioLegend, cat. no. 420801) and acquired using an Attune NxT flow cytometer (Invitrogen). Neutrophils were defined as viable Ly6G+ CD11b+ leukocytes. Monocytes were defined as viable CD11b+ Ly6C+ Ly6G– leukocytes. Alveolar macrophage were defined as viable CD11blo CD11c+ I-A/I-Elo MerTK+ Siglec-F+ leukocytes. Interstitial macrophage were defined as viable CD11b+ CD11c+ I-A/I-E+ Siglec-F- leukocytes. Dendritic cells were defined as viable CD11c+ I-A/I-E+ CD24+ Siglec-F- leukocytes. Cell-free BAL fluid was stored at 4° C and processed within 24 hours to measure

cytokine and chemokine content using LEGENDplex bead array kits (BioLegend, cat. nos. 740390 and 740451). In CD209b blockade experiments, 100 μg of anti-CD209b mAb (Invitrogen, clone 22D1; cat. no. 50-129-87) or isotype control mAb (Invitrogen, clone eBio299Arm; cat. no. 50-112-9491) was intranasally pre-administered 24 hours prior to immune complex administration, and immune complex administration and BAL were performed as described above[57]. Researchers were blinded to experimental groups and agents throughout these *in vivo* studies.

[00385] Monocyte-derived macrophage

[00386] Monocytes isolated from healthy donor peripheral blood were cultured for 144 hours in complete RPMI-1640 media containing 10% fetal bovine serum (FBS, Hyclone), non-essential amino acids (Gibco), sodium pyruvate (Gibco), and penicillin-streptomycin-glutamine (Gibco) and supplemented with recombinant human macrophage-colony stimulating factor (M-CSF; Peprotech) and IL-4 (Peprotech) to induce expression of CD209[35,58]. FcγR expression was confirmed by flow cytometry using BV421 anti-CD16 (clone 3G8; cat. no. 302038), FITC anti-CD32a (STEMCELL, clone IV.3; cat. no. 60012FI), APC anti-CD32b (clone S18005H; cat. no. 398304), and PerCP-Cy5.5 anti-CD209 (clone 9E9A8; cat. no. 330110) purchased from BioLegend unless noted otherwise. In some experiments, MDMs were transfected with 200 nM of *Cd209*-targeting (Horizon Discovery, cat. no. L-003468-01-0010) or non-targeting control siRNA pools (Horizon Discovery, cat. no. D-001810-10-05) using DharmaFect 3 (Horizon Discovery, cat. no. NC1650394) according to manufacturer recommendations.

[00387] Immunofluorescent staining and confocal microscopy assessment of REST induction and activation by sialylated IgG immune complexes

[00388] Cells were fixed with 4% PFA/PBS for 10 minutes, washed with PBS, quenched in 0.1M glycine (Sigma-Aldrich)/PBS for 10 minutes, washed thrice with PBS, and permeabilized in 0.5% TritonX-100 (Sigma-Aldrich)/PBS for 5 minutes. Following a subsequent PBS wash, cells were blocked in 2% BSA (Sigma-Aldrich)/PBS for 30 minutes and primary stained with rabbit anti-REST (Invitrogen, clone JE32-25) (or rabbit IgG isotype) at 1:100 in blocking solution for one hour. Following three five-minute PBS washes, cells were secondary stained with 1:1000 Hoechst 33342 (Abcam Inc.), 1:400 Alexa Fluor™ 488 phalloidin (Invitrogen), and 1:500 Alexa Fluor™ 647 Goat anti-Rabbit IgG (H+L) (Fisher Scientific, cat. no. A21245,) in blocking solution for one hour. Cells were washed thrice with PBS and coverslips mounted on slides with ProLong®Gold Antifade Reagent (Cell Signaling Technology). Following overnight curing, coverslips were imaged using an

LSM880 inverted, confocal microscope (Zeiss) at the Stanford University Cell Sciences Imaging Core Facility. For each donor and experimental condition, 10 images, each containing 11 1μm Z-slices, were collected at 40x magnification. All steps were performed at RT.

[00389] Analysis and quantification of REST immunofluorescent confocal images

[00390] Using Fiji, the multichannel, Z-sliced image files were separated and sum (REST) or max (Hoechst and phalloidin) Z-projected[59]. Images were subsequently analyzed for REST expression and nuclearization using a custom pipeline in CellProfiler v4.2.5[60]. Briefly, cell nuclei were identified as primary objects based on Hoechst staining, while phalloidin staining was used to identify the cell bodies as secondary objects. The two objects were further linked, allowing automated detection of whole cells, as well as discrimination between cytosolic and nuclear compartments. Background subtraction of REST signal based on isotype staining was performed and relevant measurements were taken, including whole cell REST intensities, nuclear-specific REST intensities, and nuclear REST colocalization. The data were exported to .csv files and statistically analyzed in GraphPad Prism. The presented images were generated by overlaying identified object outlines, namely whole cell and nucleus, onto a REST image.

[00391] Human alveolar macrophage stimulation

[00392] Human Amφ were thawed and immediately cultured in RPMI 1640 complete media containing 10% FBS (Hyclone), non-essential amino acids (Gibco), sodium pyruvate (Gibco), and penicillin-streptomycin-glutamine (Gibco). Cells were cultured overnight with either sialylated (S) or asialylated (S0) pooled patient IgG. The following morning, Amφ were stimulated with immune complexes as described above. 4 hours after stimulation, cells were processed for immunofluorescent staining as described below, processed for subsequent RNA sequencing as described above, or kept in culture for an additional 20 hours. At the end of 24 hours, cell-free supernatant was collected, stored at 4°C, and processed within 24 hours to measure cytokine and chemokine content using LEGENDplex bead array kits (BioLegend, cat. no. 740390).

[00393] Assessment of REST activity on NF-κB reporter cell line

[00394] THP1-Blue NF-κB cells (Invivogen) were cultured in a round-bottom 96-well plate at a cell density of 2e5 cells/mL of complete RPMI 1640 media supplemented with 10% fetal bovine serum (Hyclone), penicillin-streptomycin-glutamine (Gibco), normocin, and blasticidin according to manufacturer recommendations. Cells were differentiated into macrophage with 10ng/mL phorbol 12-myristate 13-acetate (PMA; Thermo Fisher Scientific)

over 24 hours followed by a 24 hour rest period. THP1-derived macrophage were subsequently cultured in complete media containing 20ng/mL recombinant human IL-4 (Peprotech) for an additional 48 hours. CD209 expression was determined by flow cytometry.

[00395] $CD209^+$ THP1-derived macrophage were pretreated with combinations of 50μg/mL sialylated IgG, 50μg/mL neutrally-glycosylated, control IgG, 50μM X5050 (Sigma), or DMSO vehicle control for 24 hours. Cells were subsequently stimulated with 100ng/mL lipopolysaccharide (LPS; eBioscience), 10ng/mL TNFα (Peprotech), or afucosylated IgG-HA immune complexes in fresh, complete media. 24 hours later, supernatant was collected, mixed with QUANTI-Blue solution (Invivogen), and SEAP activity was quantitatively measured using a spectrophotometer at 650nm according to manufacturer instructions. Background signal of pretreated but unstimulated cells was subtracted from measurements of the respectively pretreated and stimulated cells.

[00396] For overexpression, THP1-Blue NF-κB cells were cultured in a round-bottom 96-well plate as described above. Cells were transfected with 100ng/well of either FLAG-tagged REST or empty FLAG control plasmid (Addgene Plasmids #41903 and #12521) using Lipofectamine 3000 (Thermo Fisher Scientific), according to manufacturer instructions. After 48 hours, cells were stimulated with either 100 ng/ml or 10 ng/ml LPS. 24 hours later, supernatant was collected, and SEAP activity quantitatively measured as described above.

[00397] Human IgG1 Fc domains

[00398] Sialylated Fc-F241A was generated by co-expression of human IgG1 Fc-F241A and specific enzymes to facilitate terminal alpha 2,6 sialic acid linkage to the sugar molecule present on ASN297. sFc was confirmed to be ~85% 2,6 sialylated at ASN297 by HILIC-HPLC-FLD glycan analysis.

[00399] Human alveolar macrophage samples

[00400] Human alveolar macrophages from BALF via Washington University: Alveolar macrophages were obtained from healthy human subjects undergoing elective outpatient research bronchoscopy in a prospective interventional study. BALF was centrifuged at 300 x g for 15 minutes at 4°C and pelleted cells were purified over a 30%/40% column before cryopreservation. Research bronchoscopies of healthy human subjects were approved by the Washington University Institutional Review Board (approval #2018-08-115).

[00401] Human alveolar macrophages from BALF via National Jewish Human Lung Tissue Consortium: De-identified human lungs were procured from deceased organ donors by either Donor Alliance (Denver, CO, USA) or the International Institute for the

Advancement of Medicine (Edison, NJ, USA). Donors were non-smokers between 21 and 60 years of age who had no history of lung disease and died of non-pulmonary causes. All donors were ventilated endotracheally for three days or less prior to organ donation. Lung tissues were processed immediately upon receipt and always within 24 hours of death. The right middle lobe of the lung was isolated, a catheter-tip 60 cc syringe was wedged into the lobar bronchus, and lavage with phosphate buffered saline (PBS, Gibco, cat. no. 20012-027) was performed. Lavage cells were rinsed with PBS, filtered through 70 mM strainer (Thermo Fisher Scientific, cat. no. 8-771-2) and banked by freezing in RPMI 1640 media (Corning, cat. no. 17-105-CV) containing 40% v/v fetal bovine serum (FBS, Gemini Bio-Products, cat. no. 100-500) and 10% v/v DMSO (Millipore Sigma, cat. no. 1167431000). Cellular contents isolated from the filtered lung lavage fluid were 90-95% Amφ.

6.2.3 References Cited in Example 6.2

1 WHO. *Influenza (Seasonal)*, <https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)> (2023).

2 Ito, T. *et al.* Molecular basis for the generation in pigs of influenza A viruses with pandemic potential. *J Virol* **72**, 7367-7373, doi:10.1128/JVI.72.9.7367-7373.1998 (1998).

3 Kozlov, M. & Mallapaty, S. Bird flu outbreak in US cows: why scientists are concerned. *Nature* **628**, 484-485, doi:10.1038/d41586-024-01036-1 (2024).

4 Black, S. *et al.* Hemagglutination inhibition antibody titers as a correlate of protection for inactivated influenza vaccines in children. *Pediatr Infect Dis J* **30**, 1081-1085, doi:10.1097/INF.0b013e3182367662 (2011).

5 Bean, R. *et al.* Mucosal correlates of protection after influenza viral challenge of vaccinated and unvaccinated healthy volunteers. *mBio* **15**, e0237223, doi:10.1128/mbio.02372-23 (2024).

6 Wang, T. T. *et al.* Anti-HA Glycoforms Drive B Cell Affinity Selection and Determine Influenza Vaccine Efficacy. *Cell* **162**, 160-169, doi:10.1016/j.cell.2015.06.026 (2015).

7 Thulin, N. K. & Wang, T. T. The Role of Fc Gamma Receptors in Broad Protection against Influenza Viruses. *Vaccines (Basel)* **6**, doi:10.3390/vaccines6030036 (2018).

8 Pincetic, A. *et al.* Type I and type II Fc receptors regulate innate and adaptive immunity. *Nature immunology* **15**, 707-716, doi:10.1038/ni.2939 (2014).

9 Wang, T. T. IgG Fc Glycosylation in Human Immunity. *Current topics in microbiology and immunology*, doi:10.1007/82_2019_152 (2019).

10 Shields, R. L. *et al.* Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. *The Journal of biological chemistry* **277**, 26733-26740, doi:10.1074/jbc.M202069200 (2002).

11 Umana, P., Jean-Mairet, J., Moudry, R., Amstutz, H. & Bailey, J. E. Engineered glycoforms of an antineuroblastoma IgG1 with optimized antibody-dependent cellular cytotoxic activity. *Nature biotechnology* **17**, 176-180, doi:10.1038/6179 (1999).

12 Gonzalez, J. C., Chakraborty, S., Thulin, N. K. & Wang, T. T. Heterogeneity in IgG-CD16 signaling in infectious disease outcomes. *Immunological reviews* **309**, 64-74, doi:10.1111/imr.13109 (2022).

13 Kaneko, Y., Nimmerjahn, F. & Ravetch, J. V. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science* **313**, 670-673, doi:10.1126/science.1129594 (2006).

14 Anthony, R. M., Kobayashi, T., Wermeling, F. & Ravetch, J. V. Intravenous gammaglobulin suppresses inflammation through a novel T(H)2 pathway. *Nature* **475**, 110-113, doi:10.1038/nature10134 (2011).

15 Fiebiger, B. M., Maamary, J., Pincetic, A. & Ravetch, J. V. Protection in antibody- and T cell-mediated autoimmune diseases by antiinflammatory IgG Fcs requires type II FcRs. *Proceedings of the National Academy of Sciences of the United States of America* **112**, E2385-2394, doi:10.1073/pnas.1505292112 (2015).

16 DiLillo, D. J., Palese, P., Wilson, P. C. & Ravetch, J. V. Broadly neutralizing anti-influenza antibodies require Fc receptor engagement for in vivo protection. *The Journal of clinical investigation* **126**, 605-610, doi:10.1172/JCI84428 (2016).

17 He, W. *et al.* Alveolar macrophages are critical for broadly-reactive antibody-mediated protection against influenza A virus in mice. *Nat Commun* **8**, 846, doi:10.1038/s41467-017-00928-3 (2017).

18 Kalil, A. C. & Thomas, P. G. Influenza virus-related critical illness: pathophysiology and epidemiology. *Crit Care* **23**, 258, doi:10.1186/s13054-019-2539-x (2019).

19 Fukuyama, S. & Kawaoka, Y. The pathogenesis of influenza virus infections: the contributions of virus and host factors. *Current opinion in immunology* **23**, 481-486, doi:10.1016/j.coi.2011.07.016 (2011).

20 Gill, J. R. *et al.* Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. *Arch Pathol Lab Med* **134**, 235-243, doi:10.5858/134.2.235 (2010).

21 Heaton, N. S. *et al.* Long-term survival of influenza virus infected club cells drives immunopathology. *J Exp Med* **211**, 1707-1714, doi:10.1084/jem.20140488 (2014).

22 Wang, T. T., Bournazos, S. & Ravetch, J. V. Immunological responses to influenza vaccination: lessons for improving vaccine efficacy. *Current opinion in immunology* **53**, 124-129, doi:10.1016/j.coi.2018.04.026 (2018).

23 Smith, P., DiLillo, D. J., Bournazos, S., Li, F. & Ravetch, J. V. Mouse model recapitulating human Fcgamma receptor structural and functional diversity. *Proceedings of the National Academy of Sciences of the United States of America* **109**, 6181-6186, doi:10.1073/pnas.1203954109 (2012).

24 Yu, T. *et al.* Repressor Element 1 Silencing Transcription Factor (REST) Governs Microglia-Like BV2 Cell Migration via Progranulin (PGRN). *Neural Plast* **2020**, 8855822, doi:10.1155/2020/8855822 (2020).

25 Zuccato, C. *et al.* Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nat Genet* **35**, 76-83, doi:10.1038/ng1219 (2003).

26 Yu, H. B., Johnson, R., Kunarso, G. & Stanton, L. W. Coassembly of REST and its cofactors at sites of gene repression in embryonic stem cells. *Genome Res* **21**, 1284-1293, doi:10.1101/gr.114488.110 (2011).

27 Hwang, J. Y. & Zukin, R. S. REST, a master transcriptional regulator in neurodegenerative disease. *Curr Opin Neurobiol* **48**, 193-200, doi:10.1016/j.conb.2017.12.008 (2018).

28 McGann, J. C. *et al.* The Genome-Wide Binding Profile for Human RE1 Silencing Transcription Factor Unveils a Unique Genetic Circuitry in Hippocampus. *J Neurosci* **41**, 6582-6595, doi:10.1523/JNEUROSCI.2059-20.2021 (2021).

29 Galani, I. E. *et al.* Interferon-lambda Mediates Non-redundant Front-Line Antiviral Protection against Influenza Virus Infection without Compromising Host Fitness. *Immunity* **46**, 875-890 e876, doi:10.1016/j.immuni.2017.04.025 (2017).

30 Tailleux, L. *et al.* DC-SIGN induction in alveolar macrophages defines privileged target host cells for mycobacteria in patients with tuberculosis. *PLoS Med* **2**, e381, doi:10.1371/journal.pmed.0020381 (2005).

31 Hoepel, W. *et al.* High titers and low fucosylation of early human anti-SARS-CoV-2 IgG promote inflammation by alveolar macrophages. *Sci Transl Med* **13**, doi:10.1126/scitranslmed.abf8654 (2021).

32 Chakraborty, S. *et al.* Early non-neutralizing, afucosylated antibody responses are associated with COVID-19 severity. *Sci Transl Med*, eabm7853, doi:10.1126/scitranslmed.abm7853 (2022).

33 Jin, L., Liu, Y., Wu, Y., Huang, Y. & Zhang, D. REST Is Not Resting: REST/NRSF in Health and Disease. *Biomolecules* **13**, doi:10.3390/biom13101477 (2023).

34 Kent, W. J. *et al.* The human genome browser at UCSC. *Genome Res* **12**, 996-1006, doi:10.1101/gr.229102 (2002).

35 Nascimento, C. R., Rodrigues Fernandes, N. A., Gonzalez Maldonado, L. A. & Rossa Junior, C. Comparison of monocytic cell lines U937 and THP-1 as macrophage models for in vitro studies. *Biochem Biophys Rep* **32**, 101383, doi:10.1016/j.bbrep.2022.101383 (2022).

36 Forrester, M. A. *et al.* Similarities and differences in surface receptor expression by THP-1 monocytes and differentiated macrophages polarized using seven different conditioning regimens. *Cell Immunol* **332**, 58-76, doi:10.1016/j.cellimm.2018.07.008 (2018).

37 Charbord, J. *et al.* High throughput screening for inhibitors of REST in neural derivatives of human embryonic stem cells reveals a chemical compound that promotes expression of neuronal genes. *Stem Cells* **31**, 1816-1828, doi:10.1002/stem.1430 (2013).

38 Zhang, D. *et al.* Non-CpG methylation by DNMT3B facilitates REST binding and gene silencing in developing mouse hearts. *Nucleic Acids Res* **45**, 3102-3115, doi:10.1093/nar/gkw1258 (2017).

39 Rovira, M. *et al.* REST is a major negative regulator of endocrine differentiation during pancreas organogenesis. *Genes Dev* **35**, 1229-1242, doi:10.1101/gad.348501.121 (2021).

40 Cheng, Y., Song, H., Ming, G. L. & Weng, Y. L. Epigenetic and epitranscriptomic regulation of axon regeneration. *Mol Psychiatry* **28**, 1440-1450, doi:10.1038/s41380-023-02028-9 (2023).

42 Anthony, R. M. & Nimmerjahn, F. The role of differential IgG glycosylation in the interaction of antibodies with FcgammaRs in vivo. *Curr Opin Organ Transplant* **16**, 7-14, doi:10.1097/MOT.0b013e328342538f (2011).

43 Kristic, J. *et al.* Glycans are a novel biomarker of chronological and biological ages. *J Gerontol A Biol Sci Med Sci* **69**, 779-789, doi:10.1093/gerona/glt190 (2014).

44 Giron, L. B. *et al.* Immunoglobulin G N-glycan markers of accelerated biological aging during chronic HIV infection. *Nat Commun* **15**, 3035, doi:10.1038/s41467-024-47279-4 (2024).

45 Ferrucci, L. & Fabbri, E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* **15**, 505-522, doi:10.1038/s41569-018-0064-2 (2018).

46 Franceschi, C. & Campisi, J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* **69 Suppl 1**, S4-9, doi:10.1093/gerona/glu057 (2014).

47 Franceschi, C., Garagnani, P., Parini, P., Giuliani, C. & Santoro, A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* **14**, 576-590, doi:10.1038/s41574-018-0059-4 (2018).

48 Hernandez-Vargas, E. A. *et al.* Effects of aging on influenza virus infection dynamics. *J Virol* **88**, 4123-4131, doi:10.1128/JVI.03644-13 (2014).

49 Krammer, F. *et al.* Influenza. *Nat Rev Dis Primers* **4**, 3, doi:10.1038/s41572-018-0002-y (2018).

50 Langer, J. *et al.* High Clinical Burden of Influenza Disease in Adults Aged >/= 65 Years: Can We Do Better? A Systematic Literature Review. *Adv Ther* **40**, 1601-1627, doi:10.1007/s12325-023-02432-1 (2023).

51 Memoli, M. J. *et al.* Validation of the wild-type influenza A human challenge model H1N1pdMIST: an A(H1N1)pdm09 dose-finding investigational new drug study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **60**, 693-702, doi:10.1093/cid/ciu924 (2015).

52 Galani, I. E. *et al.* Untuned antiviral immunity in COVID-19 revealed by temporal type I/III interferon patterns and flu comparison. *Nat Immunol* **22**, 32-40, doi:10.1038/s41590-020-00840-x (2021).

53 Sievers, B. L. *et al.* Antibodies elicited by SARS-CoV-2 infection or mRNA vaccines have reduced neutralizing activity against Beta and Omicron pseudoviruses. *Sci Transl Med* **14**, eabn7842, doi:10.1126/scitranslmed.abn7842 (2022).

54 Love, M. I., Huber, W. & Anders, S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol* **15**, 550, doi:10.1186/s13059-014-0550-8 (2014).

55 Subramanian, A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A* **102**, 15545-15550, doi:10.1073/pnas.0506580102 (2005).

56 Zheng, H. *et al.* Multi-cohort analysis of host immune response identifies conserved protective and detrimental modules associated with severity across viruses. *Immunity* **54**, 753-768 e755, doi:10.1016/j.immuni.2021.03.002 (2021).

57 Chakraborty, S. *et al.* Early non-neutralizing, afucosylated antibody responses are associated with COVID-19 severity. *Sci Transl Med* **14**, eabm7853, doi:10.1126/scitranslmed.abm7853 (2022).

58 Pang, L. *et al.* Bu Fei Decoction attenuates the tumor associated macrophage stimulated proliferation, migration, invasion and immunosuppression of non-small cell lung cancer, partially via IL-10 and PD-L1 regulation. *Int J Oncol* **51**, 25-38, doi:10.3892/ijo.2017.4014 (2017).

59 Schindelin, J. *et al.* Fiji: an open-source platform for biological-image analysis. *Nat Methods* **9**, 676-682, doi:10.1038/nmeth.2019 (2012).

60 Stirling, D. R. *et al.* CellProfiler 4: improvements in speed, utility and usability. *BMC Bioinformatics* **22**, 433, doi:10.1186/s12859-021-04344-9 (2021).

7. EMBODIMENTS

1. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

2. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

3. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

4. The method of any one of embodiments 1 to 3, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST.

5. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

6. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

7. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

8. The method of any one of embodiments 1 to 7, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing dyspnoea, tachypnoea, and/or hypoxia.

9. The method of any one of embodiments 1 to 8, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein has a sustained fever over 102° F.

10. The method of any one of embodiments 1 to 9, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing moderate to severe chest or stomach pain.

11. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

12. The method of embodiment 11, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST.

13. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin

(IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

14. The method of any one of embodiments 11 to 13, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease.

15. The method of embodiment 14, wherein the human subject at high risk for moderate to severe respiratory virus disease is less than 5 years old or 50 years old or older.

16. The method of embodiment 14 or 15, wherein human subject at high risk for moderate to severe respiratory virus disease has diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system.

17. The method of any one of embodiments 1 to 16, wherein the human subject has 10% or less of total IgG1 sialylated in a serum sample from the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

18. The method of any one of embodiments 1 to 17, wherein the human subject has 10% or less of IgG1 G2SFS in a serum sample from the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

19. The method of any one of embodiments 1 to 18, wherein the respiratory virus is influenza virus.

20. The method of embodiment 19, wherein the influenza virus is an influenza A virus.

21. The method of embodiment 20, wherein the influenza A virus is an H1 or H3 subtype.

22. The method of any one of embodiments 1 to 18, wherein the respiratory virus is a human respiratory syncytial virus.

23. The method of any one of embodiments 1 to 18, wherein the respiratory virus is a human metapneumovirus.

24. The method of any one of embodiments 1 to 18, wherein the respiratory virus is a human parainfluenza virus.

25. The method of any one of embodiments 1 to 18, wherein the respiratory virus is a severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

26. The method of any one of embodiments 1 to 18, wherein the respiratory virus is an adenovirus or coronavirus.

27. The method of any one of embodiments 1 to 18, wherein the respiratory virus is a human bocavirus.

28. The method of any one of embodiments 1 to 27, wherein no significant difference in neutralization of the respiratory virus by the hypersialylated IVIg or the IgG Fc region-containing protein relative to asialylated IVIg or the same IgG Fc region-containing protein in which the sialylation has been removed, respectively, is detected as assessed in an *in vitro* neutralization assay.

29. The method of any one of embodiments 1 to 28, wherein the hypersialylated IVIg or the IgG Fc region-containing protein does not prevent binding of the respiratory virus to its host cell receptor as assessed in an *in vitro* assay.

30. The method of any one of embodiments 1 to 29, wherein the levels of one or more proinflammatory cytokines in a bronchoalveolar lavage (BAL) sample from the human subject are reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to the levels of the one or more proinflammatory cytokines in a BAL sample from the same human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

31. The method of embodiment 30, wherein the one or more proinflammatory cytokines include one or more of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1 alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-gamma, and TNF-beta.

32. The method of any one of embodiments 1 to 31, wherein the levels of one or more monocyte/macrophage chemotactic factors in a BAL sample from the human subject are reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to the levels of the one or more monocyte/macrophage chemotactic in a BAL sample from the same human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

33. The method of embodiment 32, wherein the one or more monocyte/macrophage chemotactic factors include one or more of GM-CSF, CXCL1, CXCL2, CXCL5, CXCL10, and CXCL11.

34. The method of any one of embodiments 1 to 33, wherein neutrophil and monocyte infiltration in a BAL sample from the human subject is reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to neutrophil and monocyte infiltration in a BAL sample from the same human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

35. The method of any one of embodiments 1 to 34, wherein no significant difference in the titer of the respiratory virus is detected following administration of the hypersialylated IVIg or the IgG Fc region-containing protein to an animal model for the respiratory virus relative to the titer of the respiratory virus detected following administration of asialylated IVIg, the same IgG Fc region-containing protein in which the sialylation has been removed, or phosphate buffered saline to the same type of animal model.

36. The method of any one of embodiments 1 to 35, wherein the hypersialylated IVIg or the IgG Fc region-containing protein suppresses the expression one or more of genes induced by the respiratory virus that are involved in the inflammatory response.

37. The method of any one of embodiments 1 to 35, wherein the hypersialylated IVIg or the IgG Fc region-containing protein upregulates the expression of DC-SIGN.

38. The method of any one of embodiments 1 to 37, wherein the hypersialylated IVIg or the IgG Fc region-containing protein upregulates the expression of Siglec G.

39. The method of any one of embodiments 1 to 37, wherein the hypersialylated IVIg or the IgG Fc region-containing protein suppresses NF-KB signaling.

40. The method of any one of embodiments 1 to 39, wherein the hypersialylated IVIg comprises higher α2,6-linked sialic acid in the N-linked glycans of Fc regions than an unmodified IVIg composition.

41. The method of embodiment 40, wherein the hypersialylated IVIg comprises at least 20% higher α2,6-linked sialic acid in the N-linked glycans of Fc regions than an unmodified IVIg composition.

42. The method of any one of embodiments 1 to 41, wherein the hypersialylated IVIg includes antibody that binds to an antigen of the respiratory virus.

43. The method of any one of embodiments 1 to 42, wherein the hypersialylated IVIg includes antibody that binds to an envelope protein or glycoprotein of the respiratory virus.

44. The method of any one of embodiments 1 to 39, wherein the IgG Fc region-containing protein is binds to an antigen of the respiratory virus.

45. The method of embodiment 44, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

46. The method of any one of embodiments 1 to 39, wherein the IgG Fc region-containing protein is an antibody.

47. The method of embodiment 46, wherein the antibody binds to an antigen of the respiratory virus.

48. The method of embodiment 47, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

49. The method of any one of embodiments 1 to 39, wherein the IgG Fc region-containing protein consists of a hypersialylated IgG Fc region.

50. The method of any one of embodiments 1 to 39, or 44 to 49, wherein the hypersialylated IgG Fc region is a hypersialylated human IgG1 Fc region.

51. The method of any one of embodiments 1 to 39, or 44 to 49, wherein the hypersialylated IgG Fc region is at least 95% identical to the amino acid sequence of SEQ ID NO:1.

52. The method of any one of embodiments 1 to 39, or 44 to 49, wherein the hypersialylated IgG Fc region consists of the amino acid sequence of SEQ ID NO:1.

53. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

54. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

55. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

56. The method of any one of embodiments 53 to 55, wherein the IgG Fc region-containing protein induces REST.

57. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

58. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

59. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

60. The method of any one of embodiments 53 to 59, wherein the human subject prior to administration of the IgG Fc region-containing protein is experiencing dyspnoea, tachypnoea, and/or hypoxia.

61. The method of any one of embodiments 53 to 60, wherein the human subject prior to administration of the IgG Fc region-containing protein has a sustained fever over 102° F.

62. The method of any one of embodiments 53 to 61, wherein the human subject prior to administration of the IgG Fc region-containing protein is experiencing moderate to severe chest or stomach pain.

63. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

64. The method of embodiment 63, wherein the IgG Fc region-containing protein induces REST.

65. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

66. The method of any one of embodiments 63 to 65, wherein the human subject prior to administration of the IgG Fc region-containing protein is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease.

67. The method of embodiment 66, wherein the human subject at high risk for moderate to severe respiratory virus disease is less than 5 years old or 50 years old or older.

68. The method of embodiments 66 or 67, wherein human subject at high risk for moderate to severe respiratory virus disease has diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system.

69. The method of any one of embodiments 63 to 68, wherein the human subject has 10% or less of total IgG1 sialylated in a serum sample from the human subject prior to administration of the IgG Fc region-containing protein.

70. The method of any one of embodiments 63 to 69, wherein the human subject has 10% or less of IgG1 G2SFS in a serum sample from the human subject prior to administration of the IgG Fc region-containing protein.

71. The method of any one of embodiments 63 to 70, wherein the respiratory virus is influenza virus.

72. The method of embodiment 71, wherein the influenza virus is an influenza A virus.

73. The method of embodiment 72, wherein the influenza A virus is an H1 or H3 subtype.

74. The method of any one of embodiments 63 to 70, wherein the respiratory virus is a human respiratory syncytial virus.

75. The method of any one of embodiments 63 to 70, wherein the respiratory virus is a human metapneumovirus.

76. The method of any one of embodiments 63 to 70, wherein the respiratory virus is a human parainfluenza virus.

77. The method of any one of embodiments 63 to 70, wherein the respiratory virus is a severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

78. The method of any one of embodiments 63 to 70, wherein the respiratory virus is an adenovirus or a coronavirus.

79. The method of any one of embodiments 63 to 70, wherein the respiratory virus is a human bocavirus.

80. The method of any one of embodiments 63 to 79, wherein no significant difference in neutralization of the respiratory virus by the IgG Fc region-containing protein relative to the same IgG Fc region-containing protein in which the sialylation has been removed, is detected as assessed in an *in vitro* neutralization assay.

81. The method of any one of embodiments 63 to 80, wherein the IgG Fc region-containing protein does not prevent binding of the respiratory virus to its host cell receptor as assessed in an *in vitro* assay.

82. The method of any one of embodiments 63 to 82, wherein the levels of one or more proinflammatory cytokines in a bronchoalveolar lavage (BAL) sample from the human subject are reduced after administration of the IgG Fc region-containing protein relative to the levels of the one or more proinflammatory cytokines in a BAL sample from the same human subject prior to administration of the IgG Fc region-containing protein.

83. The method of embodiment 82, wherein the one or more proinflammatory cytokines include one or more of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1 alpha,

granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-gamma, and TNF-beta.

84. The method of any one of embodiments 63 to 83, wherein the levels of one or more monocyte/macrophage chemotactic factors in a BAL sample from the human subject are reduced after administration of the IgG Fc region-containing protein relative to the levels of the one or more monocyte/macrophage chemotactic factors in a BAL sample from the same human subject prior to administration of the IgG Fc region-containing protein.

85. The method of embodiment 84, wherein the one or more monocyte/macrophage chemotactic factors include one or more of GM-CSF, CXCL1, CXCL2, CXCL5, CXCL10, and CXCL11.

86. The method of any one of embodiments 63 to 85, wherein neutrophil and monocyte infiltration in a BAL sample from the human subject is reduced after administration of the IgG Fc region-containing protein relative to neutrophil and monocyte infiltration in a BAL sample from the same human subject prior to administration of the IgG Fc region-containing protein.

87. The method of any one of embodiments 63 to 86, wherein no significant difference in the titer of the respiratory virus is detected following administration of the IgG Fc region-containing protein to an animal model for the respiratory virus relative to the titer of the respiratory virus detected following administration of the same IgG Fc region-containing protein in which the sialylation has been removed, or phosphate buffered saline to the same type of animal model.

88. The method of any one of embodiments 63 to 87, wherein the IgG Fc region-containing protein suppresses the expression of one or more of genes induced by the respiratory virus that are involved in the inflammatory response.

89. The method of any one of embodiments 63 to 88, wherein the IgG Fc region-containing protein upregulates the expression of DC-SIGN.

90. The method of any one of embodiments 63 to 89, wherein the IgG Fc region-containing protein upregulates the expression of Siglec G.

91. The method of any one of embodiments 63 to 90, wherein the IgG Fc region-containing protein suppresses NF-KB signaling.

92. The method of any one of embodiments 63 to 91, wherein the IgG Fc region-containing protein is binds to an antigen of the respiratory virus.

93. The method of embodiment 92, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

94. The method of any one of embodiments 63 to 91, wherein the IgG Fc region-containing protein is an antibody.

95. The method of embodiment 94, wherein the antibody binds to an antigen of the respiratory virus.

96. The method of embodiment 95, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

97. The method of any one of embodiments 63 to 96, wherein the modified IgG Fc region comprises the amino acid sequence of SEQ ID NO:2.

98. The method of any one of embodiments 63 to 91, wherein the protein consists of the modified IgG Fc region.

99. The method of embodiment 98, wherein the modified IgG Fc region comprises the amino acid sequence of SEQ ID NO:2.

100. The method of any one of embodiments 63 to 99, wherein the IgG Fc region-containing protein includes α2,6-linked sialic acids and/or mimics the activity of hypersialylated IgG1 Fc.

101. The method of embodiment 100, wherein the IgG Fc region containing protein comprises at least about 20% higher α2,6-linked sialic acids in N-linked glycans of Fc regions than an unmodified IVIg composition.

[00402] The foregoing is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the antibodies, IVIg, IgG Fc region-containing proteins, and methods provided herein and their equivalents, in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00403] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

We Claim:

1. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

2. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

3. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

4. The method of any one of claims 1 to 3, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST.

5. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

6. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

7. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated

intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

8. The method of any one of claims 1 to 7, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing dyspnoea, tachypnoea, and/or hypoxia.

9. The method of any one of claims 1 to 8, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein has a sustained fever over 102° F.

10. The method of any one of claims 1 to 9, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing moderate to severe chest or stomach pain.

11. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN and each include α2,6-linked sialic acids.

12. The method of claim 11, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST.

13. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each induce REST and each include α2,6-linked sialic acids.

14. The method of any one of claims 11 to 13, wherein the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease.

15. The method of claim 14, wherein the human subject at high risk for moderate to severe respiratory virus disease is less than 5 years old or 50 years old or older.

16. The method of claim 14 or 15, wherein human subject at high risk for moderate to severe respiratory virus disease has diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system.

17. The method of any one of claims 1 to 16, wherein the human subject has 10% or less of total IgG1 sialylated in a serum sample from the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

18. The method of any one of claims 1 to 17, wherein the human subject has 10% or less of IgG1 G2SFS in a serum sample from the human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

19. The method of any one of claims 1 to 18, wherein the respiratory virus is influenza virus.

20. The method of claim 19, wherein the influenza virus is an influenza A virus.

21. The method of claim 20, wherein the influenza A virus is an H1 or H3 subtype.

22. The method of any one of claims 1 to 18, wherein the respiratory virus is a human respiratory syncytial virus.

23. The method of any one of claims 1 to 18, wherein the respiratory virus is a human metapneumovirus.

24. The method of any one of claims 1 to 18, wherein the respiratory virus is a human parainfluenza virus.

25. The method of any one of claims 1 to 18, wherein the respiratory virus is a severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

26. The method of any one of claims 1 to 18, wherein the respiratory virus is an adenovirus or coronavirus.

27. The method of any one of claims 1 to 18, wherein the respiratory virus is a human bocavirus.

28. The method of any one of claims 1 to 27, wherein no significant difference in neutralization of the respiratory virus by the hypersialylated IVIg or the IgG Fc region-containing protein relative to asialylated IVIg or the same IgG Fc region-containing protein in which the sialylation has been removed, respectively, is detected as assessed in an *in vitro* neutralization assay.

29. The method of any one of claims 1 to 28, wherein the hypersialylated IVIg or the IgG Fc region-containing protein does not prevent binding of the respiratory virus to its host cell receptor as assessed in an *in vitro* assay.

30. The method of any one of claims 1 to 29, wherein the levels of one or more proinflammatory cytokines in a bronchoalveolar lavage (BAL) sample from the human subject are reduced after administration of the hypersialylated IVIg or the IgG Fc region-

containing protein relative to the levels of the one or more proinflammatory cytokines in a BAL sample from the same human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

31. The method of claim 30, wherein the one or more proinflammatory cytokines include one or more of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1 alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-gamma, and TNF-beta.

32. The method of any one of claims 1 to 31, wherein the levels of one or more monocyte/macrophage chemotactic factors in a BAL sample from the human subject are reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to the levels of the one or more monocyte/macrophage chemotactic in a BAL sample from the same human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

33. The method of claim 32, wherein the one or more monocyte/macrophage chemotactic factors include one or more of GM-CSF, CXCL1, CXCL2, CXCL5, CXCL10, and CXCL11.

34. The method of any one of claims 1 to 33, wherein neutrophil and monocyte infiltration in a BAL sample from the human subject is reduced after administration of the hypersialylated IVIg or the IgG Fc region-containing protein relative to neutrophil and monocyte infiltration in a BAL sample from the same human subject prior to administration of the hypersialylated IVIg or the IgG Fc region-containing protein.

35. The method of any one of claims 1 to 34, wherein no significant difference in the titer of the respiratory virus is detected following administration of the hypersialylated IVIg or the IgG Fc region-containing protein to an animal model for the respiratory virus relative to the titer of the respiratory virus detected following administration of asialylated IVIg, the same IgG Fc region-containing protein in which the sialylation has been removed, or phosphate buffered saline to the same type of animal model.

36. The method of any one of claims 1 to 35, wherein the hypersialylated IVIg or the IgG Fc region-containing protein suppresses the expression one or more of genes induced by the respiratory virus that are involved in the inflammatory response.

37. The method of any one of claims 1 to 35, wherein the hypersialylated IVIg or the IgG Fc region-containing protein upregulates the expression of DC-SIGN.

38. The method of any one of claims 1 to 37, wherein the hypersialylated IVIg or the IgG Fc region-containing protein upregulates the expression of Siglec G.

39. The method of any one of claims 1 to 37, wherein the hypersialylated IVIg or the IgG Fc region-containing protein suppresses NF-KB signaling.

40. The method of any one of claims 1 to 39, wherein the hypersialylated IVIg comprises higher α2,6-linked sialic acid in the N-linked glycans of Fc regions than an unmodified IVIg composition.

41. The method of claim 40, wherein the hypersialylated IVIg comprises at least 20% higher α2,6-linked sialic acid in the N-linked glycans of Fc regions than an unmodified IVIg composition.

42. The method of any one of claims 1 to 41, wherein the hypersialylated IVIg includes antibody that binds to an antigen of the respiratory virus.

43. The method of any one of claims 1 to 42, wherein the hypersialylated IVIg includes antibody that binds to an envelope protein or glycoprotein of the respiratory virus.

44. The method of any one of claims 1 to 39, wherein the IgG Fc region-containing protein is binds to an antigen of the respiratory virus.

45. The method of claim 44, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

46. The method of any one of claims 1 to 39, wherein the IgG Fc region-containing protein is an antibody.

47. The method of claim 46, wherein the antibody binds to an antigen of the respiratory virus.

48. The method of claim 47, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

49. The method of any one of claims 1 to 39, wherein the IgG Fc region-containing protein consists of a hypersialylated IgG Fc region.

50. The method of any one of claims 1 to 39, or 44 to 49, wherein the hypersialylated IgG Fc region is a hypersialylated human IgG1 Fc region.

51. The method of any one of claims 1 to 39, or 44 to 49, wherein the hypersialylated IgG Fc region is at least 95% identical to the amino acid sequence of SEQ ID NO:1.

52. The method of any one of claims 1 to 39, or 44 to 49, wherein the hypersialylated IgG Fc region consists of the amino acid sequence of SEQ ID NO:1.

53. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

54. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

55. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

56. The method of any one of claims 53 to 55, wherein the IgG Fc region-containing protein induces REST.

57. A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

58. A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

59. A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

60. The method of any one of claims 53 to 59, wherein the human subject prior to administration of the IgG Fc region-containing protein is experiencing dyspnoea, tachypnoea, and/or hypoxia.

61. The method of any one of claims 53 to 60, wherein the human subject prior to administration of the IgG Fc region-containing protein has a sustained fever over 102° F.

62. The method of any one of claims 53 to 61, wherein the human subject prior to administration of the IgG Fc region-containing protein is experiencing moderate to severe chest or stomach pain.

63. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein

comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induce and/or repress transcription of one or more genes dependent on DC-SIGN.

64. The method of claim 63, wherein the IgG Fc region-containing protein induces REST.

65. A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, wherein the IgG Fc region-containing protein induces REST.

66. The method of any one of claims 63 to 65, wherein the human subject prior to administration of the IgG Fc region-containing protein is experiencing respiratory virus disease symptoms and is at a high risk for moderate to severe respiratory virus disease.

67. The method of claim 66, wherein the human subject at high risk for moderate to severe respiratory virus disease is less than 5 years old or 50 years old or older.

68. The method of claim 66 or 67, wherein human subject at high risk for moderate to severe respiratory virus disease has diabetes, lung disease, asthma, heart disease, sickle cell anemia, kidney disease, liver disease, a metabolic disorder, or a weakened immune system.

69. The method of any one of claims 63 to 68, wherein the human subject has 10% or less of total IgG1 sialylated in a serum sample from the human subject prior to administration of the IgG Fc region-containing protein.

70. The method of any one of claims 63 to 69, wherein the human subject has 10% or less of IgG1 G2SFS in a serum sample from the human subject prior to administration of the IgG Fc region-containing protein.

71. The method of any one of claims 63 to 70, wherein the respiratory virus is influenza virus.

72. The method of claim 71, wherein the influenza virus is an influenza A virus.

73. The method of claim 72, wherein the influenza A virus is an H1 or H3 subtype.

74. The method of any one of claims 63 to 70, wherein the respiratory virus is a human respiratory syncytial virus.

75. The method of any one of claims 63 to 70, wherein the respiratory virus is a human metapneumovirus.

76. The method of any one of claims 63 to 70, wherein the respiratory virus is a human parainfluenza virus.

77. The method of any one of claims 63 to 70, wherein the respiratory virus is a severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

78. The method of any one of claims 63 to 70, wherein the respiratory virus is an adenovirus or a coronavirus.

79. The method of any one of claims 63 to 70, wherein the respiratory virus is a human bocavirus.

80. The method of any one of claims 63 to 79, wherein no significant difference in neutralization of the respiratory virus by the IgG Fc region-containing protein relative to the same IgG Fc region-containing protein in which the sialylation has been removed, is detected as assessed in an *in vitro* neutralization assay.

81. The method of any one of claims 63 to 80, wherein the IgG Fc region-containing protein does not prevent binding of the respiratory virus to its host cell receptor as assessed in an *in vitro* assay.

82. The method of any one of claims 63 to 82, wherein the levels of one or more proinflammatory cytokines in a bronchoalveolar lavage (BAL) sample from the human subject are reduced after administration of the IgG Fc region-containing protein relative to the levels of the one or more proinflammatory cytokines in a BAL sample from the same human subject prior to administration of the IgG Fc region-containing protein.

83. The method of claim 82, wherein the one or more proinflammatory cytokines include one or more of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1 alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-gamma, and TNF-beta.

84. The method of any one of claims 63 to 83, wherein the levels of one or more monocyte/macrophage chemotactic factors in a BAL sample from the human subject are reduced after administration of the IgG Fc region-containing protein relative to the levels of the one or more monocyte/macrophage chemotactic factors in a BAL sample from the same human subject prior to administration of the IgG Fc region-containing protein.

85. The method of claim 84, wherein the one or more monocyte/macrophage chemotactic factors include one or more of GM-CSF, CXCL1, CXCL2, CXCL5, CXCL10, and CXCL11.

86. The method of any one of claims 63 to 85, wherein neutrophil and monocyte infiltration in a BAL sample from the human subject is reduced after administration of the IgG Fc region-containing protein relative to neutrophil and monocyte infiltration in a BAL sample from the same human subject prior to administration of the IgG Fc region-containing protein.

87. The method of any one of claims 63 to 86, wherein no significant difference in the titer of the respiratory virus is detected following administration of the IgG Fc region-

containing protein to an animal model for the respiratory virus relative to the titer of the respiratory virus detected following administration of the same IgG Fc region-containing protein in which the sialylation has been removed, or phosphate buffered saline to the same type of animal model.

88. The method of any one of claims 63 to 87, wherein the IgG Fc region-containing protein suppresses the expression of one or more of genes induced by the respiratory virus that are involved in the inflammatory response.

89. The method of any one of claims 63 to 88, wherein the IgG Fc region-containing protein upregulates the expression of DC-SIGN.

90. The method of any one of claims 63 to 89, wherein the IgG Fc region-containing protein upregulates the expression of Siglec G.

91. The method of any one of claims 63 to 90, wherein the IgG Fc region-containing protein suppresses NF-KB signaling.

92. The method of any one of claims 63 to 91, wherein the IgG Fc region-containing protein is binds to an antigen of the respiratory virus.

93. The method of claim 92, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

94. The method of any one of claims 63 to 91, wherein the IgG Fc region-containing protein is an antibody.

95. The method of claim 94, wherein the antibody binds to an antigen of the respiratory virus.

96. The method of claim 95, wherein the antigen of the respiratory virus is an envelope protein or glycoprotein.

97. The method of any one of claims 63 to 96, wherein the modified IgG Fc region comprises the amino acid sequence of SEQ ID NO:2.

98. The method of any one of claims 63 to 91, wherein the protein consists of the modified IgG Fc region.

99. The method of claim 98, wherein the modified IgG Fc region comprises the amino acid sequence of SEQ ID NO:2.

100. The method of any one of claims 63 to 99, wherein the IgG Fc region-containing protein includes α2,6-linked sialic acids and/or mimics the activity of hypersialylated IgG1 Fc.

101. The method of claim 100, wherein the IgG Fc region containing protein comprises at least about 20% higher α2,6-linked sialic acids in N-linked glycans of Fc regions than an unmodified IVIg composition.

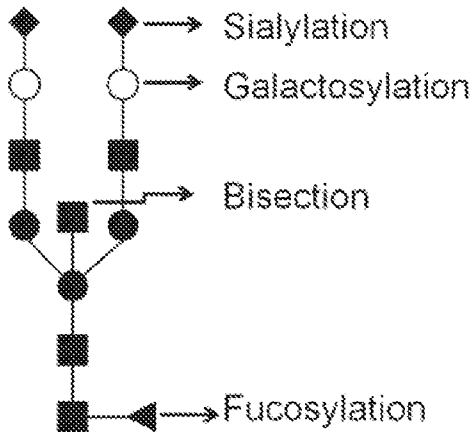

Sialylation
Galactosylation
Bisection
Fucosylation

FIG. 1A

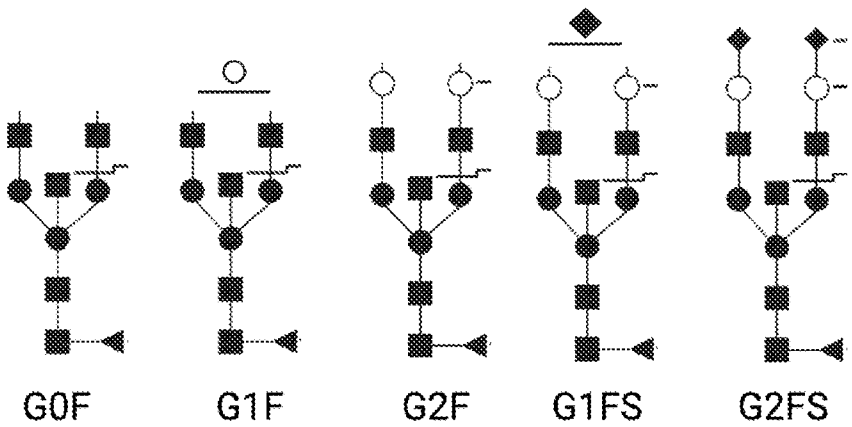
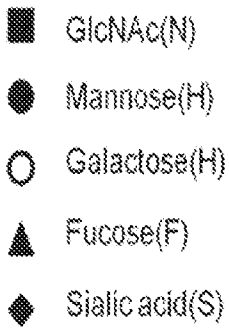

G0F
G1F
G2F
G1FS
G2FS

FIG. 1B


GlcNAc(N)
Mannose(H)
Galactose(H)
Fucose(F)
Sialic acid(S)

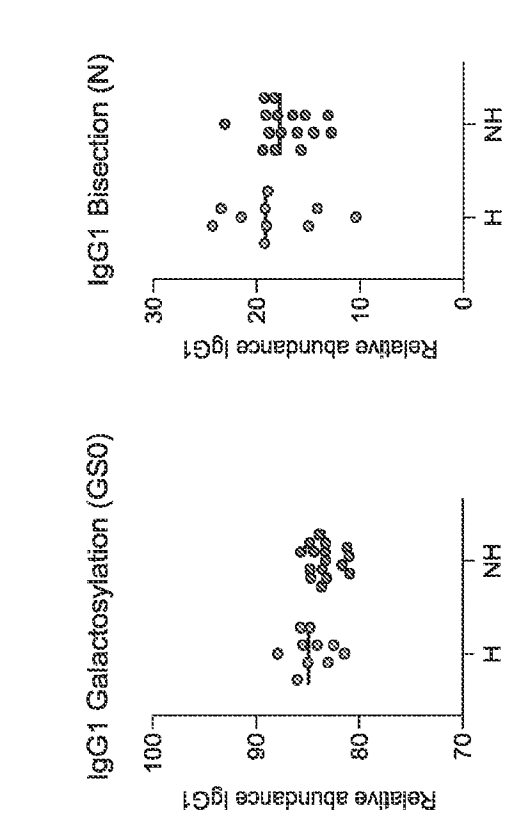


FIG. 2A

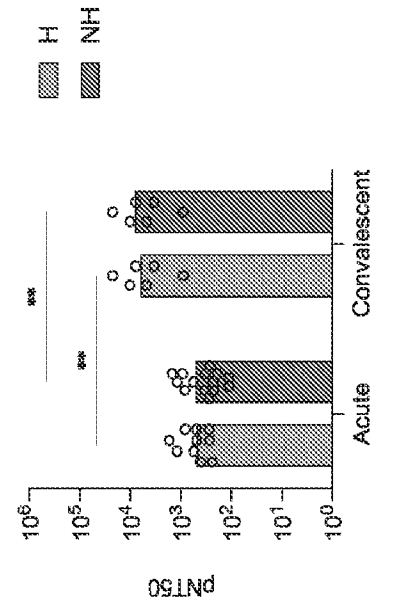


FIG. 2D

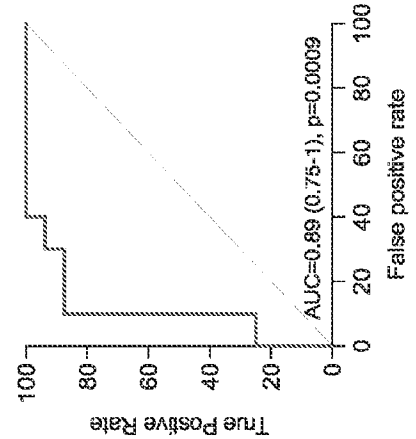


FIG. 2C

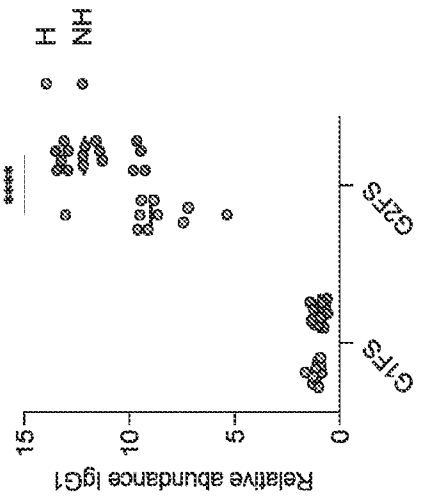


FIG. 2B

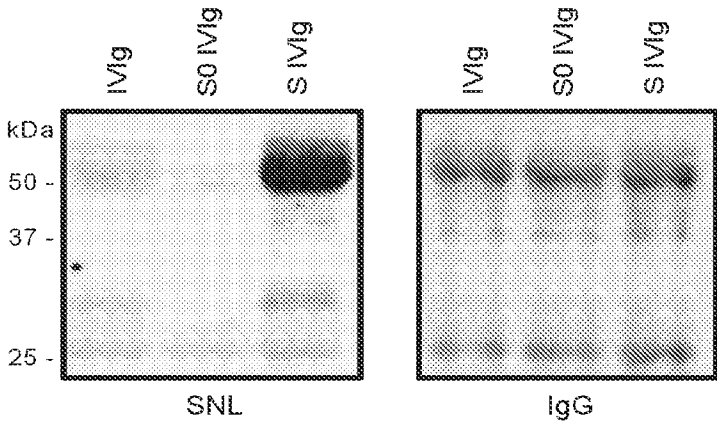


FIG. 3A

% Sialylation by Mass spec

Sample no.	S IVIg	S0 IVIg
1	22.579	0.008
2	25.075	0.007

FIG. 3B

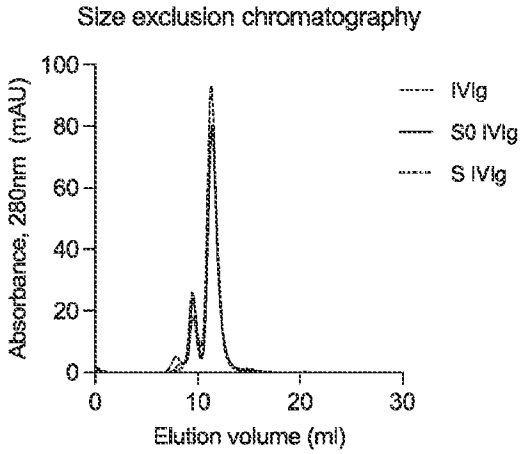


FIG. 3C

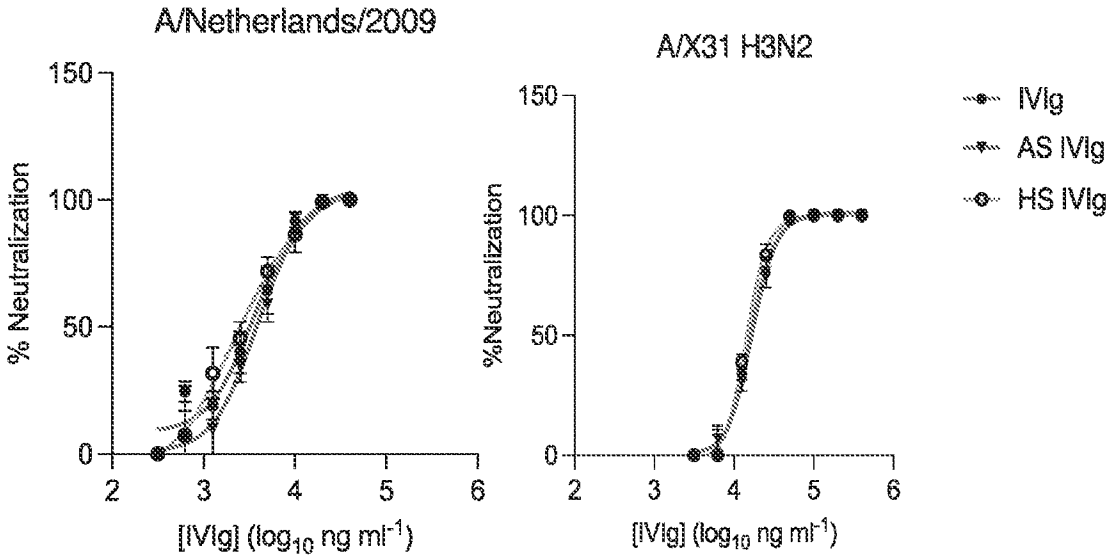

A/Netherlands/2009
A/X31 H3N2
% Neutralization
%Neutralization
[IVIg] (log10 ng ml-1)
[IVIg] (log10 ng ml-1)
IVIg
AS IVIg
HS IVIg

FIG. 3D

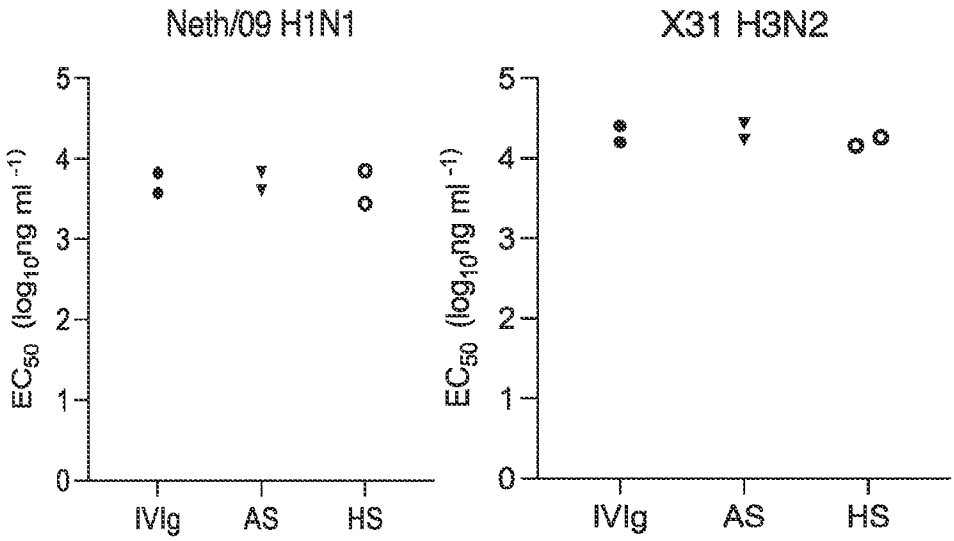

Neth/09 H1N1
X31 H3N2
EC50 (log10ng ml-1)
EC50 (log10ng ml-1)
IVIg
AS
HS
IVIg
AS
HS

FIG. 3E

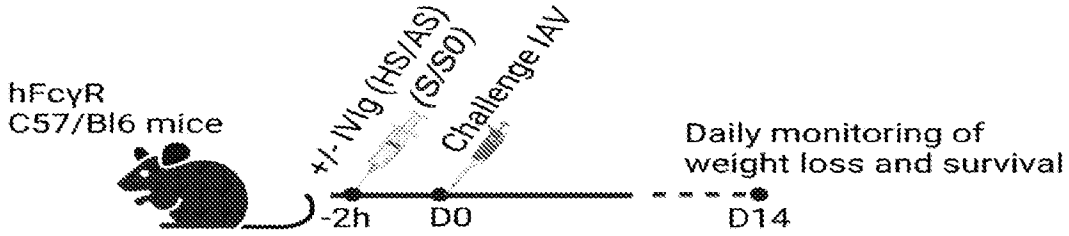

hFcγR
C57/Bl6 mice
+/- IVIg (HS/AS)
(S/S0)
Challenge IAV
Daily monitoring of
weight loss and survival
-2h
D0
D14

FIG. 4A

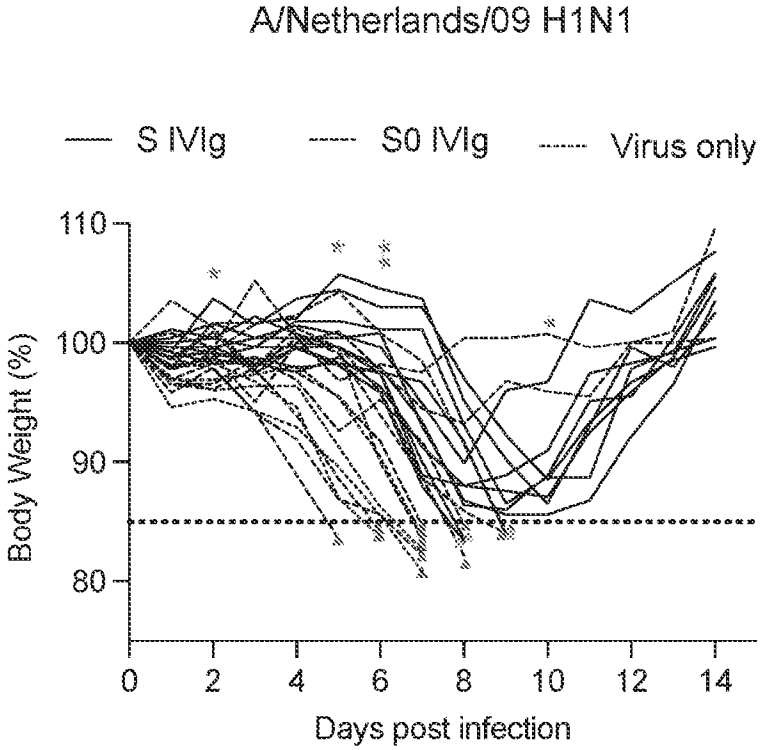

A/Netherlands/09 H1N1
S IVIg
S0 IVIg
Virus only
Body Weight (%)
110
100
90
80
0
2
4
6
8
10
12
14
Days post infection

FIG. 4B

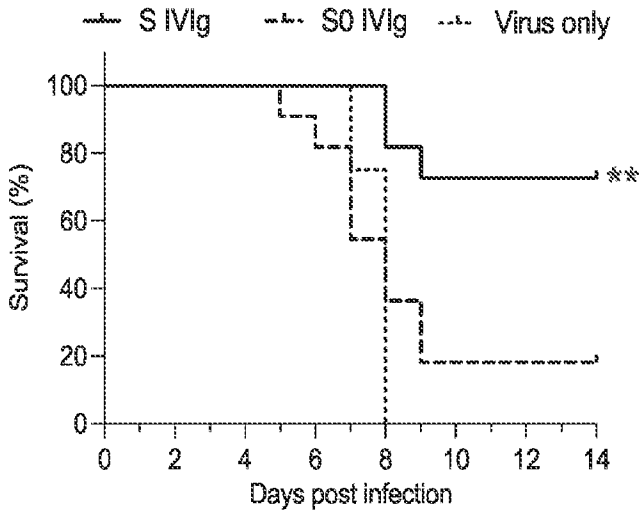


FIG. 4C

A/X31 H3N2

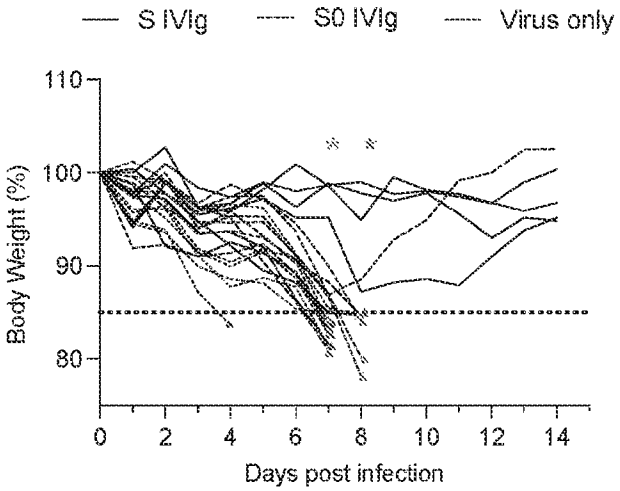


FIG. 4D

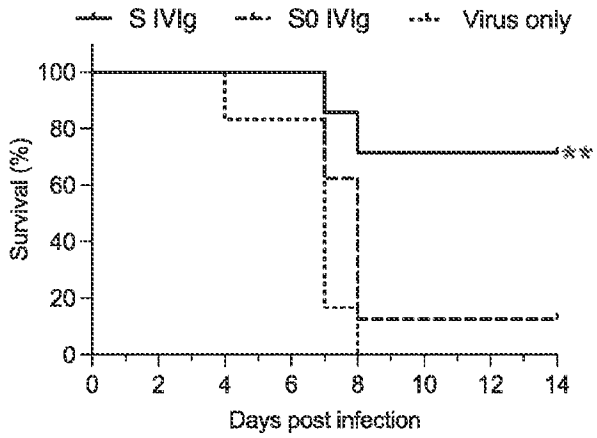


FIG. 4E

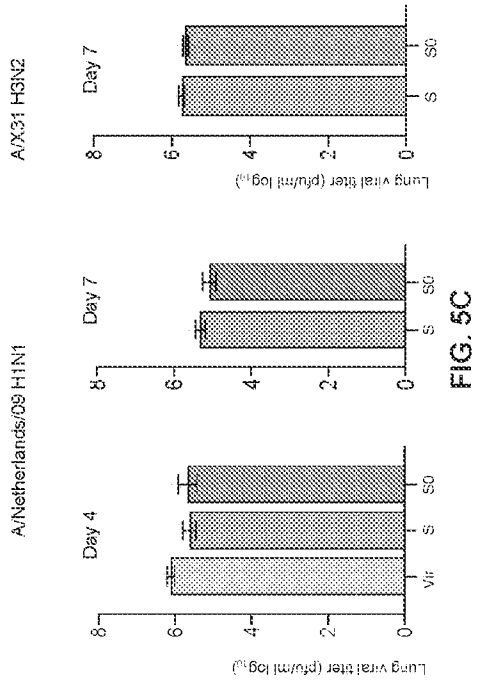


FIG. 5C

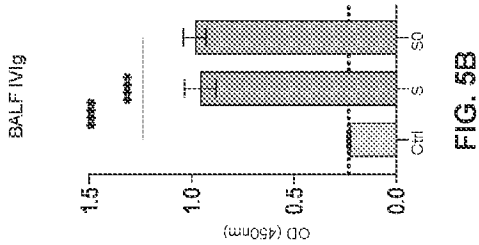


FIG. 5B

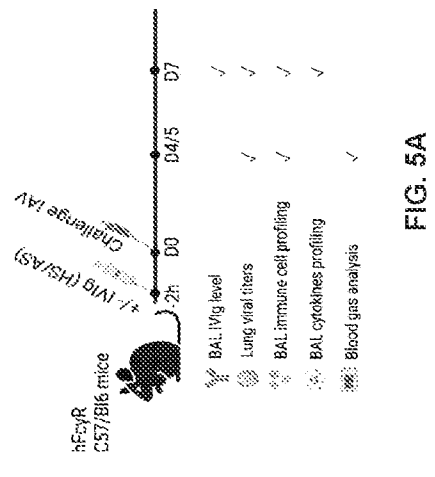
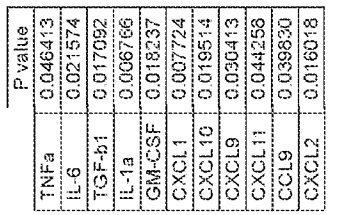


FIG. 5A



	P value
TNFa	0.046413
IL-6	0.021574
TGF-b1	0.017092
IL-1a	0.006766
GM-CSF	0.018237
CXCL1	0.007724
CXCL10	0.019514
CXCL9	0.030413
CXCL11	0.044258
CCL9	0.039830
CXCL2	0.016018

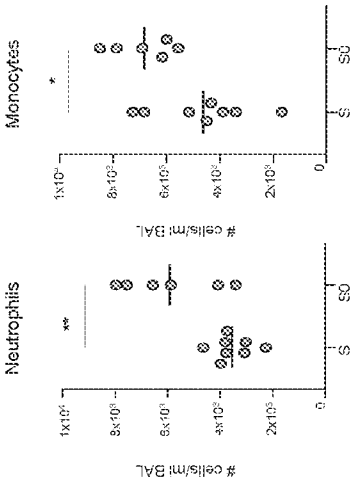


FIG. 5F

FIG. 5E

FIG. 5D

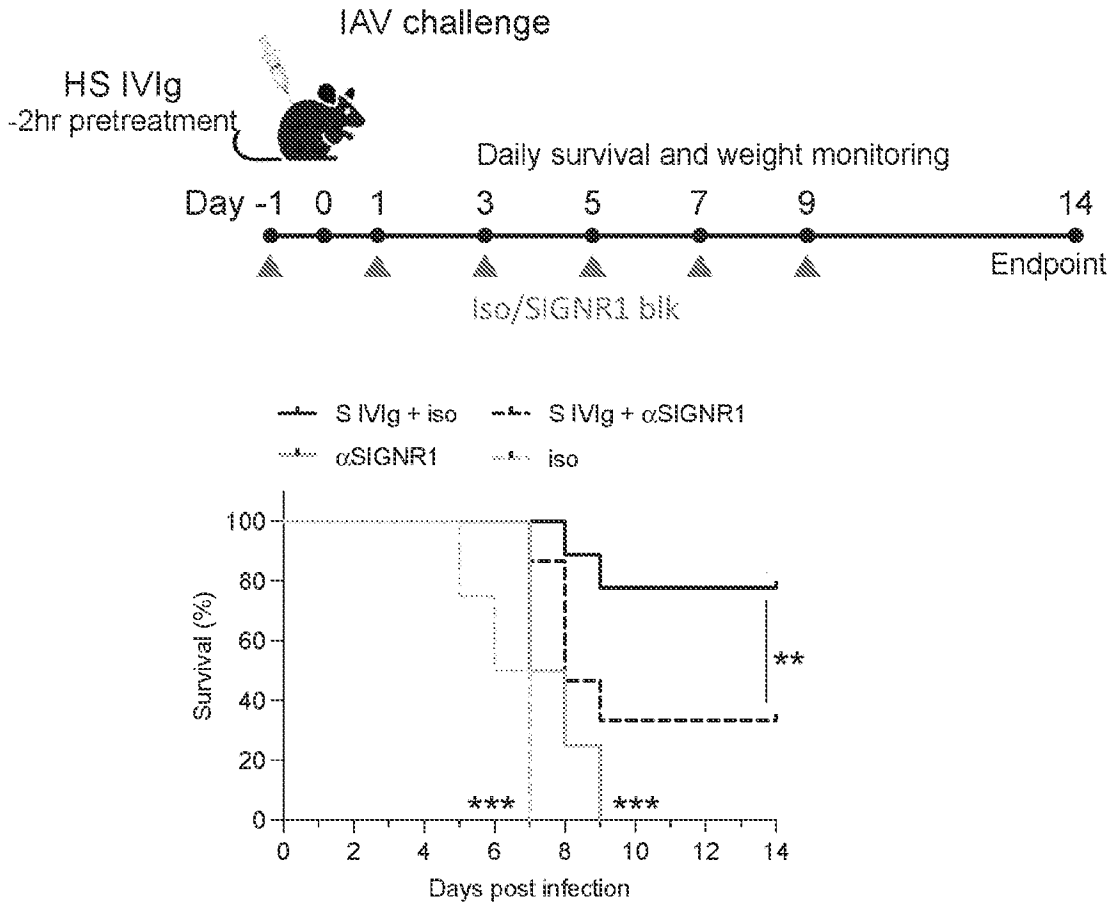

IAV challenge
HS IVIg
-2hr pretreatment
Daily survival and weight monitoring
Day -1 0 1 3 5 7 9 14
Endpoint
Iso/SIGNR1 blk
S IVIg + iso
S IVIg + αSIGNR1
αSIGNR1
iso
Survival (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14
Days post infection
**
***
***

FIG. 5G

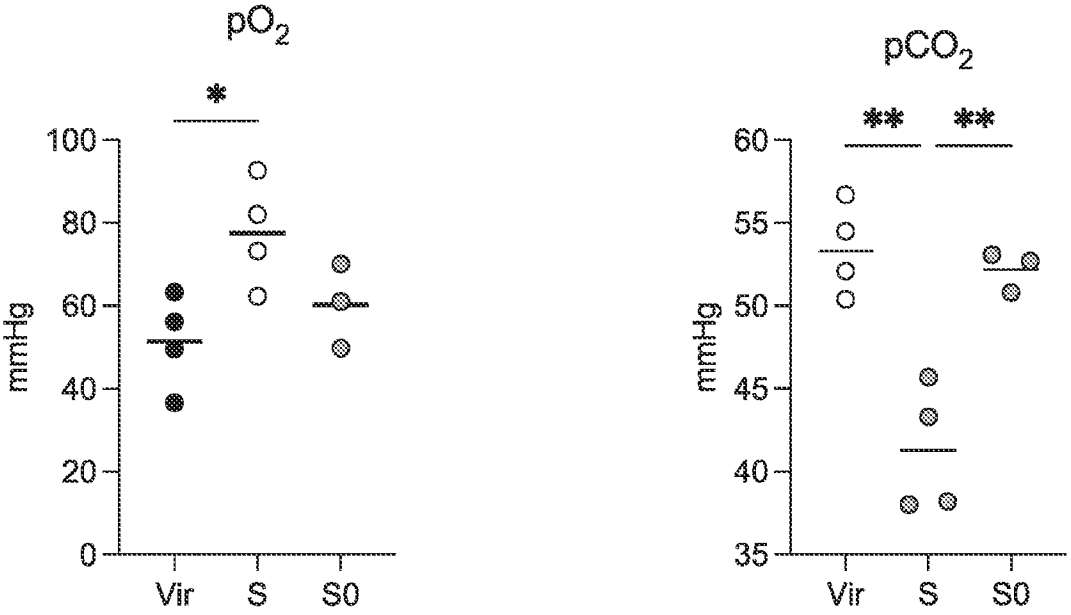

pO2
*
100
80
60
40
20
0
mmHg
Vir
S
S0
pCO2
**
**
60
55
50
45
40
35
mmHg
Vir
S
S0

FIG. 5H

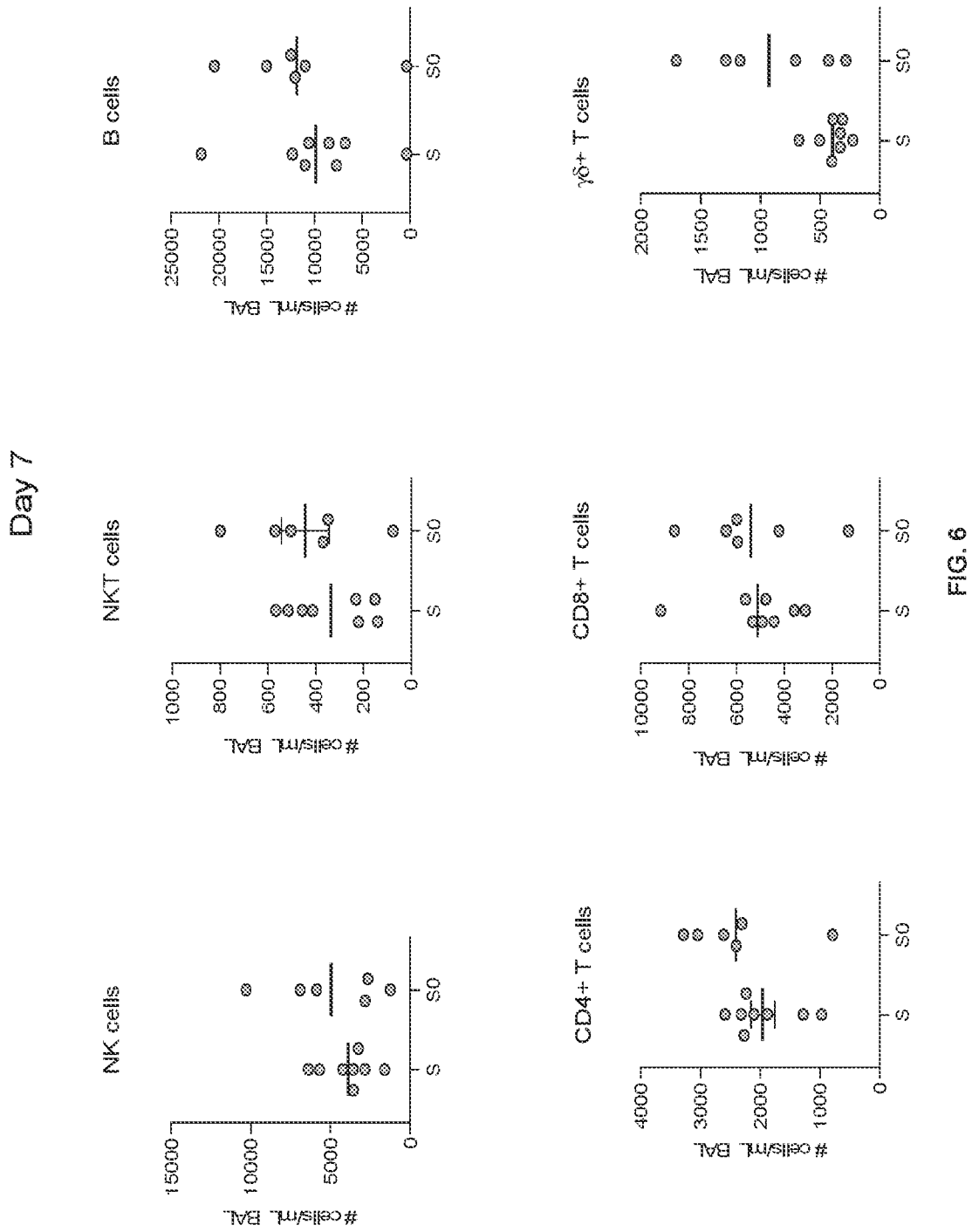

Day 7
NK cells
NKT cells
B cells
CD4+ T cells
CD8+ T cells
γδ+ T cells
cells/mL BAL
S
S0

FIG. 6

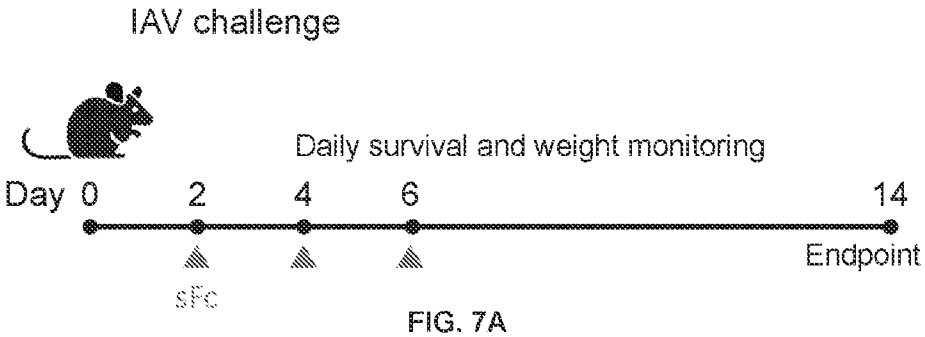


FIG. 7A

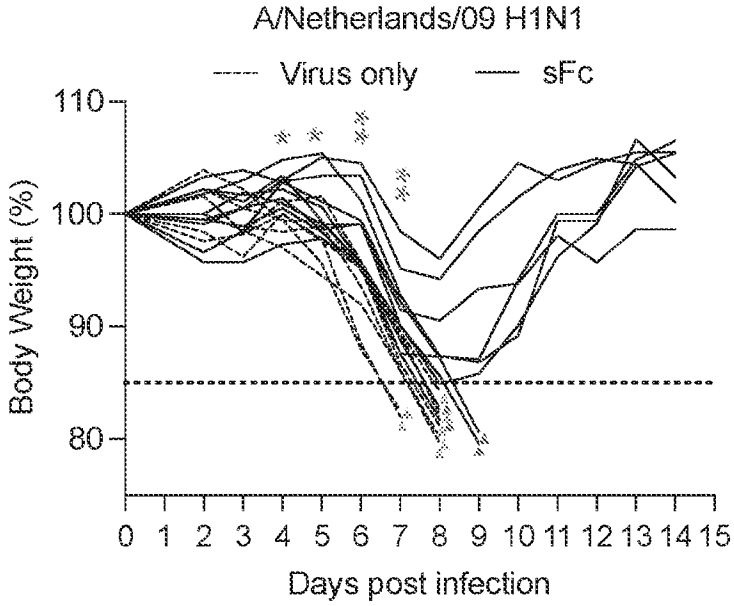


FIG. 7B

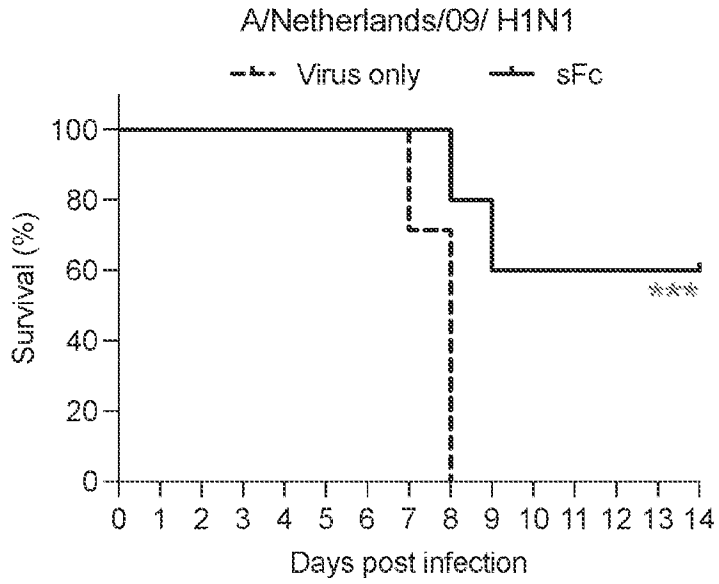


FIG. 7C

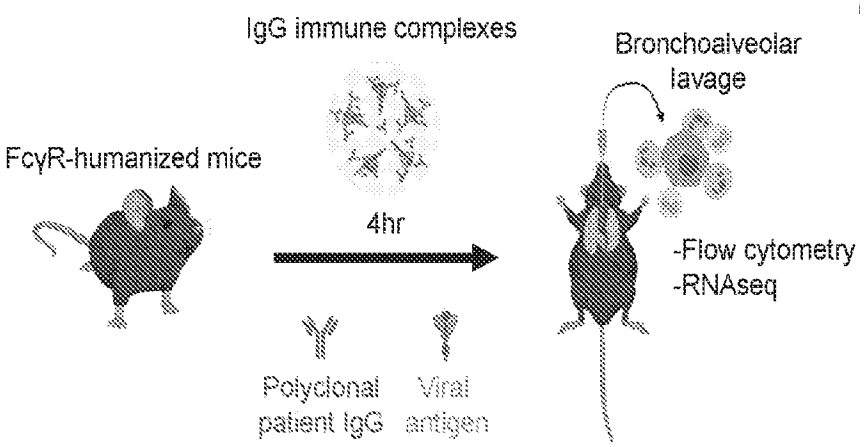
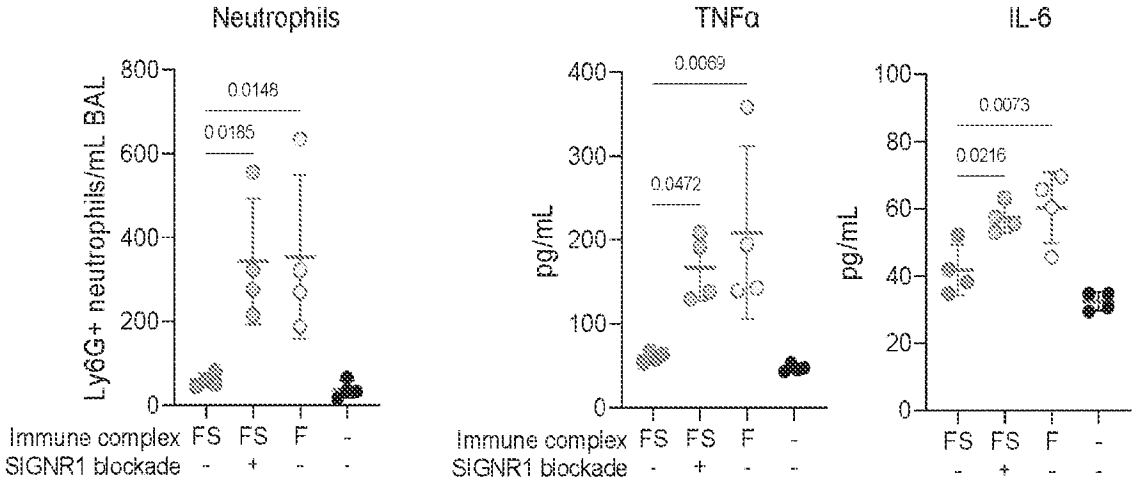


FIG. 8A



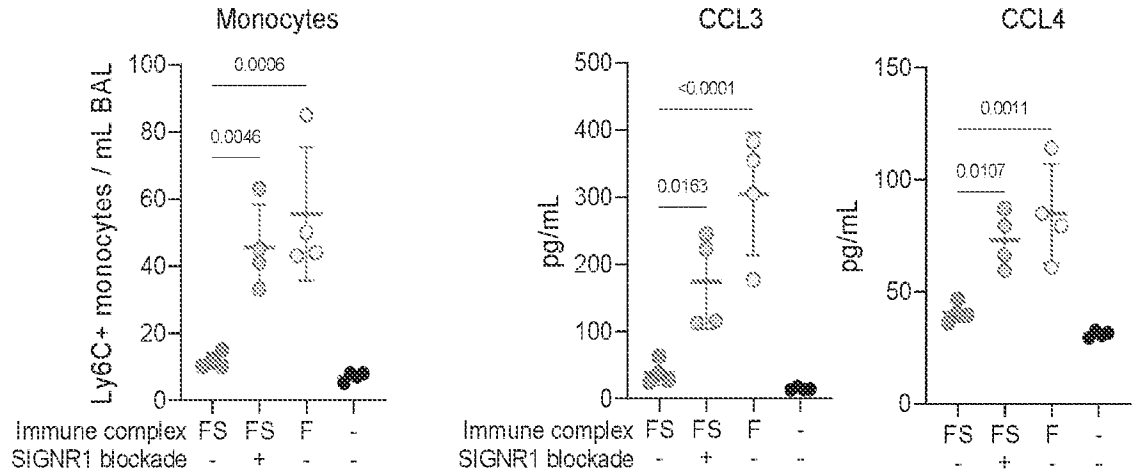
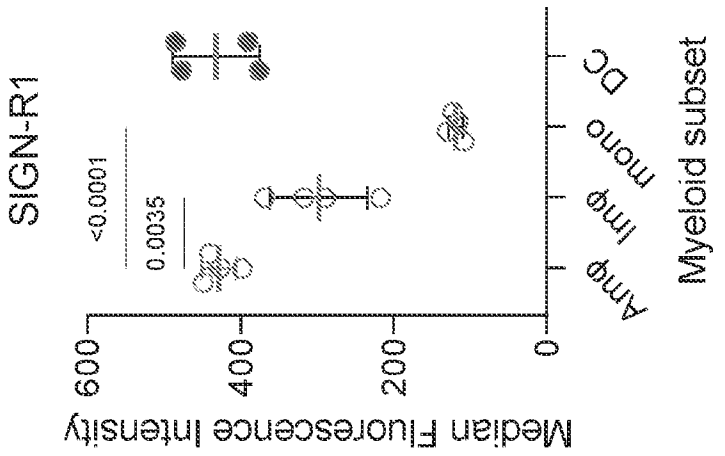


FIG. 8B

FIG. 8C


SIGN-R1
<0.0001
0.0035
Median Fluorescence Intensity
600
400
200
0
Amφ
Img
mono
DC
Myeloid subset

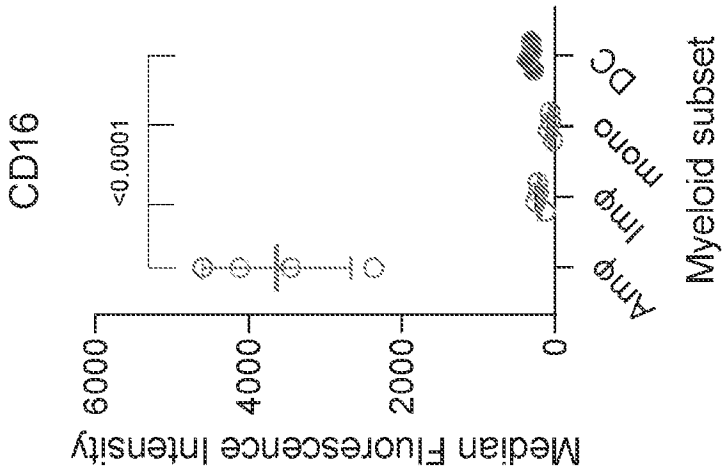

CD16
<0.0001
Median Fluorescence Intensity
6000
4000
2000
0
Amφ
Img
mono
DC
Myeloid subset

FIG. 9B

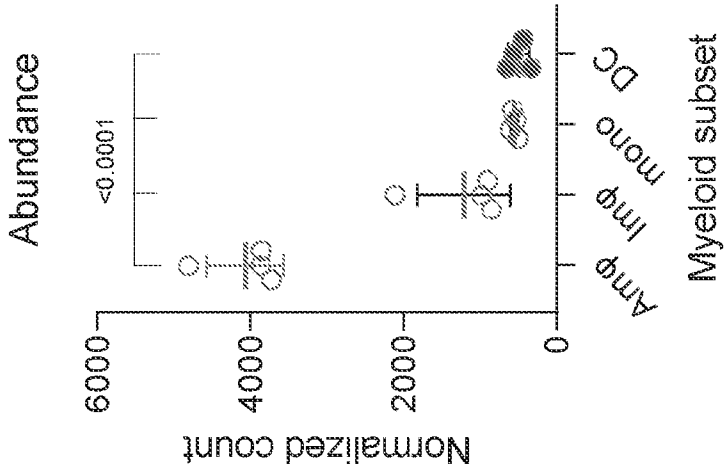

Abundance
<0.0001
Normalized count
6000
4000
2000
0
Amφ
Img
mono
DC
Myeloid subset

FIG. 9A

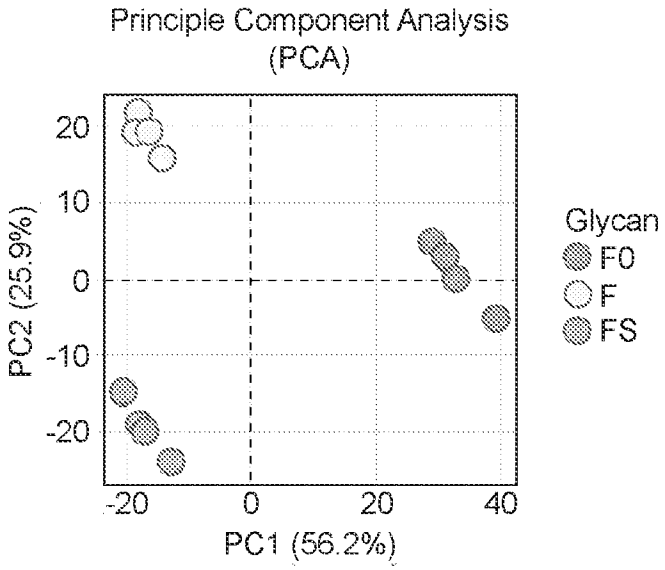

Principle Component Analysis
(PCA)
PC2 (25.9%)
PC1 (56.2%)
20
10
0
-10
-20
-20
0
20
40
Glycan
F0
F
FS

FIG. 9C

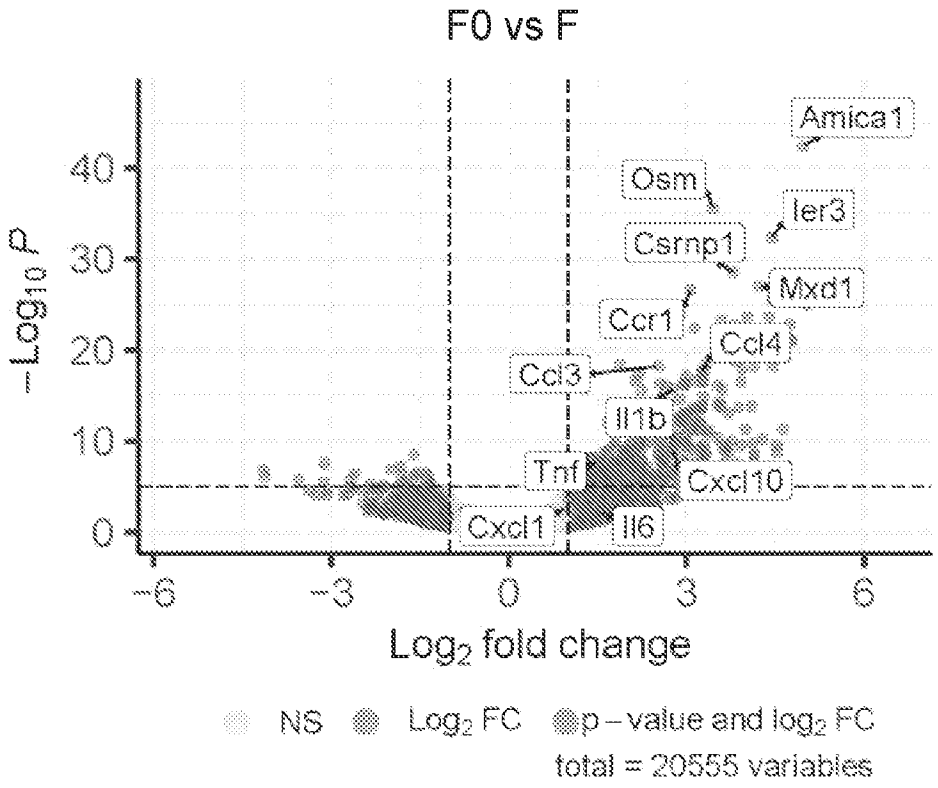

F0 vs F
$-Log_{10}P$
Log_2 fold change
Amica1
Osm
Ier3
Csrnp1
Mxd1
Ccr1
Ccl4
Ccl3
Il1b
Tnf
Cxcl10
Cxcl1
Il6
NS
Log_2 FC
p – value and log_2 FC
total = 20555 variables

FIG. 9D

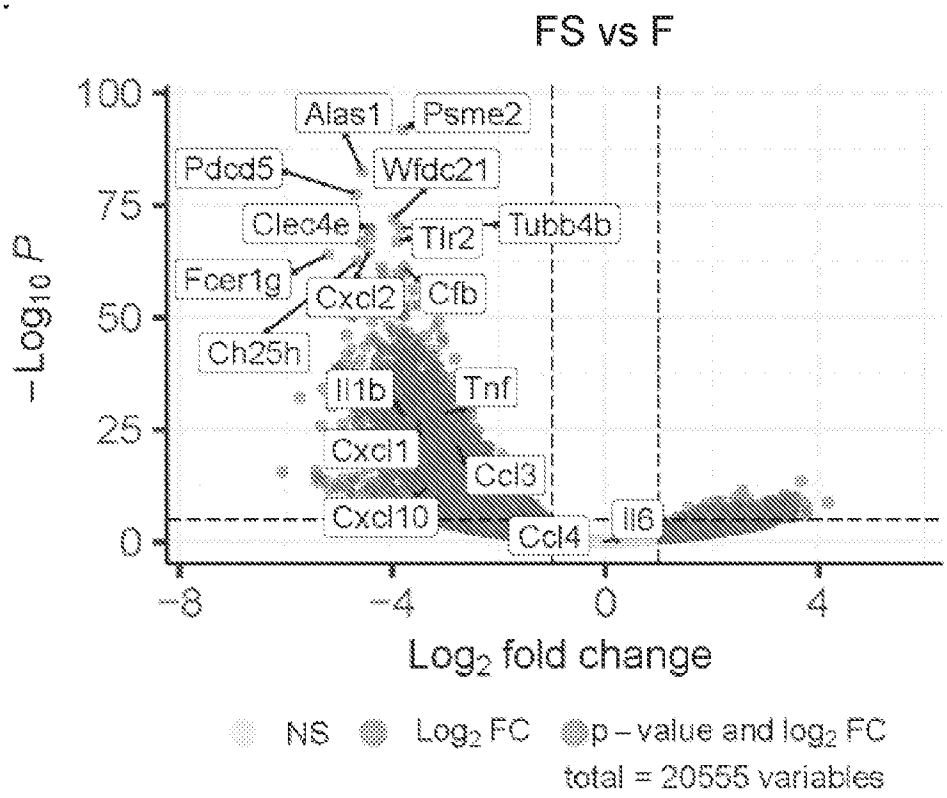

FS vs F
100
75
50
25
0
−Log10 p
Alas1
Psme2
Pdcd5
Wfdc21
Clec4e
Tlr2
Tubb4b
Fcer1g
Cxcl2
Cfb
Ch25h
Il1b
Tnf
Cxcl1
Ccl3
Cxcl10
Ccl4
Il6
−8
−4
0
4
Log2 fold change
NS
Log2 FC
p – value and log2 FC
total = 20555 variables

FIG. 9E

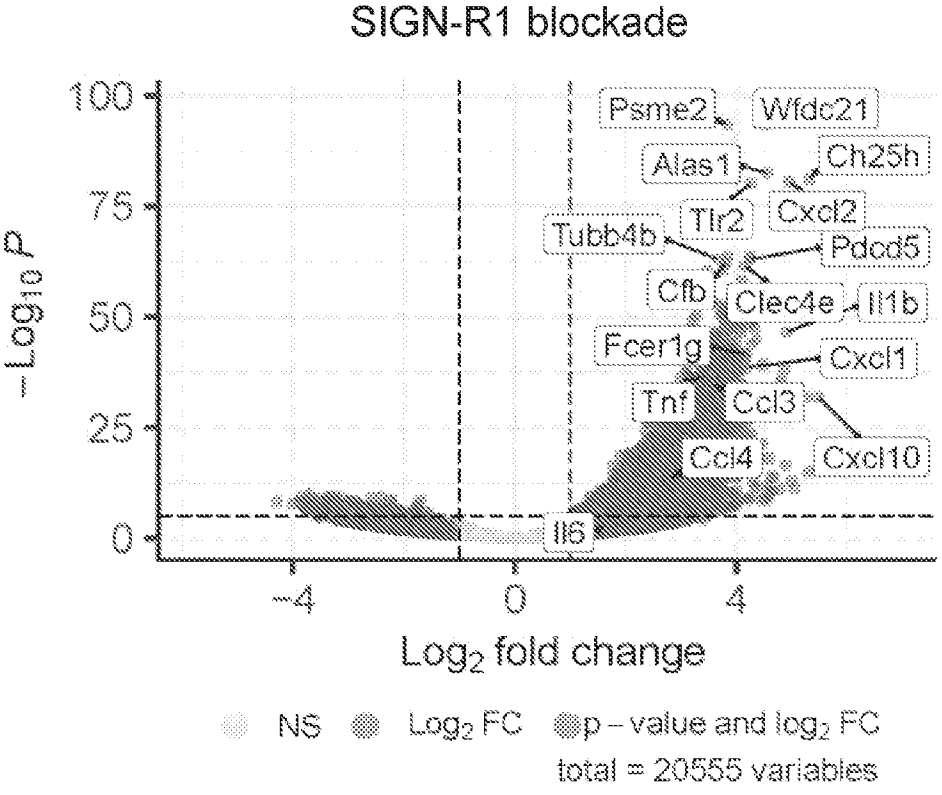

SIGN-R1 blockade
100
75
50
25
0
−Log10 p
Psme2
Wfdc21
Alas1
Ch25h
Tlr2
Cxcl2
Tubb4b
Pdcd5
Cfb
Clec4e
Il1b
Fcer1g
Cxcl1
Tnf
Ccl3
Ccl4
Cxcl10
Il6
−4
0
4
Log2 fold change
NS
Log2 FC
p – value and log2 FC
total = 20555 variables

FIG. 9F

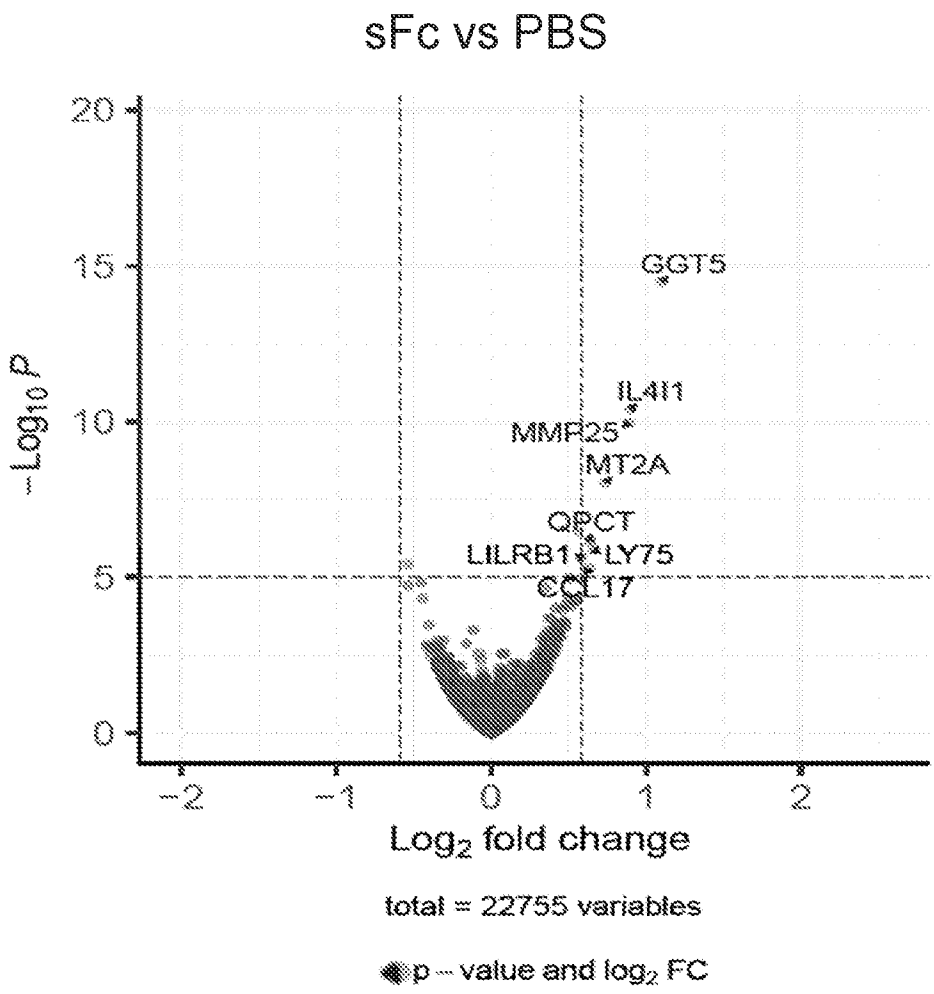

sFc vs PBS
20
15
10
5
0
−Log10 P
GGT5
IL4I1
MMP25
MT2A
QPCT
LILRB1
LY75
CCL17
−2
−1
0
1
2
Log2 fold change
total = 22755 variables
p – value and log2 FC

FIG. 10A

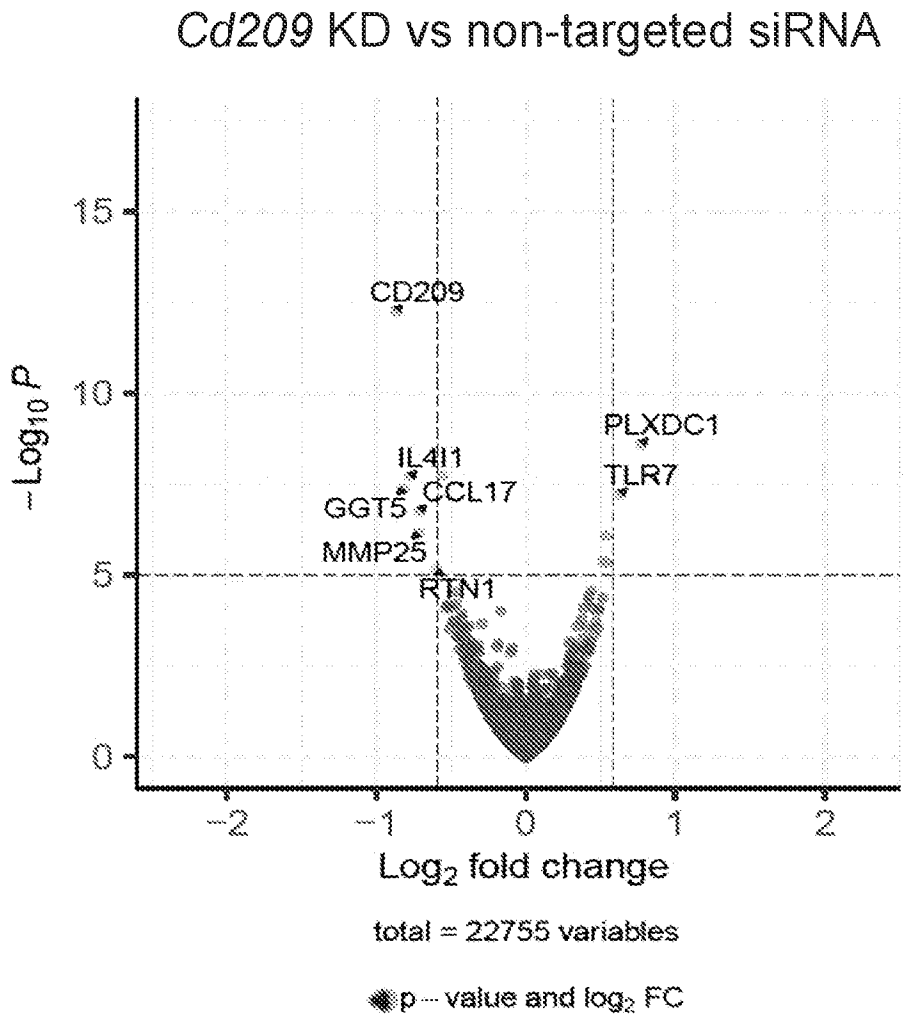

Cd209 KD vs non-targeted siRNA
15
10
5
0
−Log10 P
CD209
IL4I1
CCL17
GGT5
MMP25
RTN1
PLXDC1
TLR7
−2
−1
0
1
2
Log2 fold change
total = 22755 variables
p-value and log2 FC

FIG. 10B

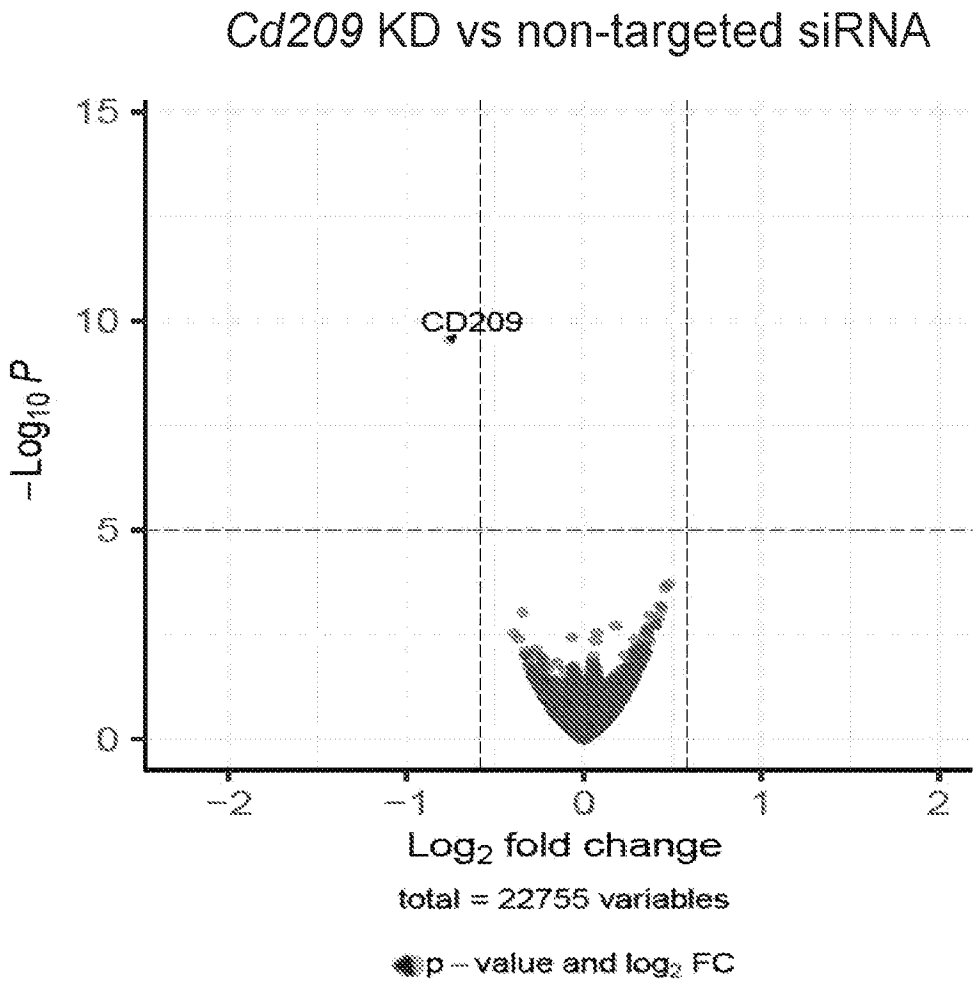

Cd209 KD vs non-targeted siRNA
15
10
5
0
−Log10 P
CD209
−2
−1
0
1
2
Log2 fold change
total = 22755 variables
p − value and log2 FC

FIG. 10C

Sialylated IC vs asialylated IC

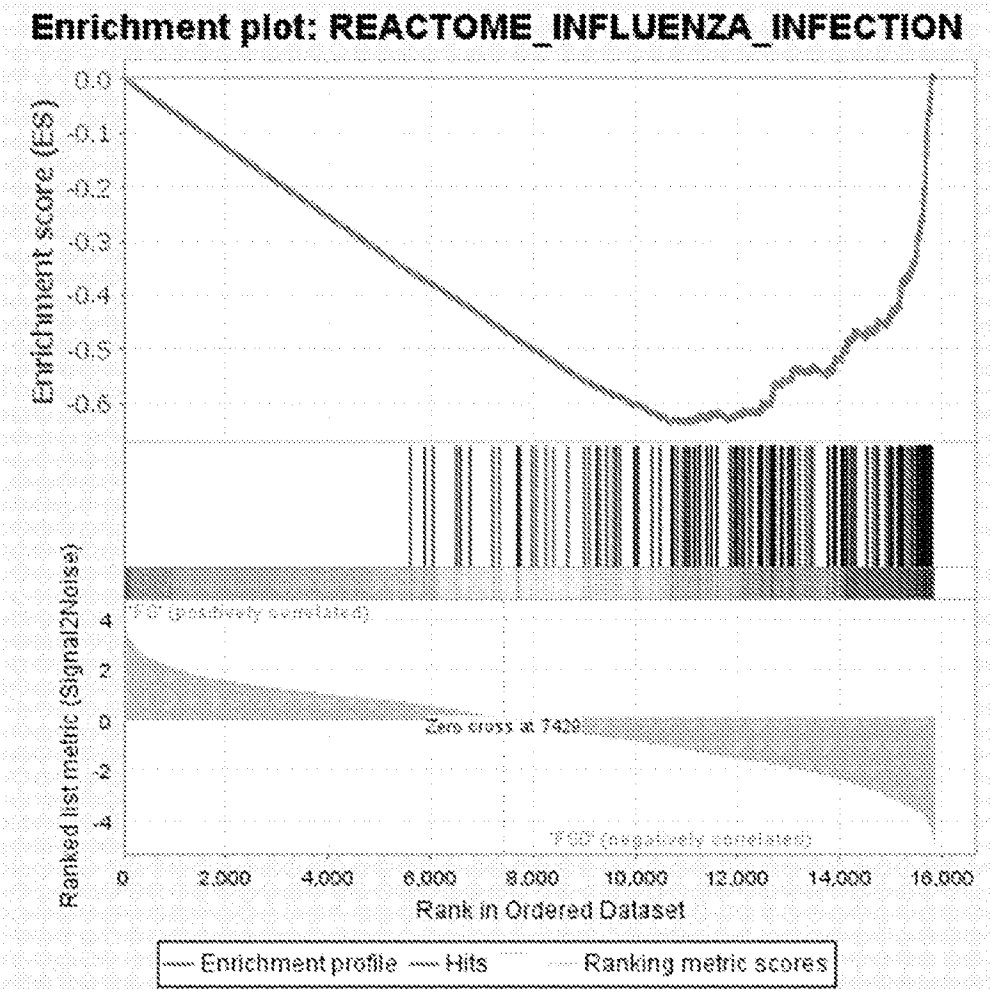


FIG. 11A

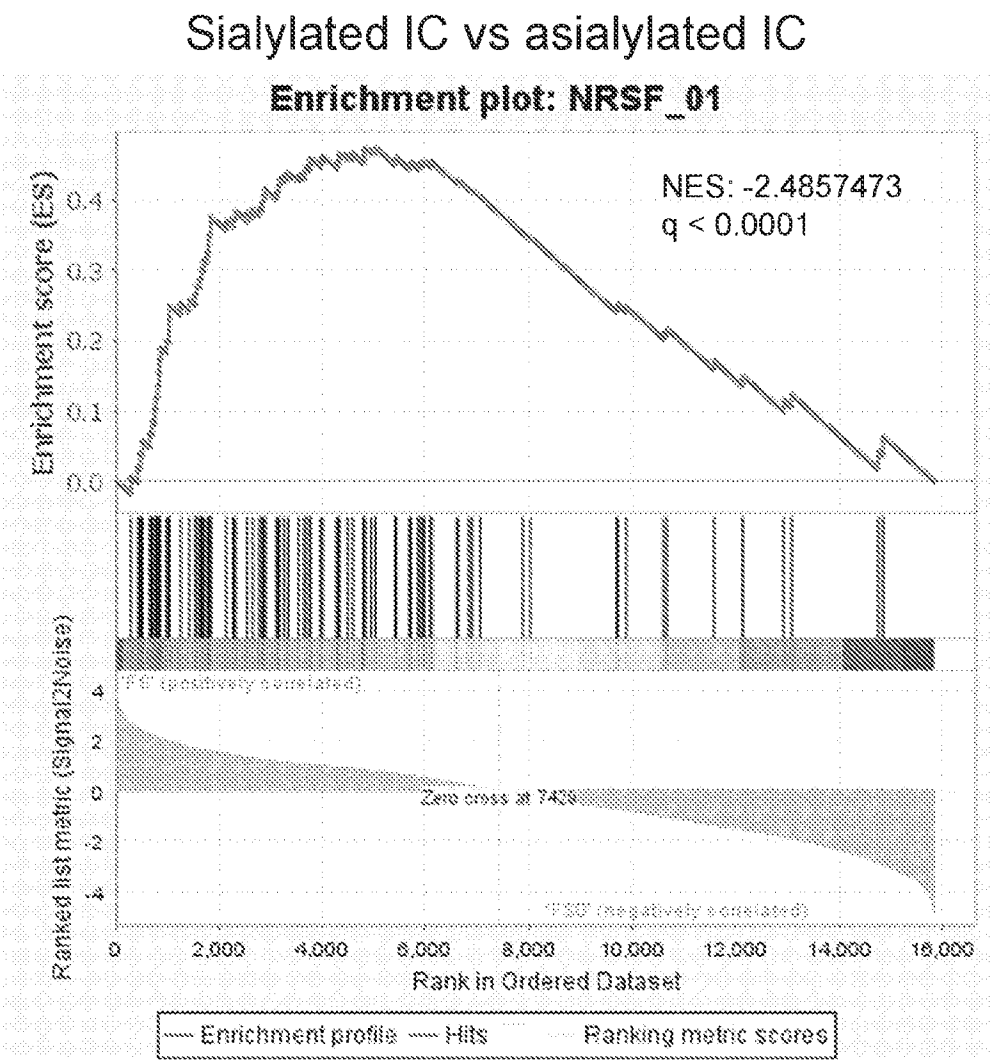

Sialylated IC vs asialylated IC
Enrichment plot: NRSF_01
NES: -2.4857473
q < 0.0001
Enrichment score (ES)
0.4
0.3
0.2
0.1
0.0
Ranked list metric (Signal2Noise)
4
2
0
-2
-4
Zero cross at 7439
0
2,000
4,000
6,000
8,000
10,000
12,000
14,000
16,000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

FIG. 11B

Description	LogP	Genes
Cytokine Signaling in Immune system	-7.9402009	HRAS,ICAM1,IFI35,JUNB,LGALS9,NFKBIB,RELB,TNF,SOCS1,UBE2M,MAPKAPK2,TRIM14,IL27
TNF-alpha/NF-kappa B signaling complex	-5.7162817	NFKBIB,NFKBIE,RELB,HRAS
Regulation of TNFR1 signaling	-3.722431	TNF,MAPKAPK2,OPTN
C-type lectin receptors (CLRs)	-3.4771361	CDC34,HRAS,RELB,UBE2M,TNF

FIG. 12A

	Adjusted p value	
Differential expressed genes	Vir vs S	S0 vs S
CDC34	0.01789858	0.00754712
HRAS	0.03634813	0.03217343
ICAM1	0.04955461	0.00860261
IFI35	0.02735501	0.005294
IL27	0.02339306	0.00201463
JUNB	2.95E-05	0.00027284
LGALS9	0.02328664	0.00473309
MAPKAPK2	0.01443558	1.91E-05
NFKBIB	0.000445	0.00754712
NFKBIE	0.04766789	0.0234999
OPTN	0.05603906	0.02043727
RELB	0.0104084	0.00160146
SOCS1	0.05409877	0.03833255
TNF	0.0226134	0.00448956
TRIM14	0.01850362	0.00045358
UBE2M	0.05488641	0.00155905

FIG. 12B

Sialic acid binding receptors on AMs

	Status		Adjusted p value	
Differential expressed genes	**Vir vs S**	**S0 vs S**	**Vir vs S**	**S0 vs S**
CD209b	NA	Down-regulated	NS	0.04146001
Siglecg	Down-regulated	Down-regulated	0.00086763	0.04472094

FIG. 12C

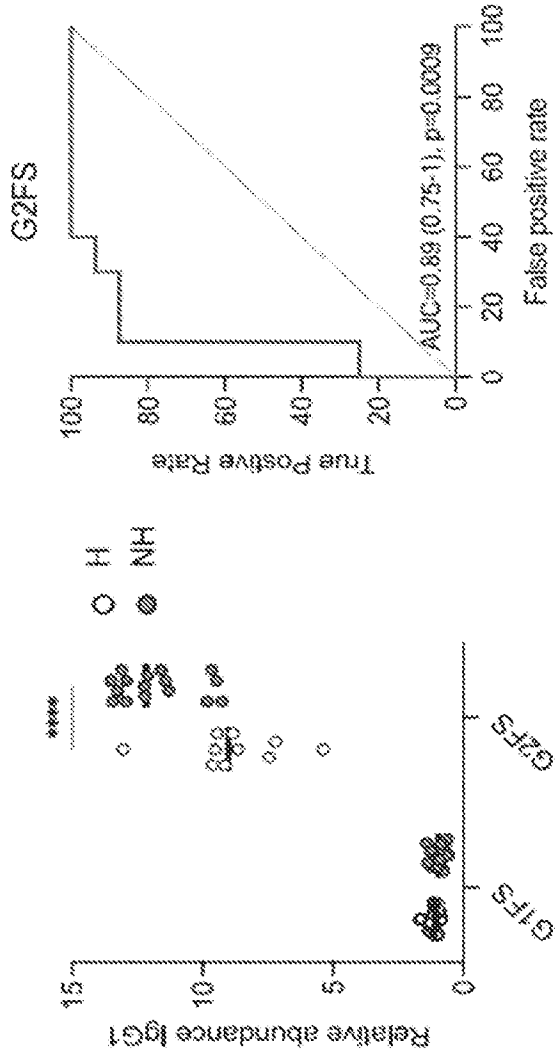


FIG. 13A

FIG. 13B

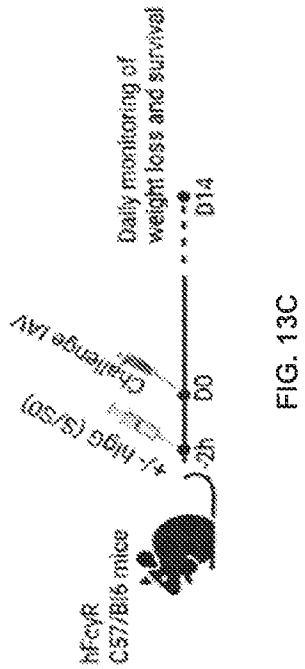


FIG. 13C

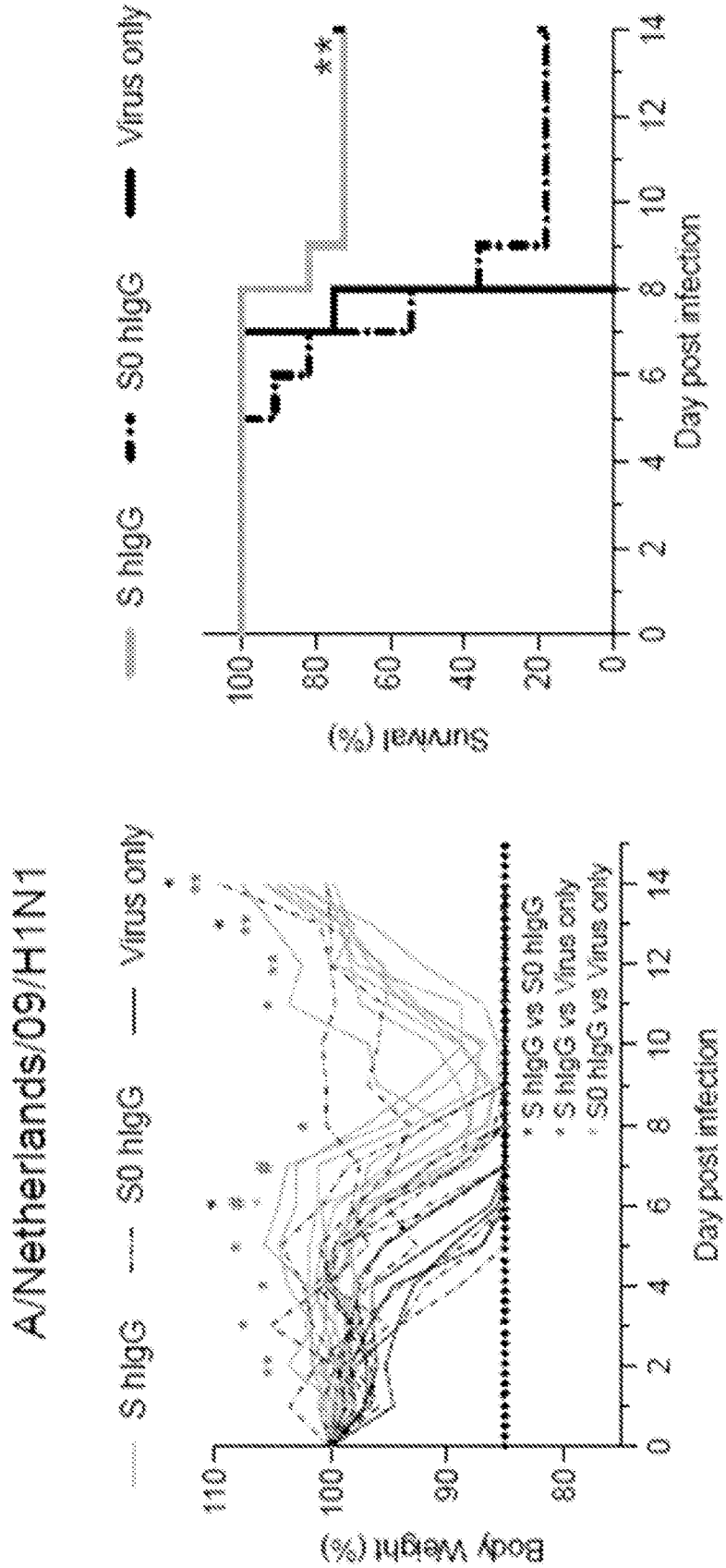

A/Netherlands/09/H1N1
S hIgG
S0 hIgG
Virus only
Body weight (%)
Day post infection
* S hIgG vs S0 hIgG
* S hIgG vs Virus only
* S0 hIgG vs Virus only
S hIgG
S0 hIgG
Virus only
Survival (%)
Day post infection

FIG. 13D

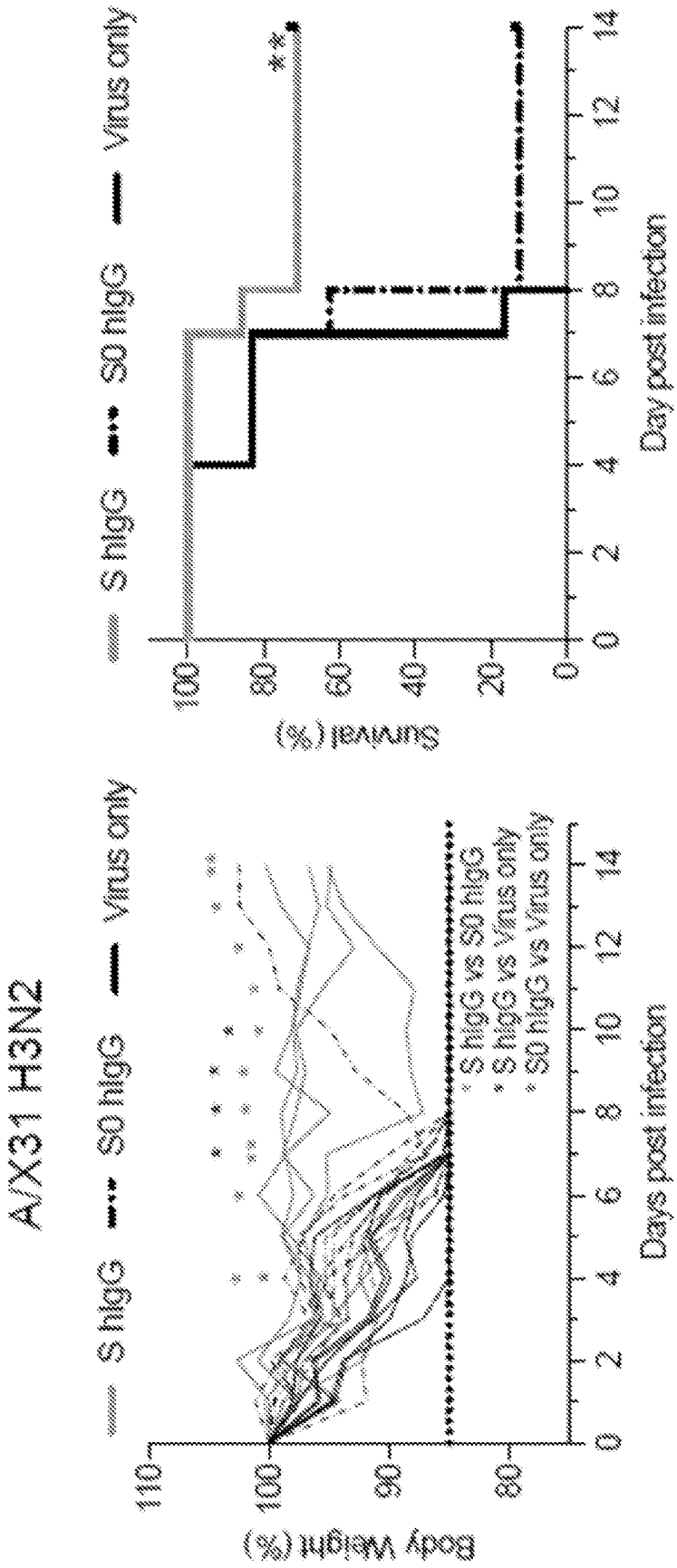

A/X31 H3N2
S hIgG
S0 hIgG
Virus only
Body Weight (%)
Days post infection
* S hIgG vs S0 hIgG
* S hIgG vs Virus only
* S0 hIgG vs Virus only
Survival (%)
Day post infection
**

FIG. 13E

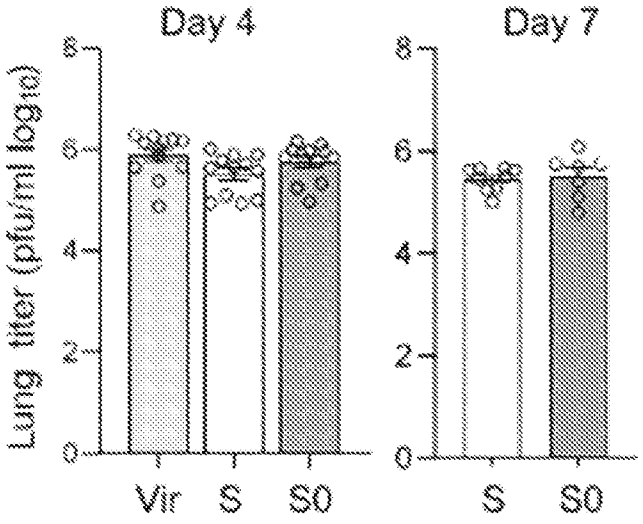


FIG. 13F

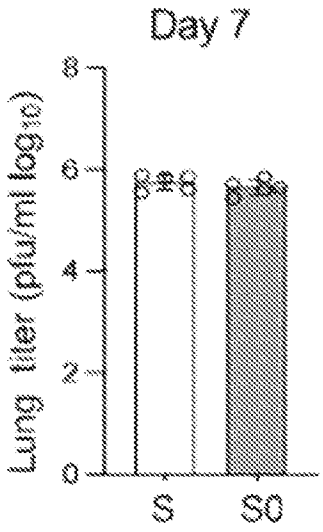


FIG. 13G

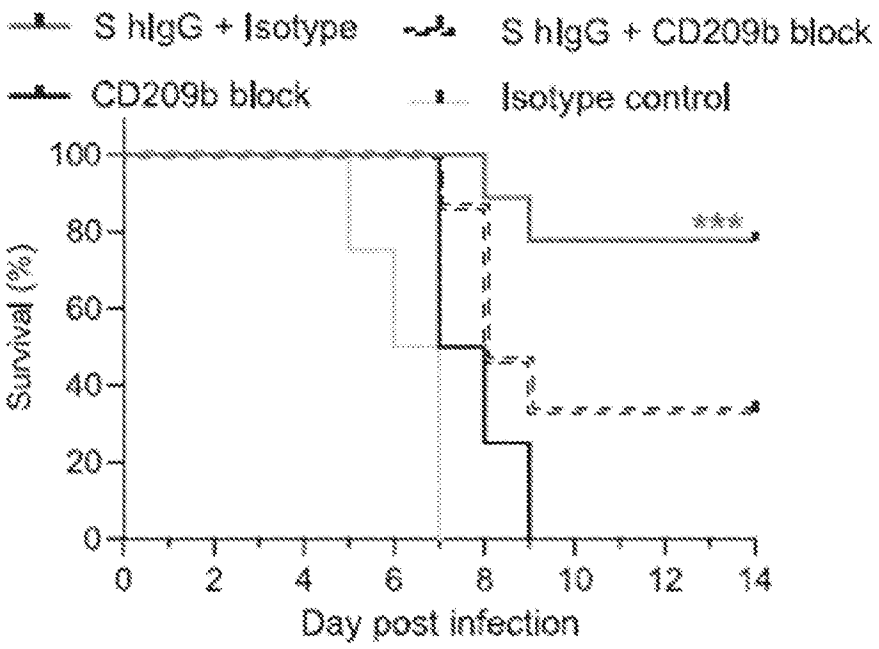


FIG. 13H

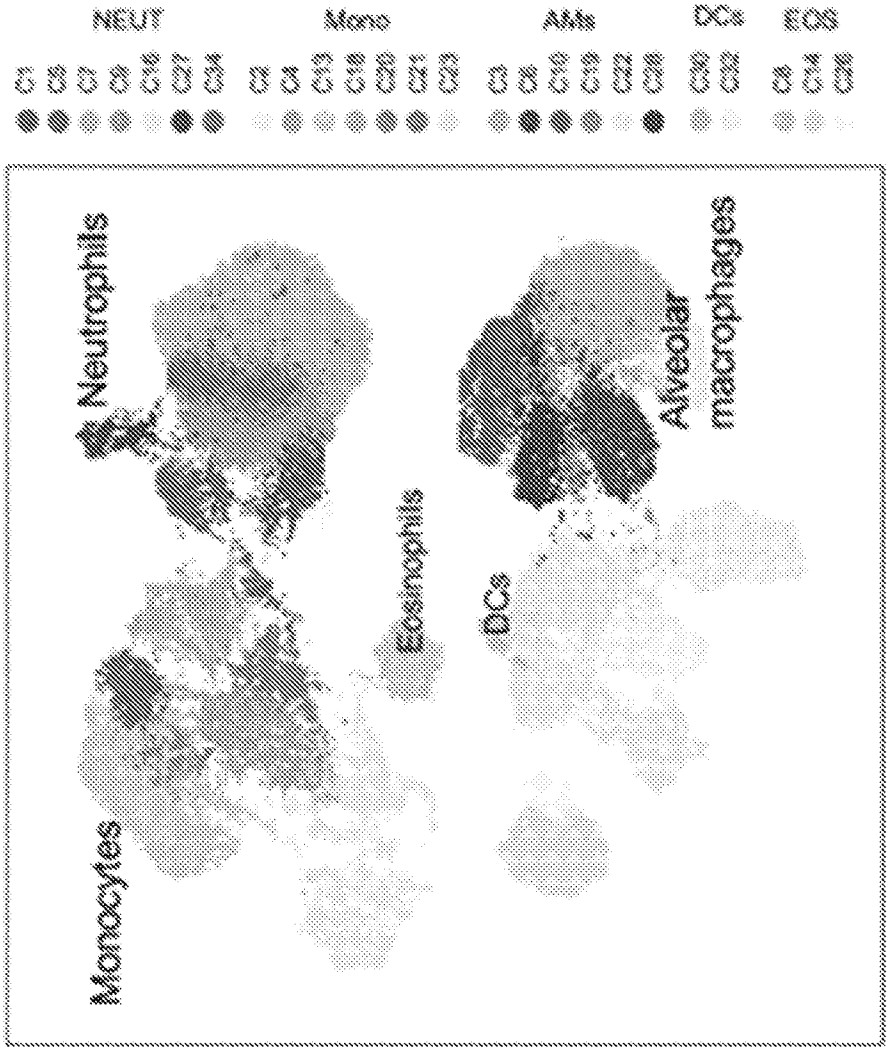

NEUT
Mono
AMs
DCs
EOS
Neutrophils
Monocytes
Eosinophils
DCs
Alveolar macrophages

FIG. 14A

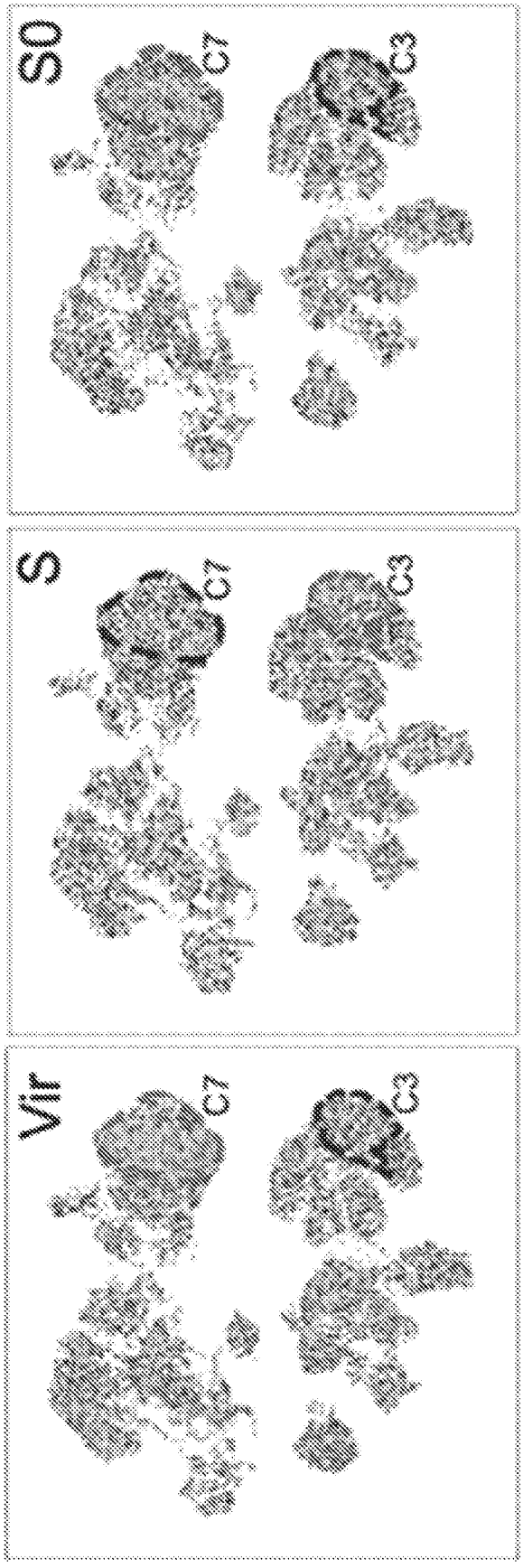


FIG. 14A (cont.)

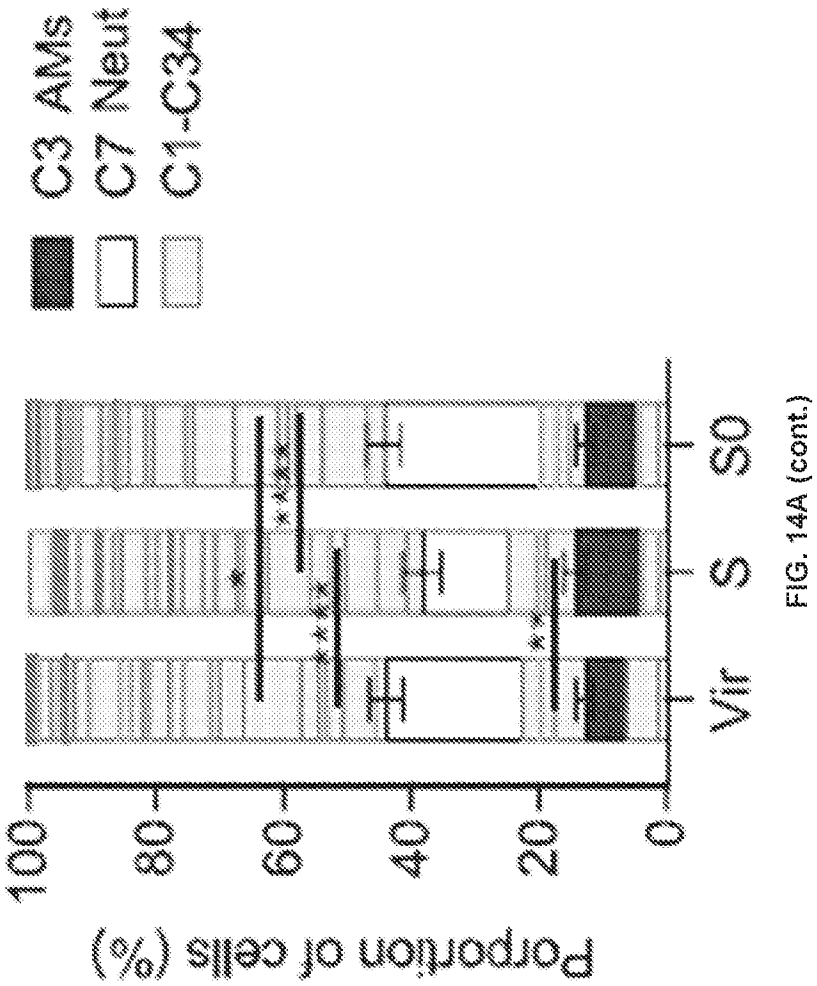

C3 AMs
C7 Neut
C1-C34
Vir
S
S0
Proportion of cells (%)
100
80
60
40
20
0
*
***
***
**

FIG. 14A (cont.)

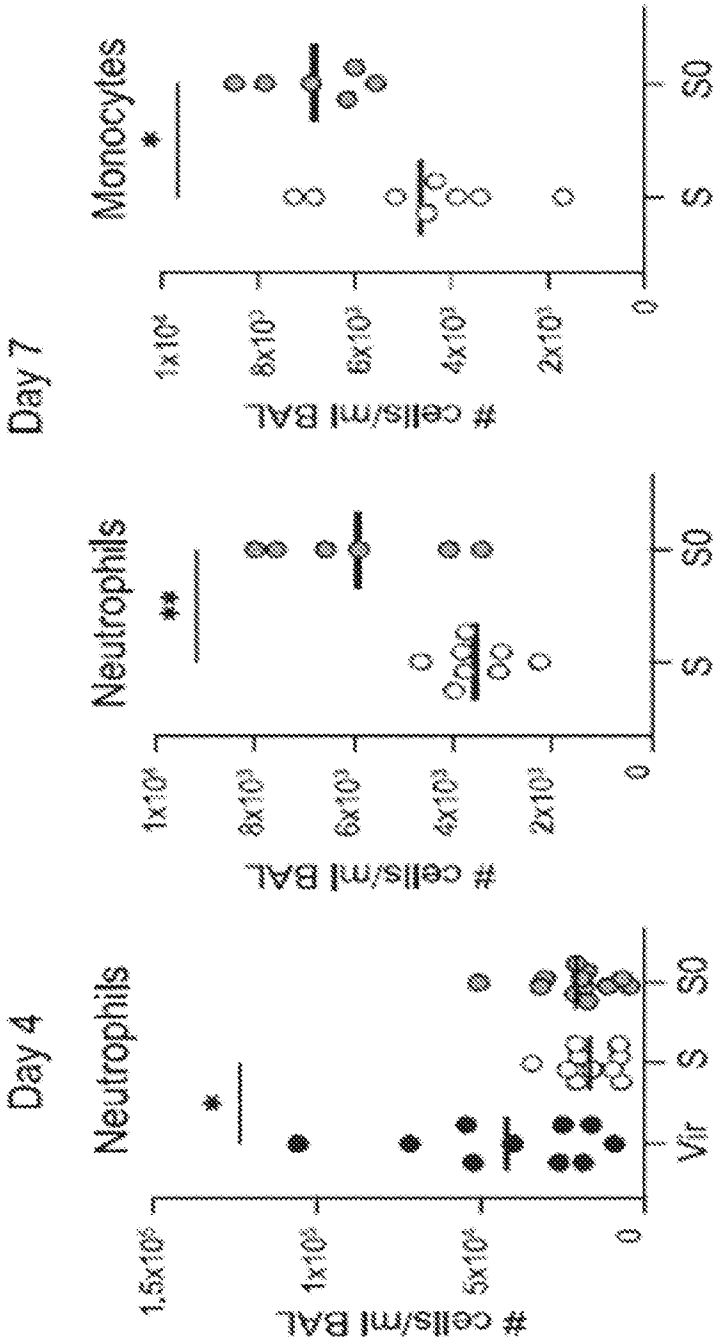

Day 4
Neutrophils
cells/ml BAL
1,5x10⁶
1x10⁶
5x10⁵
0
Vir
S
S0
Day 7
Neutrophils
cells/ml BAL
1x10⁴
8x10³
6x10³
4x10³
2x10³
0
S
S0
Monocytes
cells/ml BAL
1x10⁴
8x10³
6x10³
4x10³
2x10³
0
S
S0

FIG. 14B

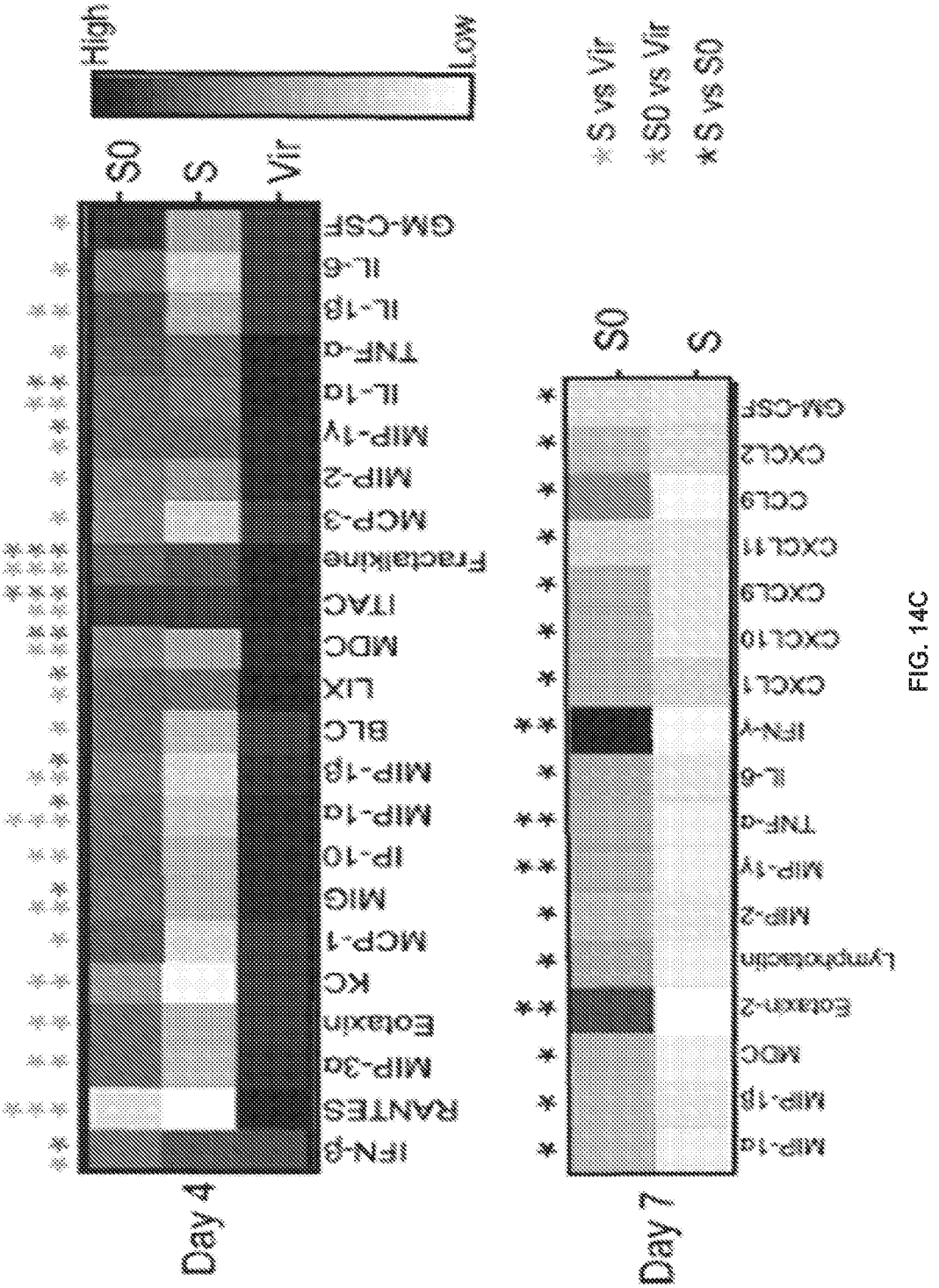

High
Low
S0
S
Vir
GM-CSF
IL-6
IL-1β
TNF-α
IL-1α
MIP-1γ
MIP-2
MCP-3
Fractalkine
ITAC
MDC
LIX
BLC
MIP-1β
MIP-1α
IP-10
MIG
MCP-1
KC
Eotaxin
MIP-3α
RANTES
IFN-β
Day 4
* S vs Vir
* S0 vs Vir
* S vs S0
S0
S
GM-CSF
CXCL2
CCL9
CXCL11
CXCL9
CXCL10
CXCL1
IFN-γ
IL-6
TNF-α
MIP-1γ
MIP-2
Lymphotactin
Eotaxin-2
MDC
MIP-1β
MIP-1α
Day 7

FIG. 14C

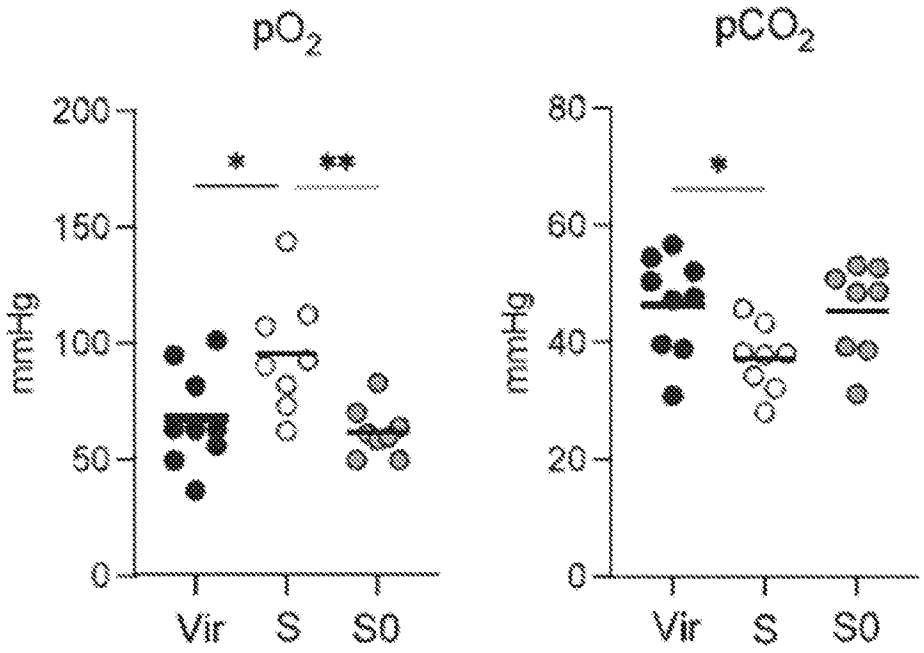


FIG. 14D

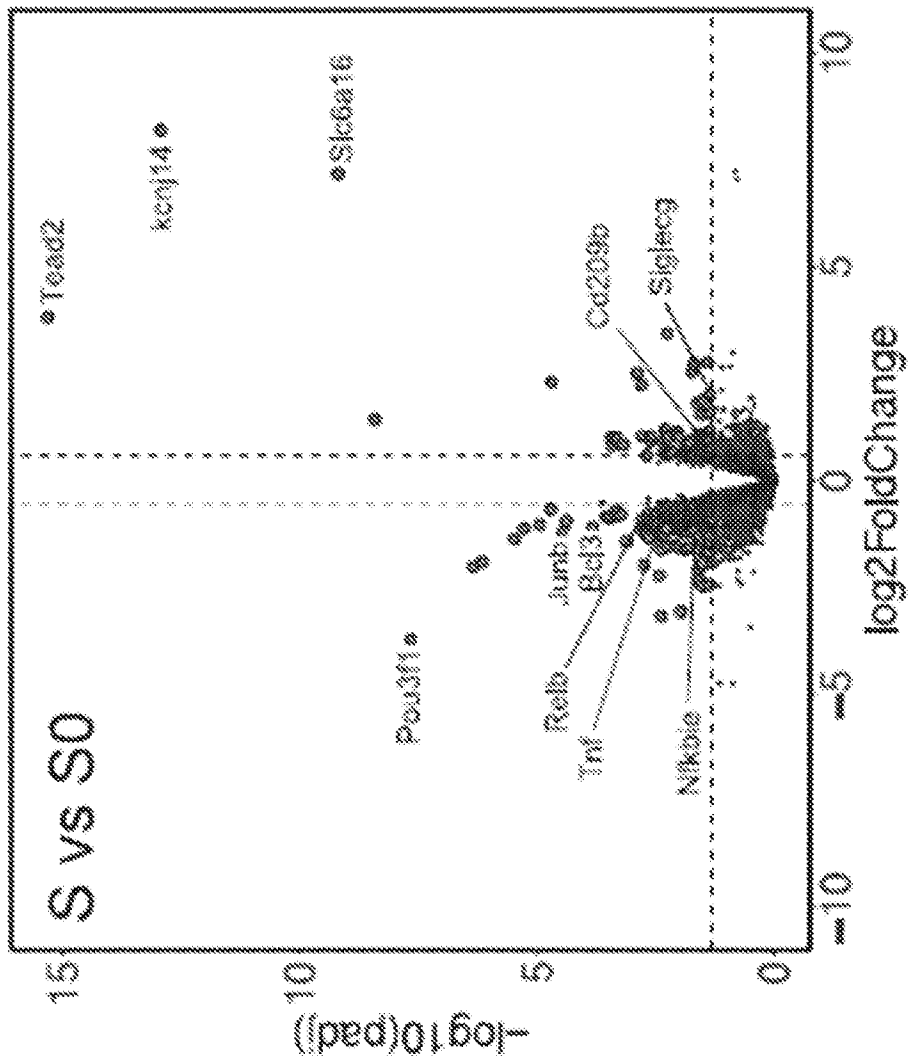

S vs S0
Tead2
Icmj14
Slc6a16
Cd209e
Siglecg
Pou3f1
Relb
Junb
Bcl3
Tnf
Nfkbie
−log10(padj)
log2FoldChange
15
10
5
0
10
5
0
−5
−10

FIG. 15A

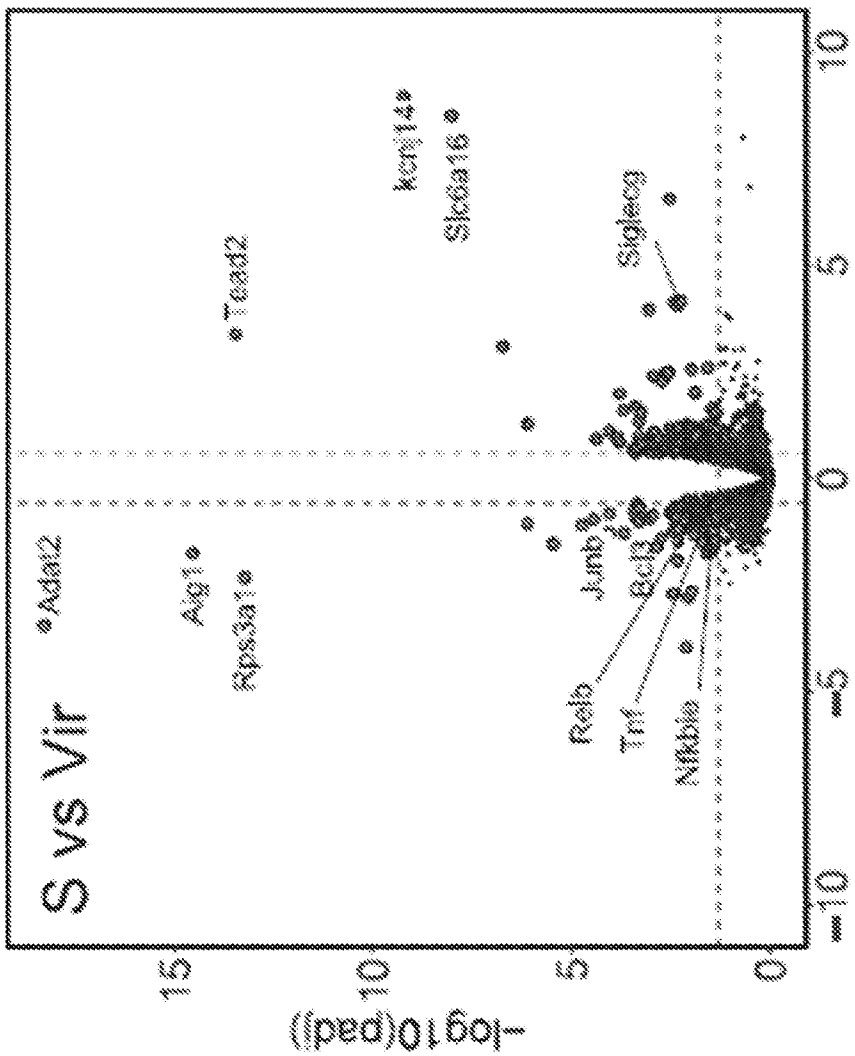

S vs Vir
Adat2
Arg1
Rps3a1
Tead2
Kcnj14
Slc6a16
Siglecg
Junb
Bcl3
Relb
Tnf
Mkbia
-log10(padj)
log2FoldChange
15
10
5
0
10
5
0
5
10

FIG. 15A (cont.)

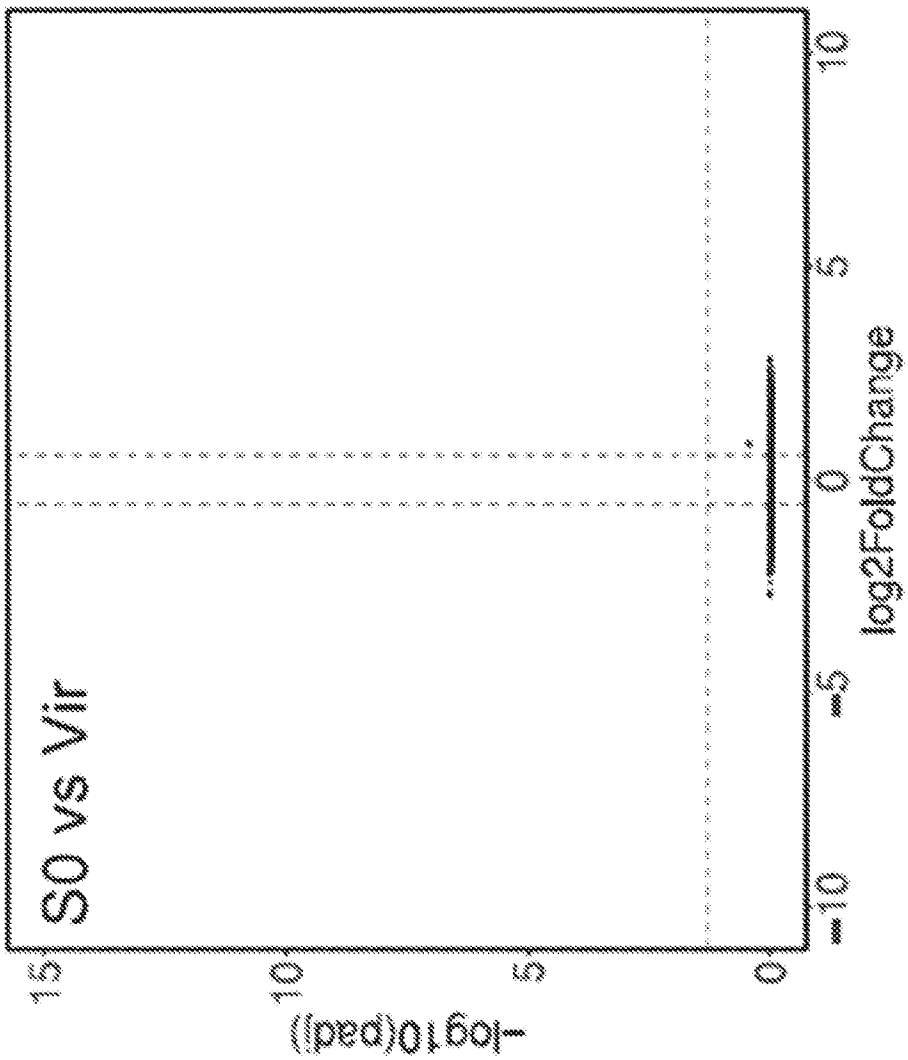


FIG. 15A (cont.)

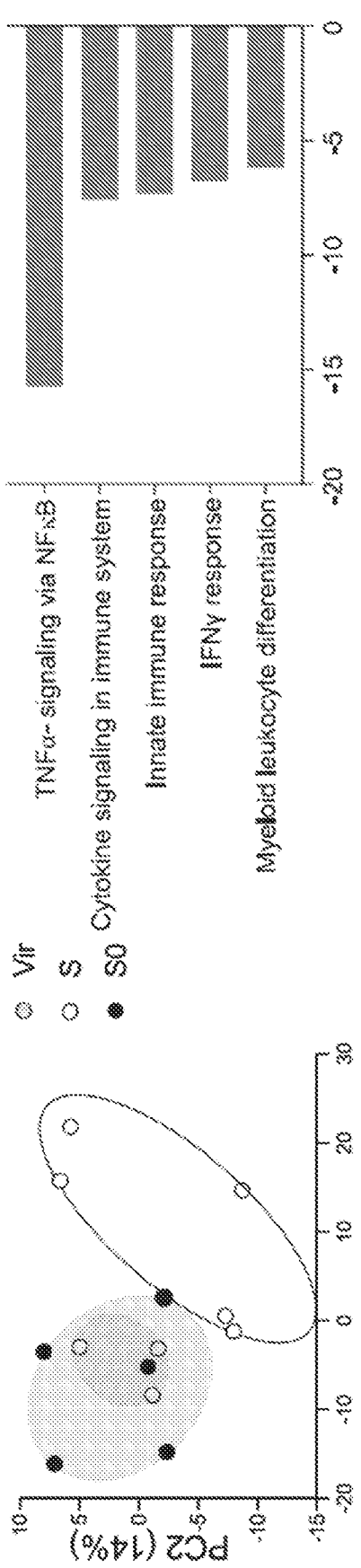


FIG. 15B

FIG. 15C

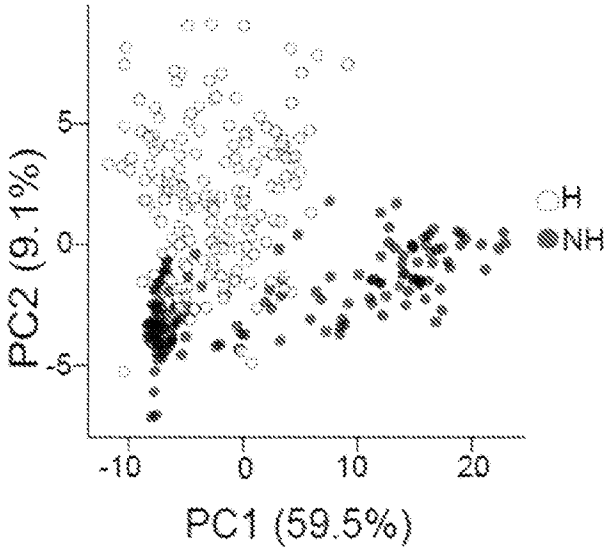


FIG. 15D

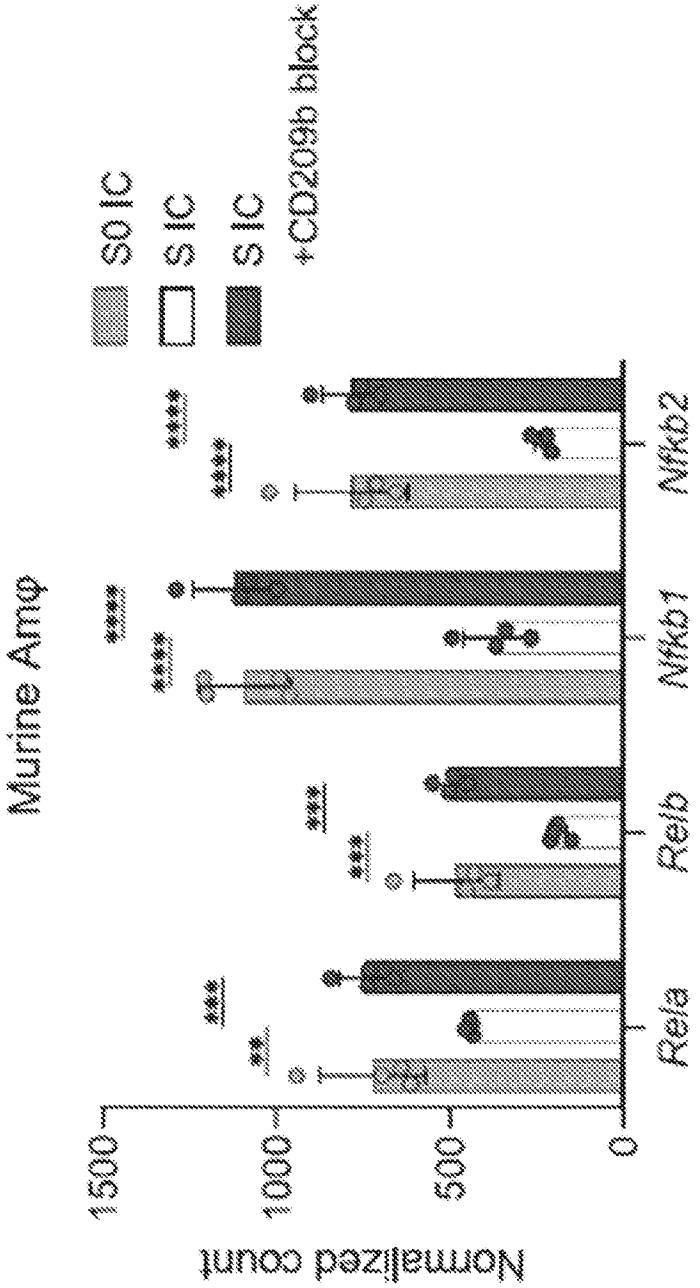

Murine Amφ
Normalized count
1500
1000
500
0
S0 IC
S IC
S IC
+CD209b block
Rela
Relb
Nfkb1
Nfkb2

FIG. 16A

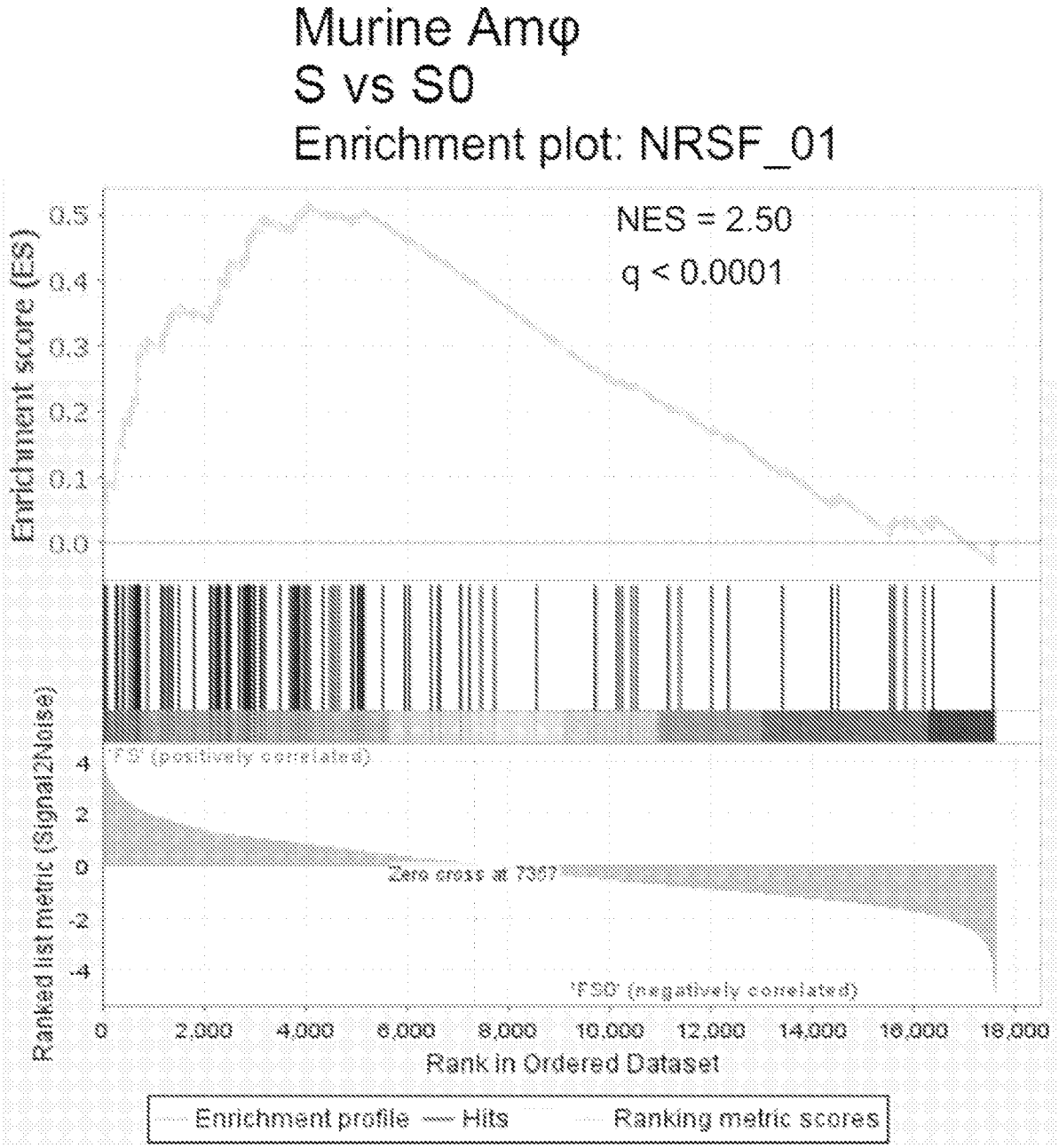

Murine Amφ
S vs S0
Enrichment plot: NRSF_01
NES = 2.50
q < 0.0001
Enrichment score (ES)
0.5
0.4
0.3
0.2
0.1
0.0
'FS' (positively correlated)
Zero cross at 7387
'FS0' (negatively correlated)
Ranked list metric (Signal2Noise)
4
2
0
-2
-4
0
2,000
4,000
6,000
8,000
10,000
12,000
14,000
16,000
18,000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

FIG. 16B

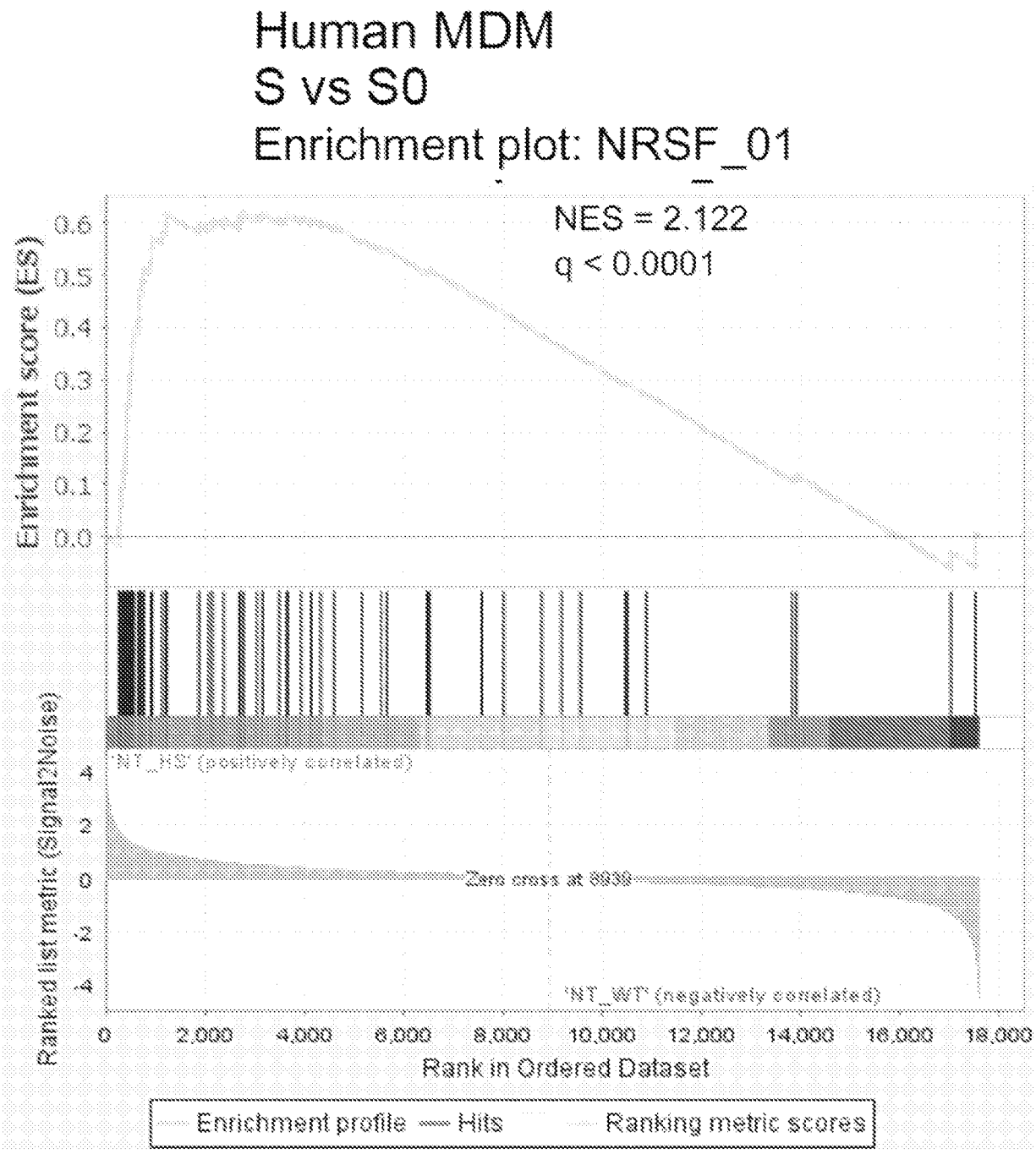

Human MDM
S vs S0
Enrichment plot: NRSF_01
NES = 2.122
q < 0.0001
Enrichment score (ES)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
'NT_HS' (positively correlated)
Zero cross at 8939
'NT_WT' (negatively correlated)
Ranked list metric (Signal2Noise)
4
2
0
-2
-4
0
2,000
4,000
6,000
8,000
10,000
12,000
14,000
16,000
18,000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

FIG. 16B (cont.)

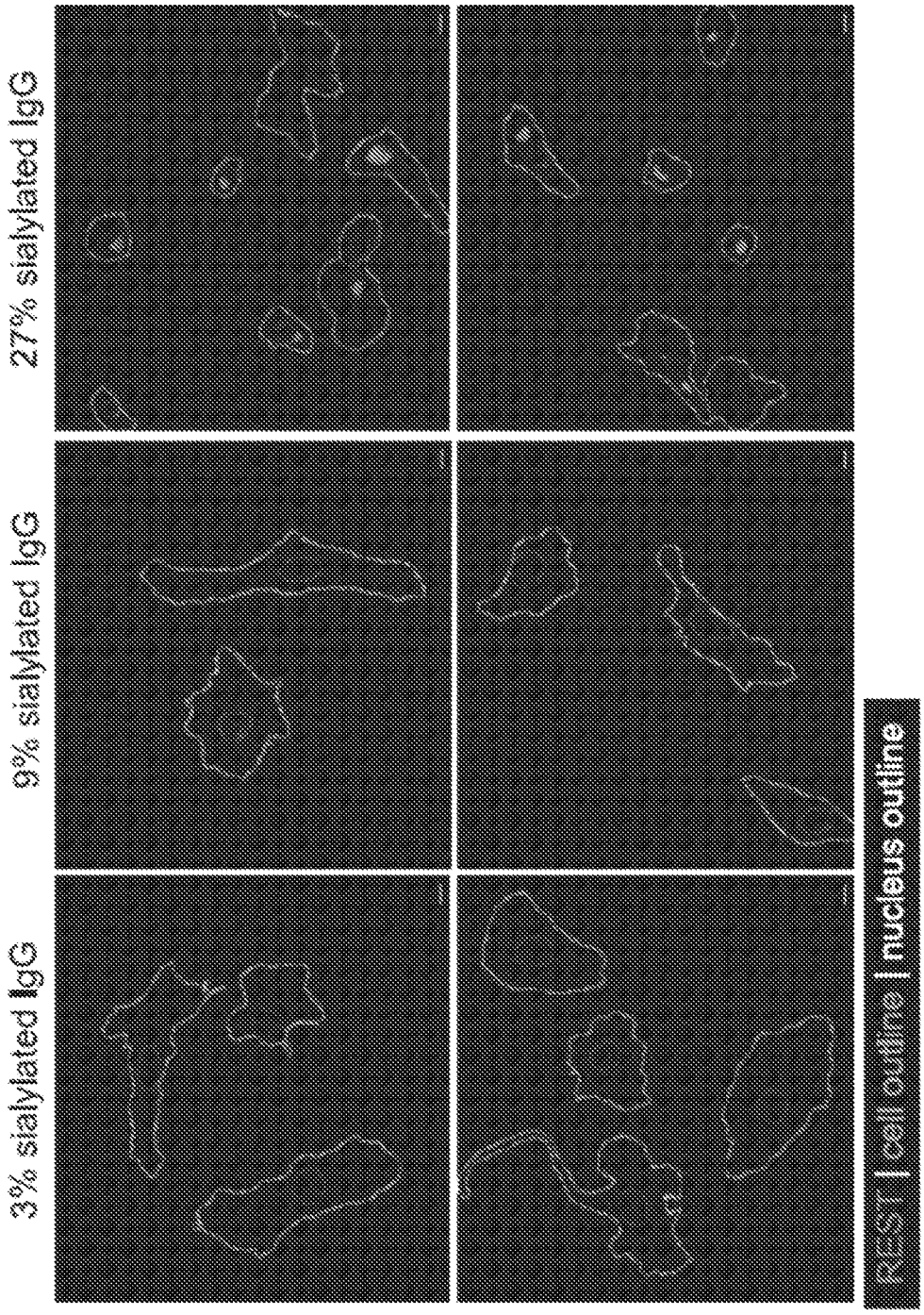

3% sialylated IgG
9% sialylated IgG
27% sialylated IgG
RITS | cell outline | nucleus outline

FIG. 16C

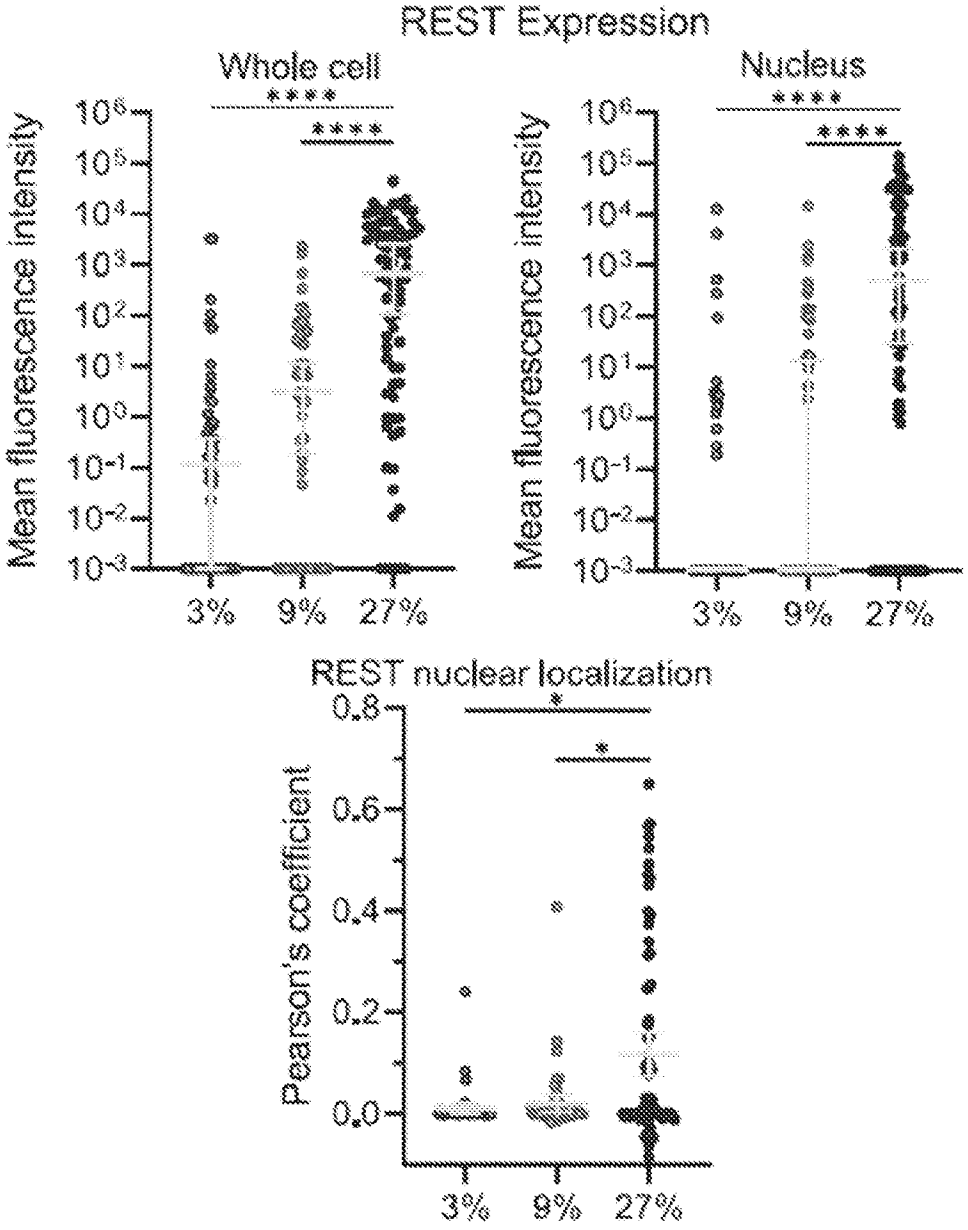

REST Expression
Whole cell
Nucleus
Mean fluorescence intensity
****
****
3%
9%
27%
REST nuclear localization
Pearson's coefficient
*
*

FIG. 16D

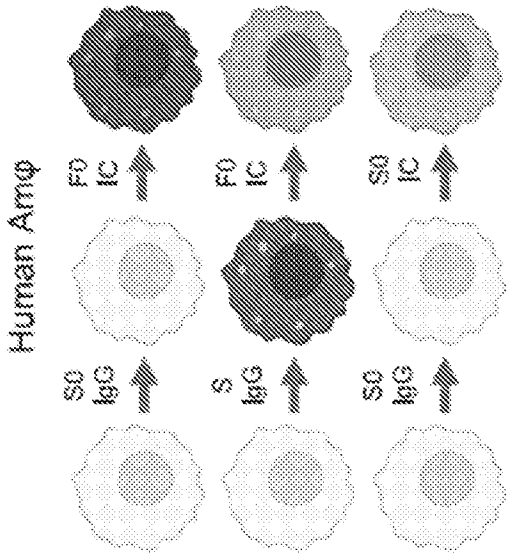


FIG. 16F

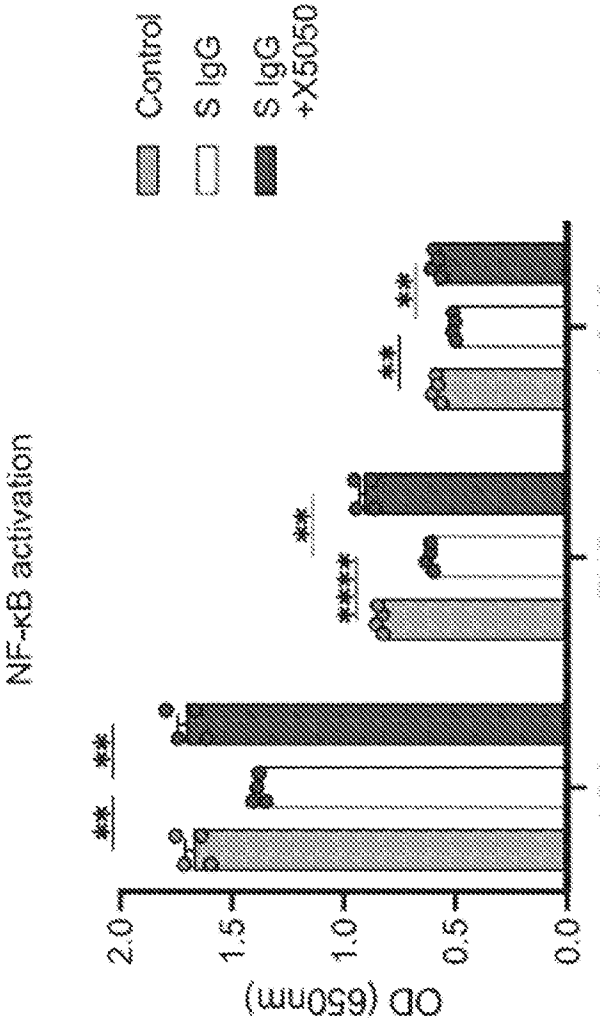


FIG. 16E

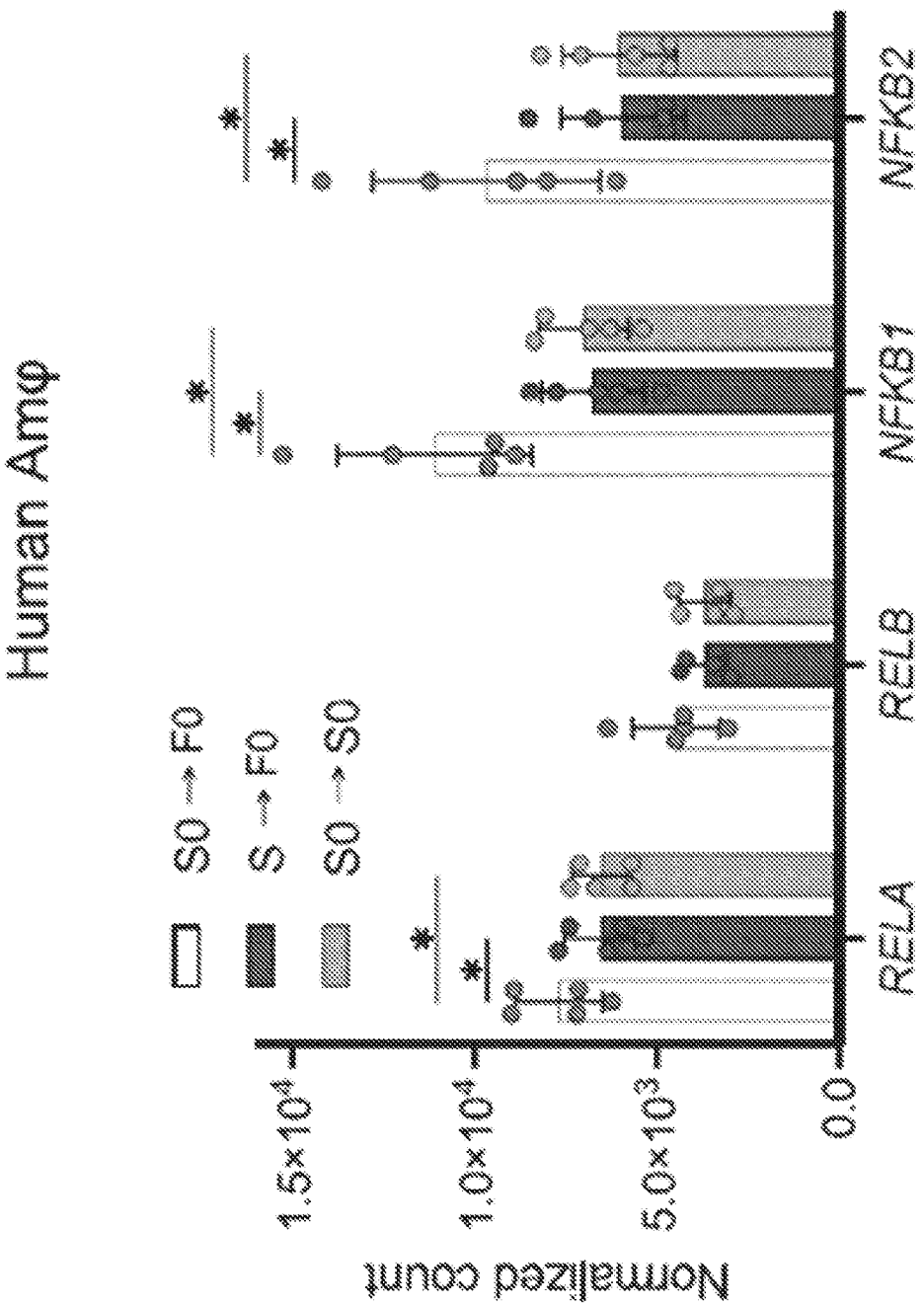

Human Amφ
Normalized count
1.5×10⁴
1.0×10⁴
5.0×10³
0.0
S0 → F0
S → F0
S0 → S0
RELA
RELB
NFKB1
NFKB2
*
*
*
*
*

FIG. 16G

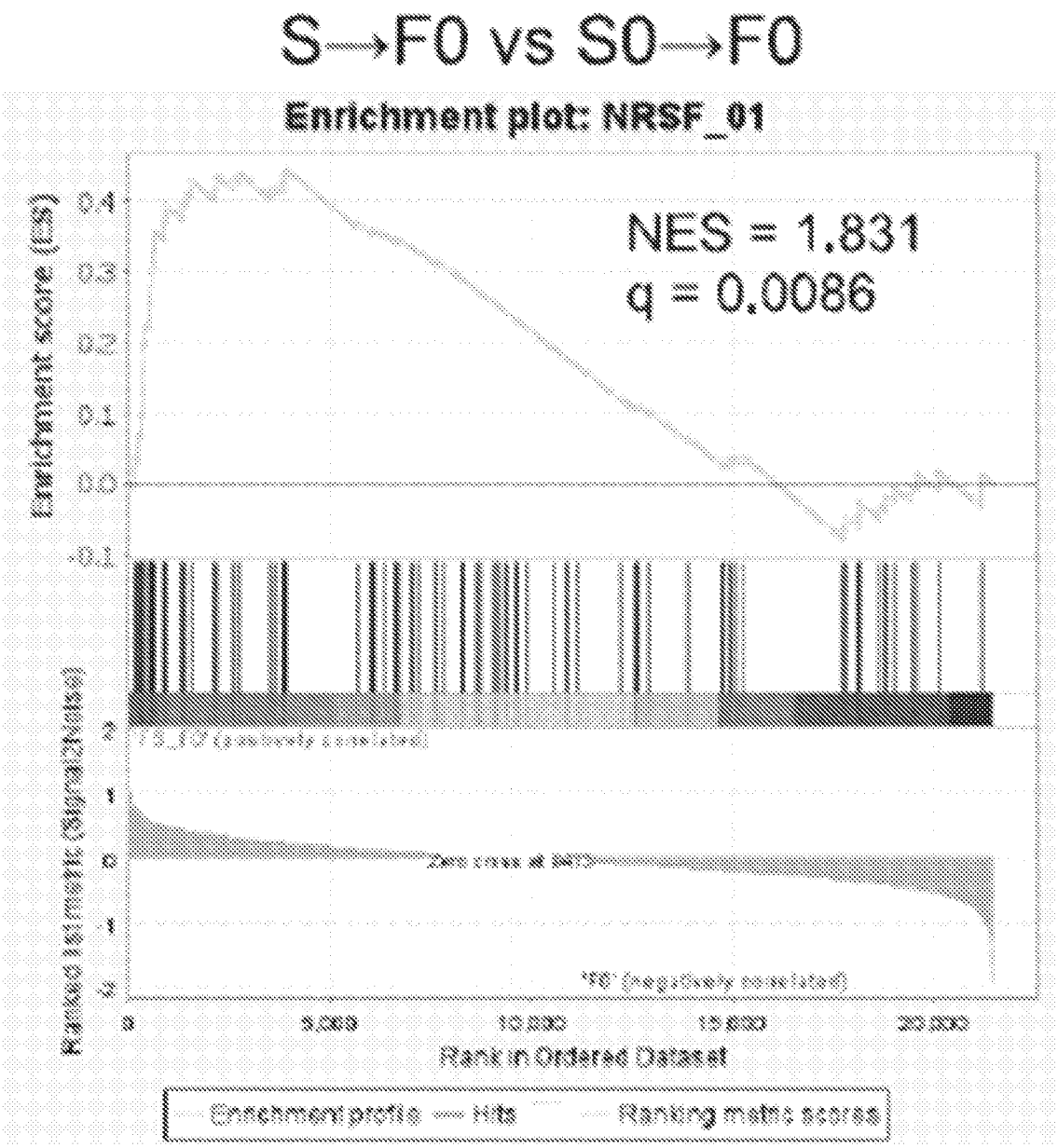

S→F0 vs S0→F0
Enrichment plot: NRSF_01
NES = 1.831
q = 0.0086
Enrichment score (ES)
Ranked list metric (Signal2Noise)
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

FIG. 16H

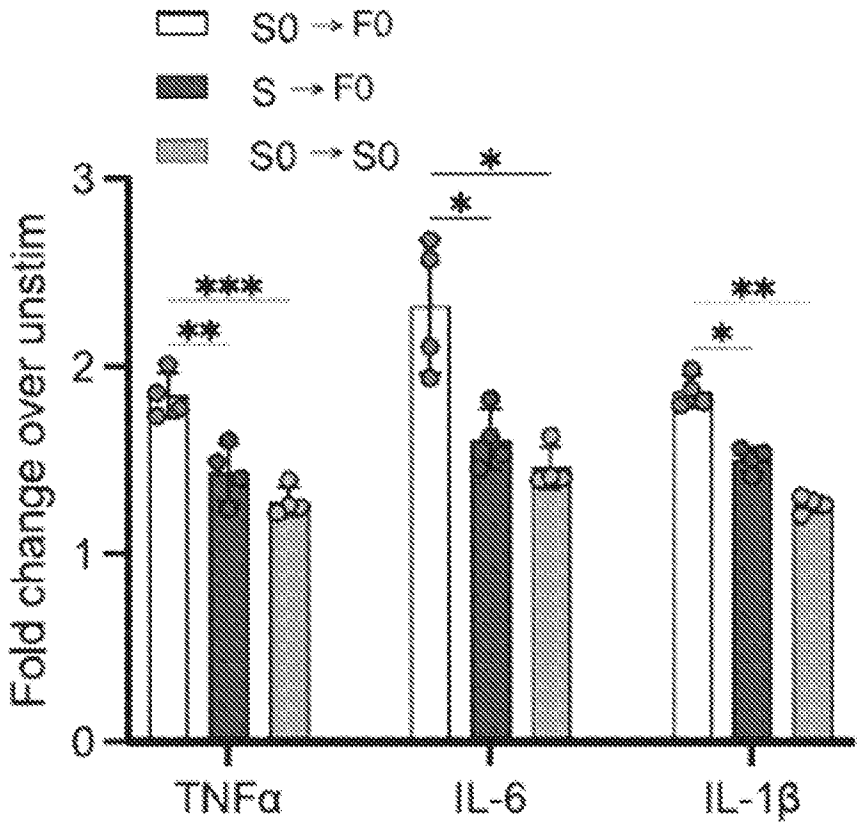


FIG. 16I

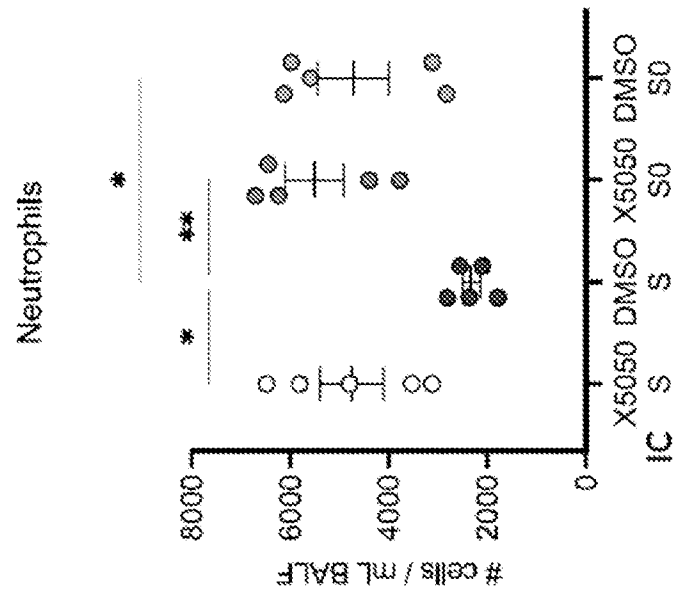


FIG. 17B

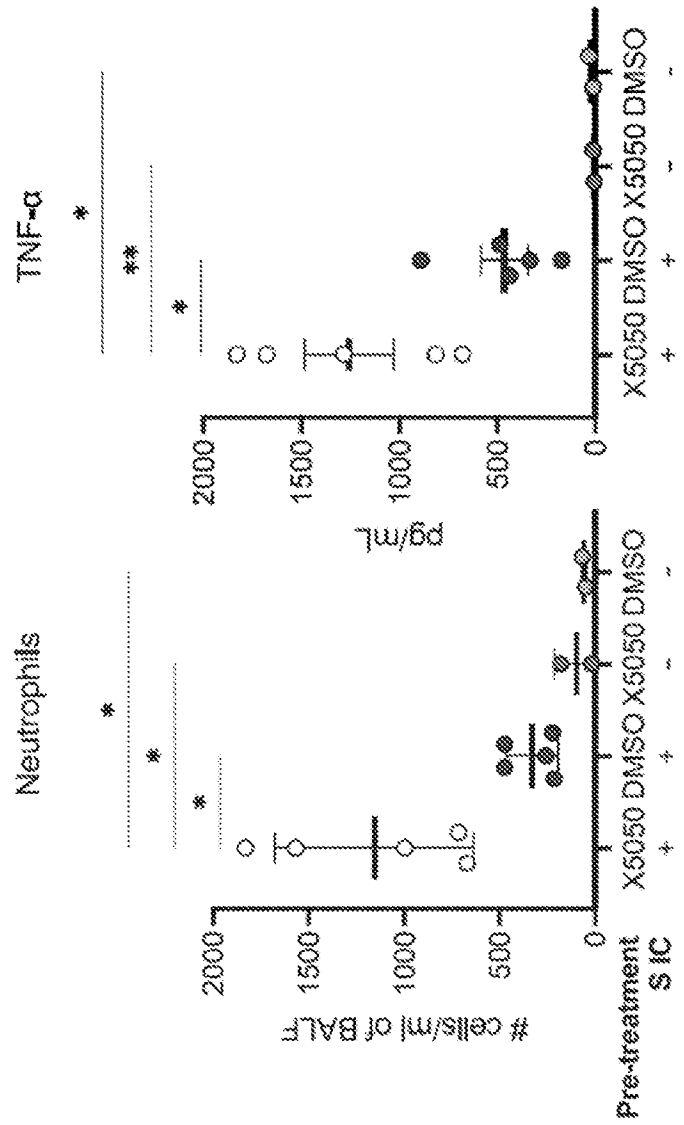


FIG. 17A

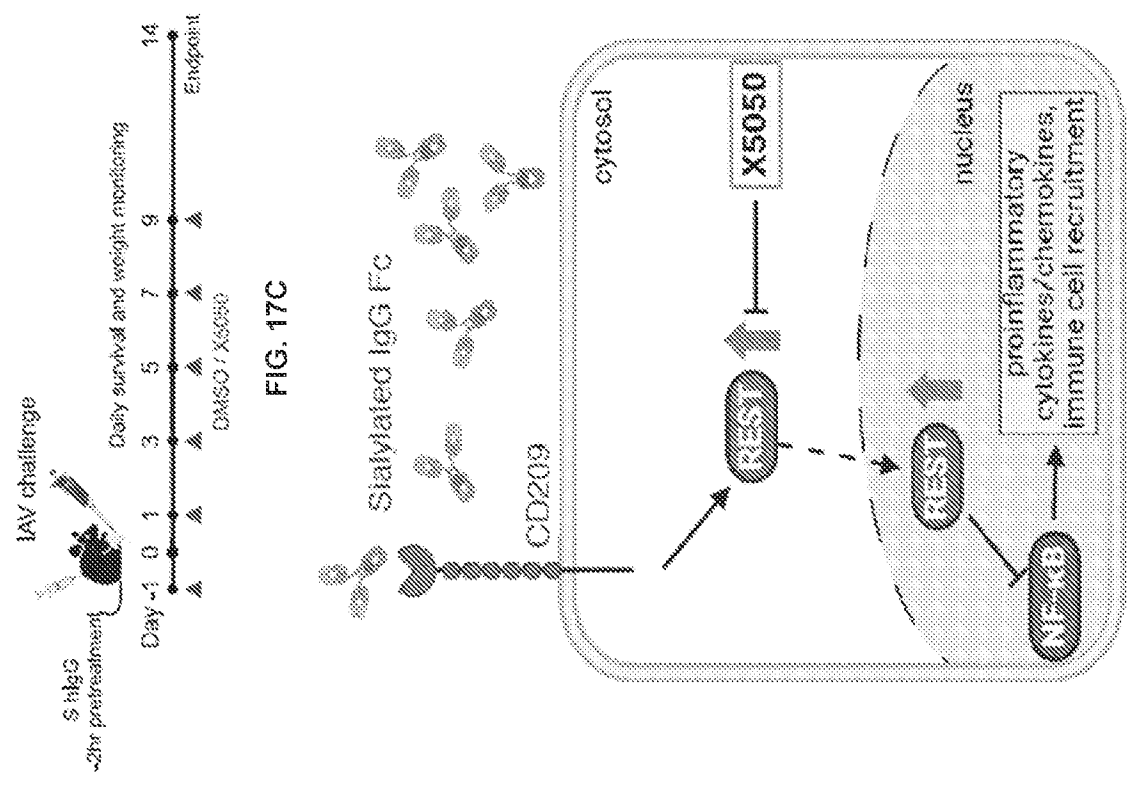
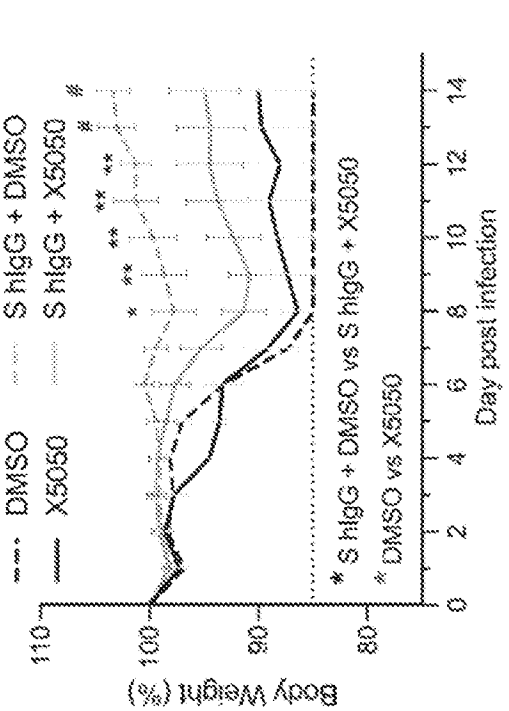


FIG. 17C

FIG. 17E



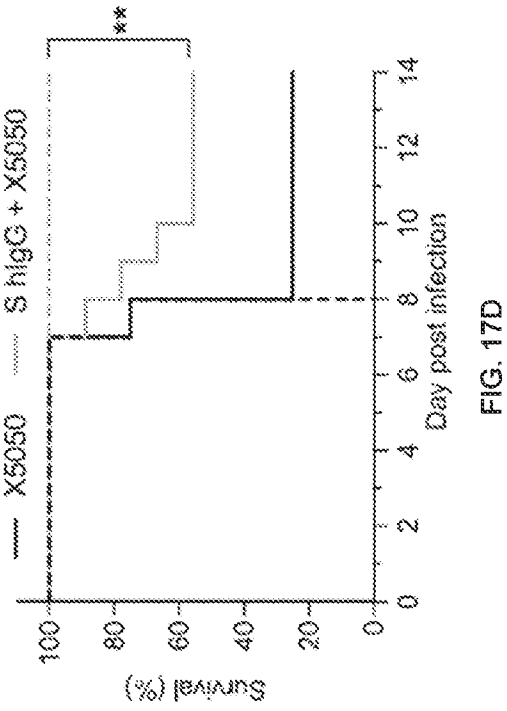


FIG. 17D

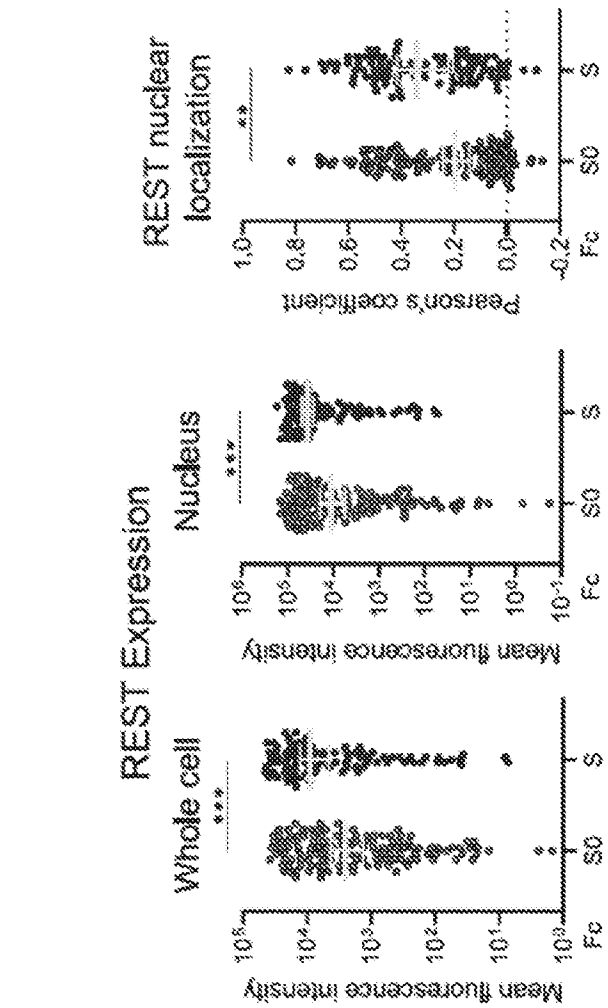


FIG. 18B

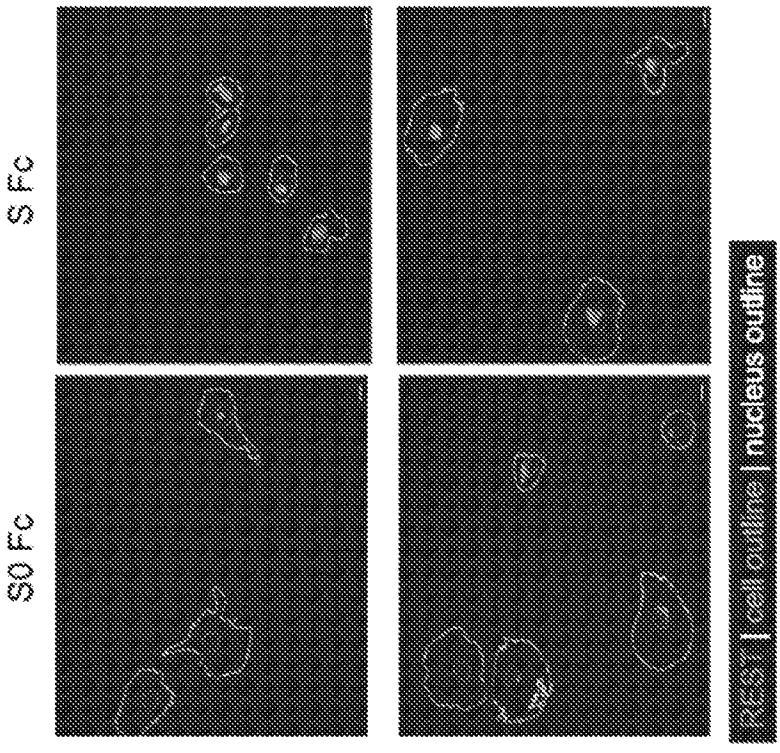


FIG. 18A

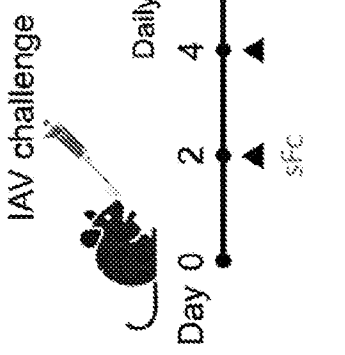


FIG. 18C

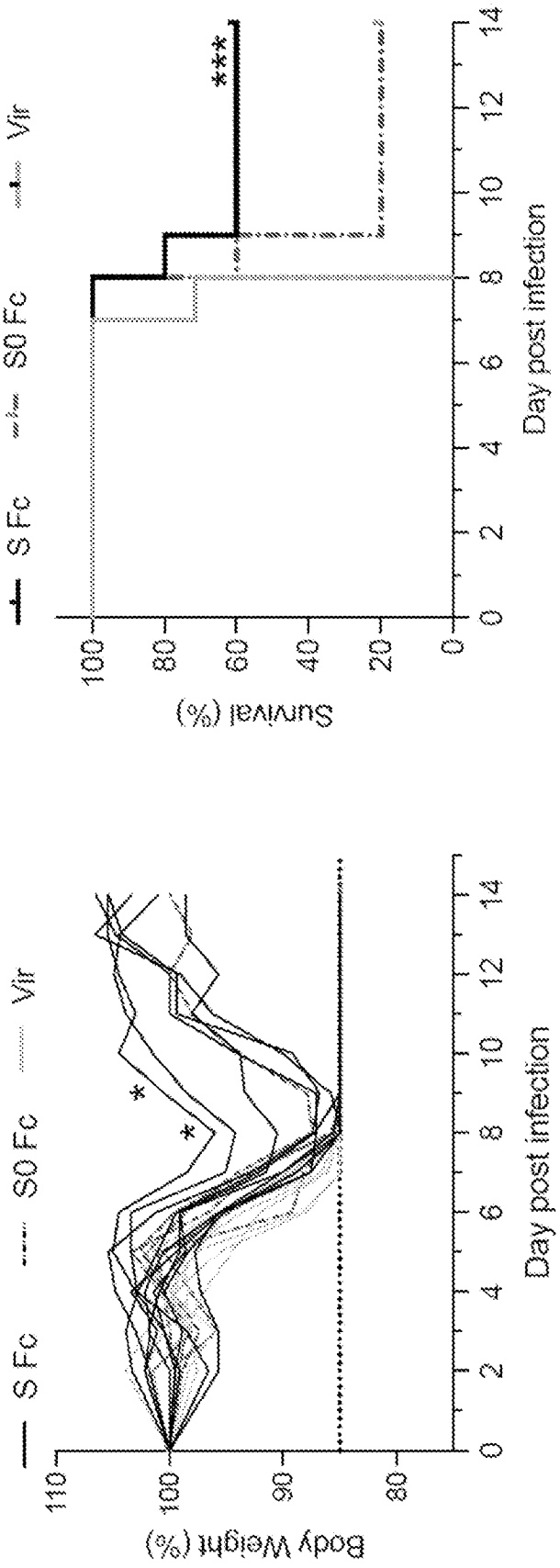
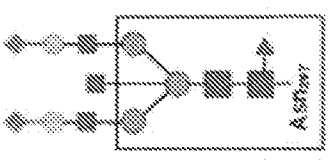


FIG. 18D



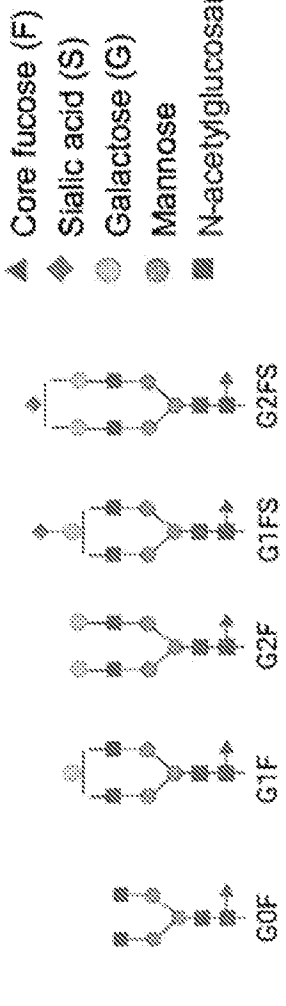


FIG. 19A

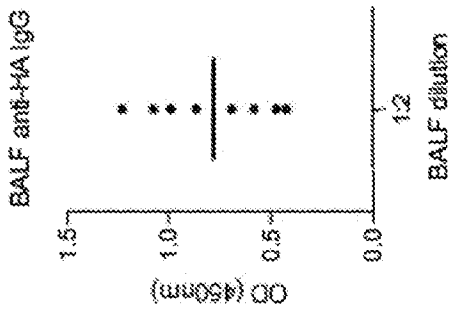


FIG. 19B

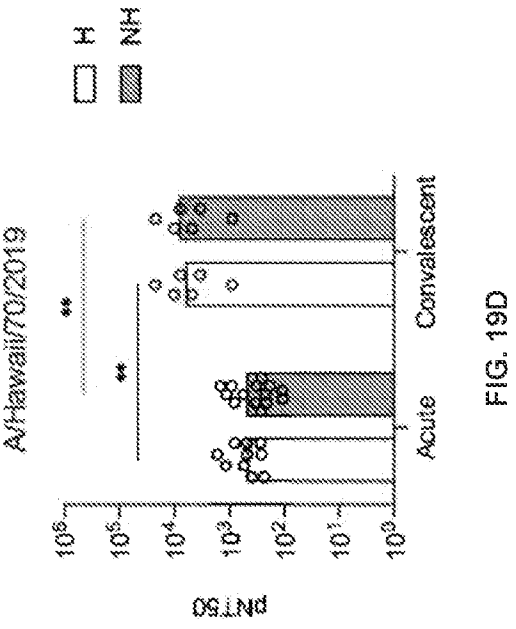


FIG. 19D

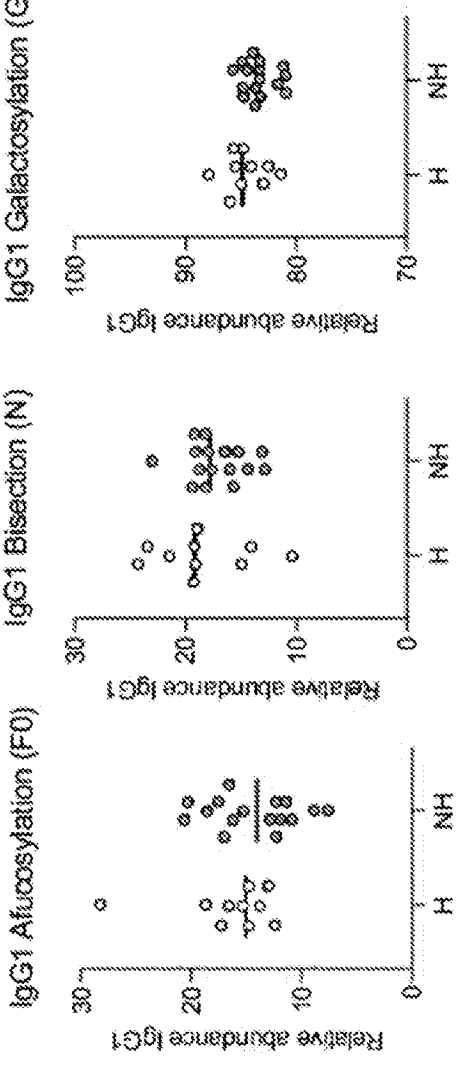


FIG. 19C

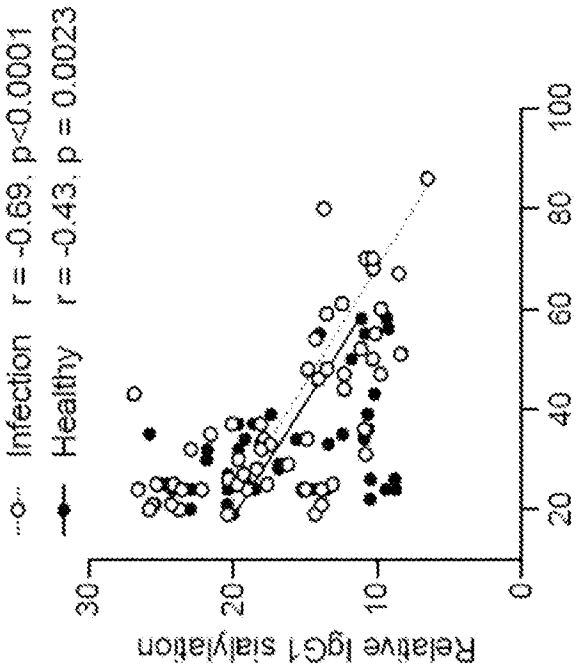


FIG. 20B

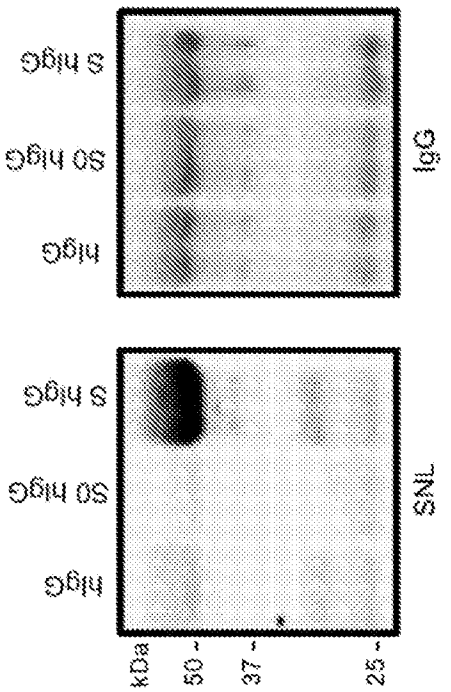


FIG. 20A

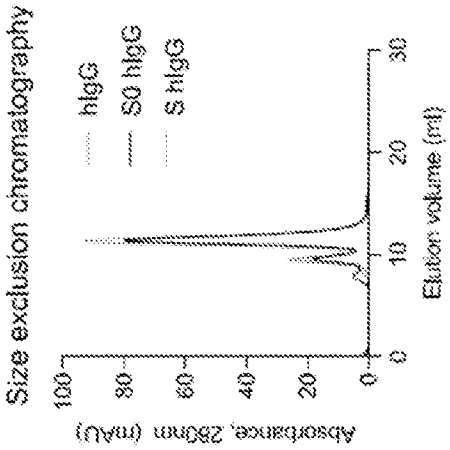


FIG. 20D

% Sialylation by Mass spec

Sample no.	S hIgG	S0 hIgG
1	22.579	0.038
2	26.075	0.007

FIG. 20C

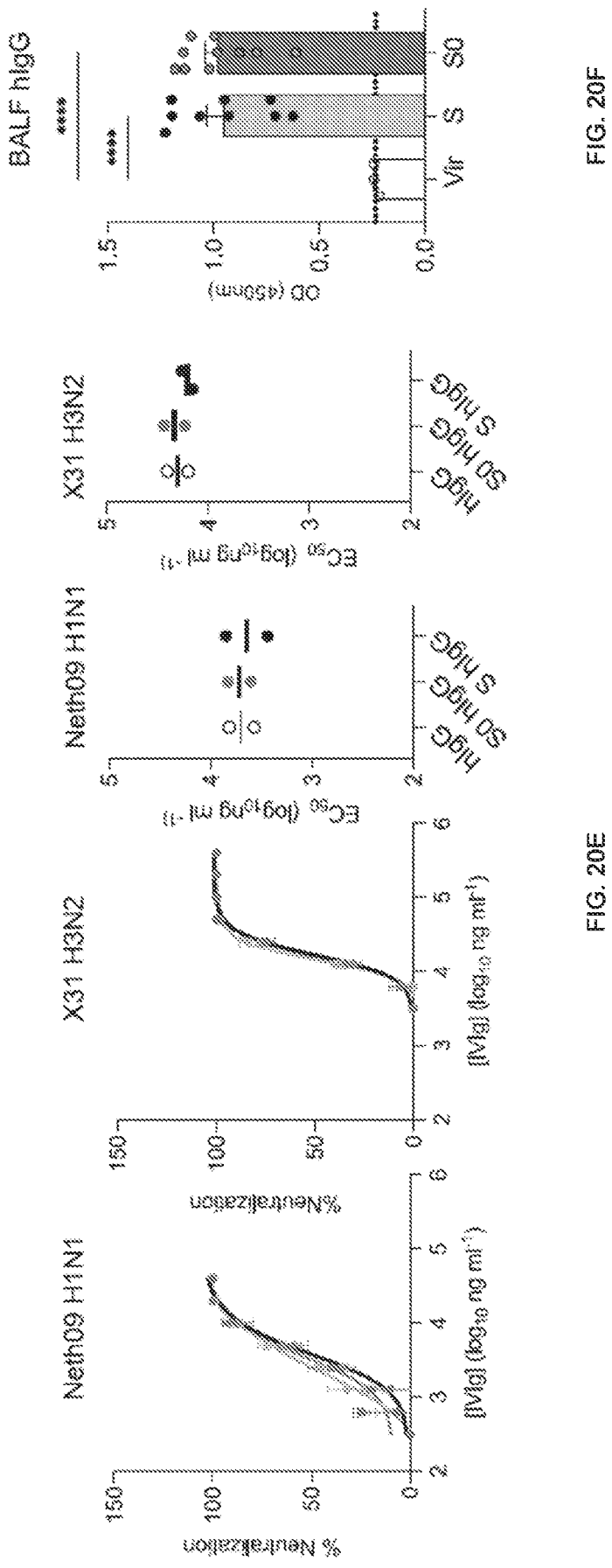


FIG. 20E

FIG. 20F

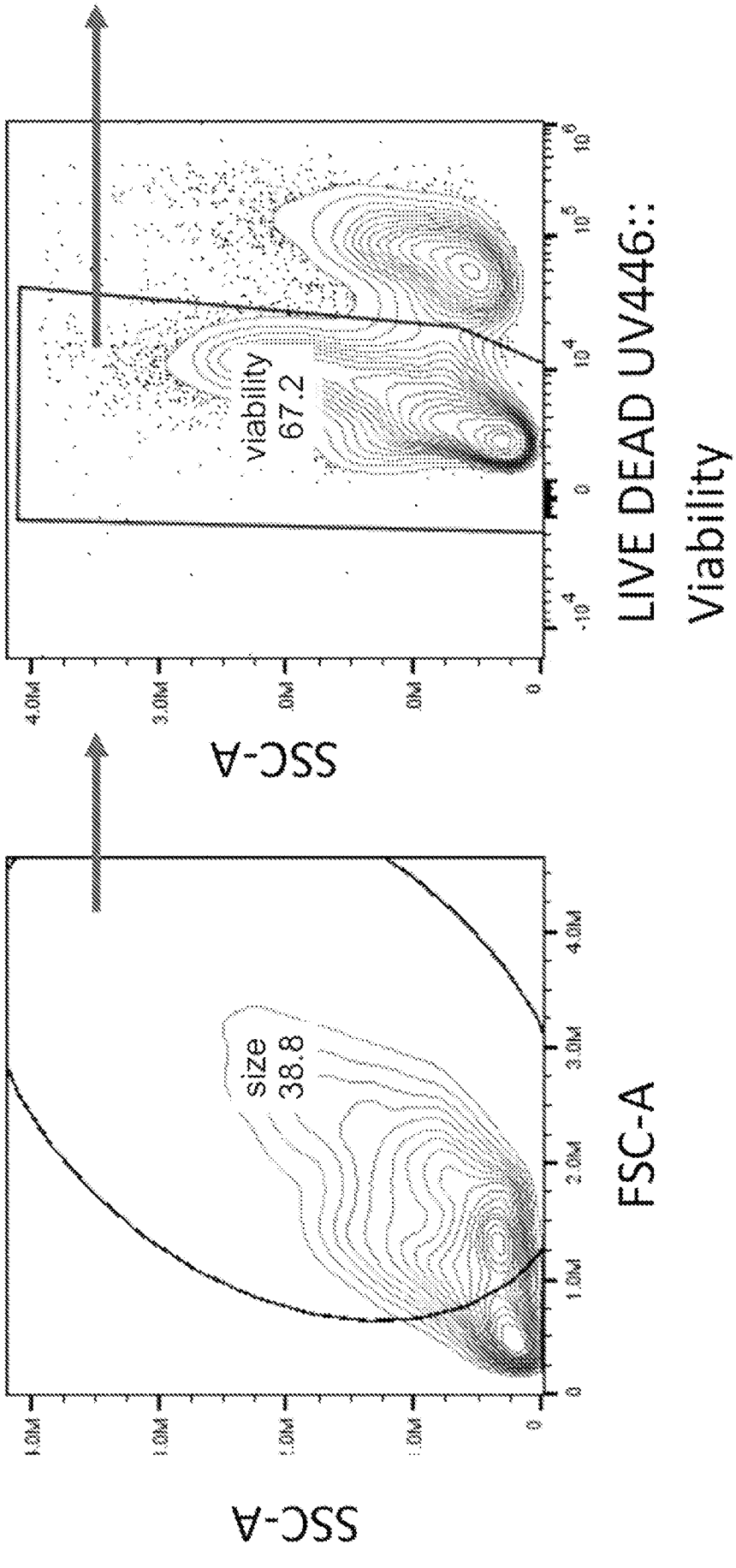

size
38.8
FSC-A
SSC-A
viability
67.2
LIVE DEAD UV446::
Viability
SSC-A

FIG. 21A

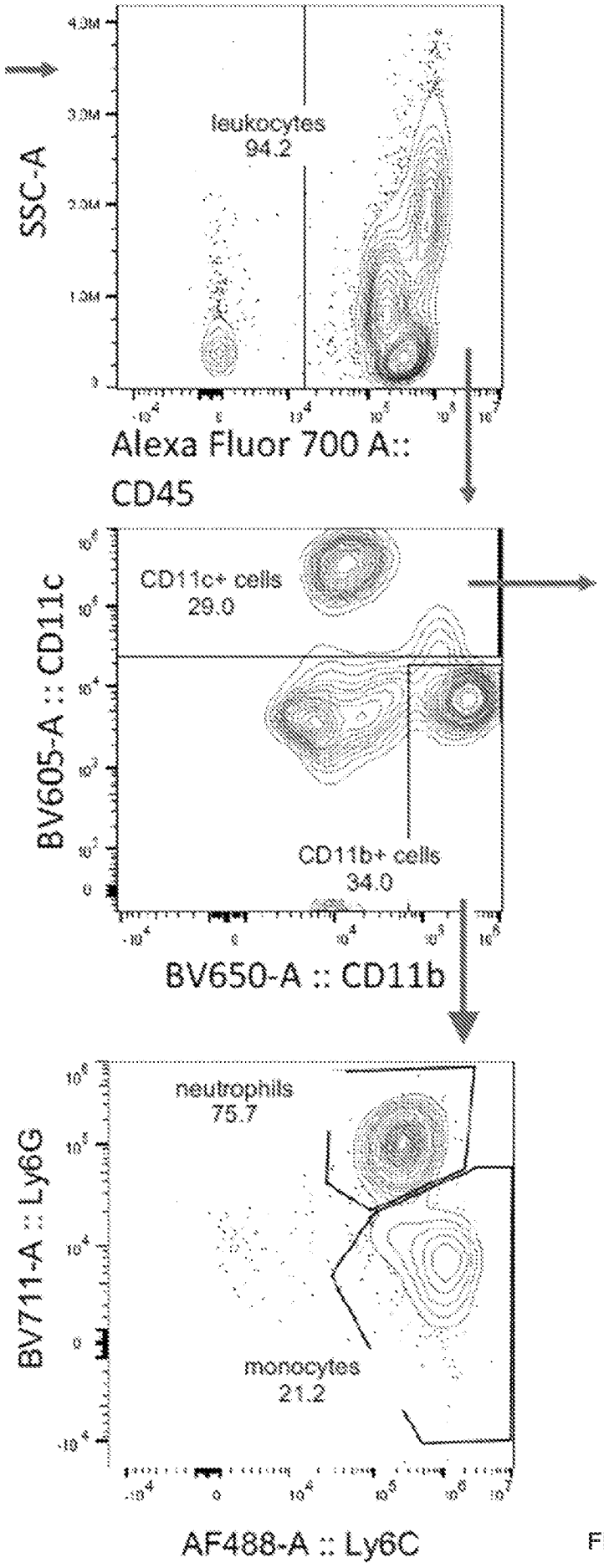

SSC-A
leukocytes
94.2
Alexa Fluor 700 A::
CD45
BV605-A :: CD11c
CD11c+ cells
29.0
CD11b+ cells
34.0
BV650-A :: CD11b
BV711-A :: Ly6G
neutrophils
75.7
monocytes
21.2
AF488-A :: Ly6C

FIG. 21A (cont.)

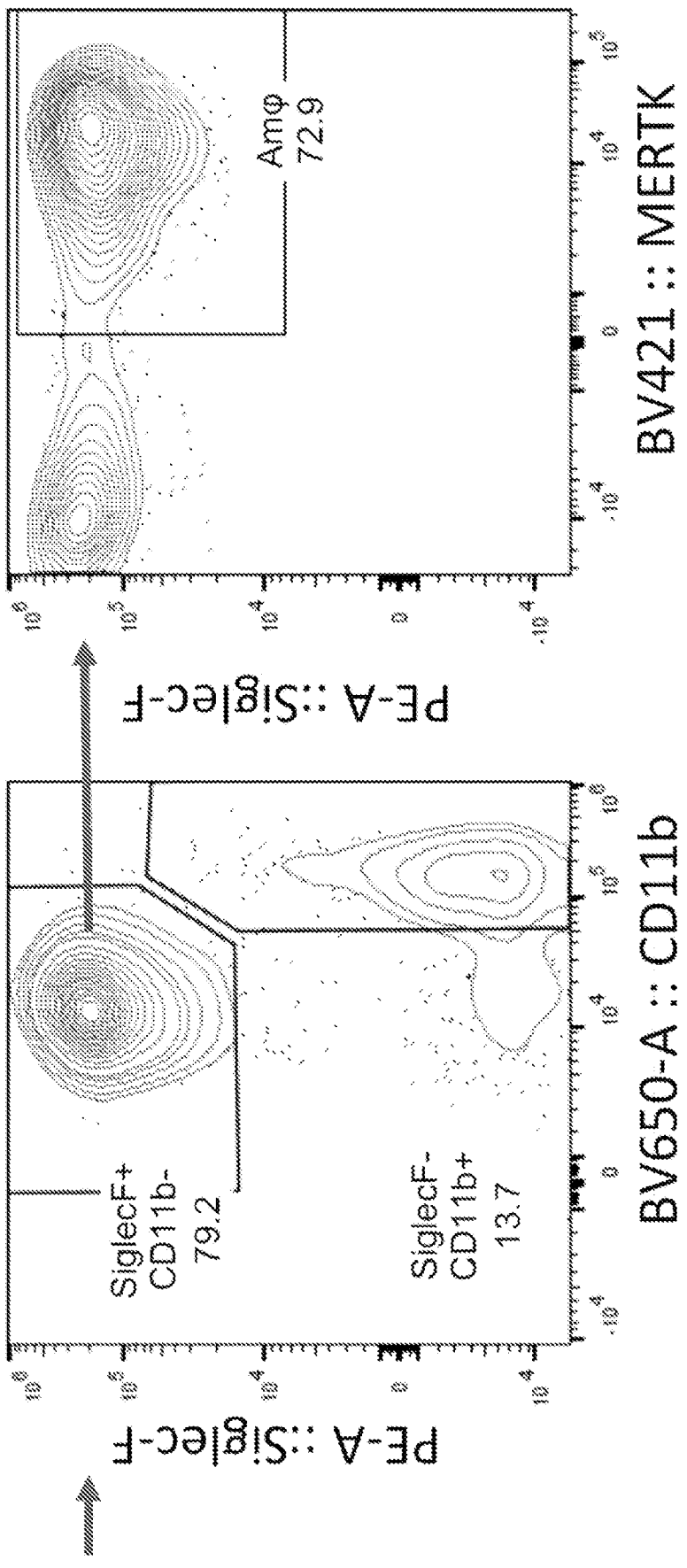

PE-A ::Siglec-F
BV650-A :: CD11b
SiglecF+
CD11b-
79.2
SiglecF-
CD11b+
13.7
PE-A ::Siglec-F
BV421 :: MERTK
Amφ
72.9

FIG. 21A (cont.)

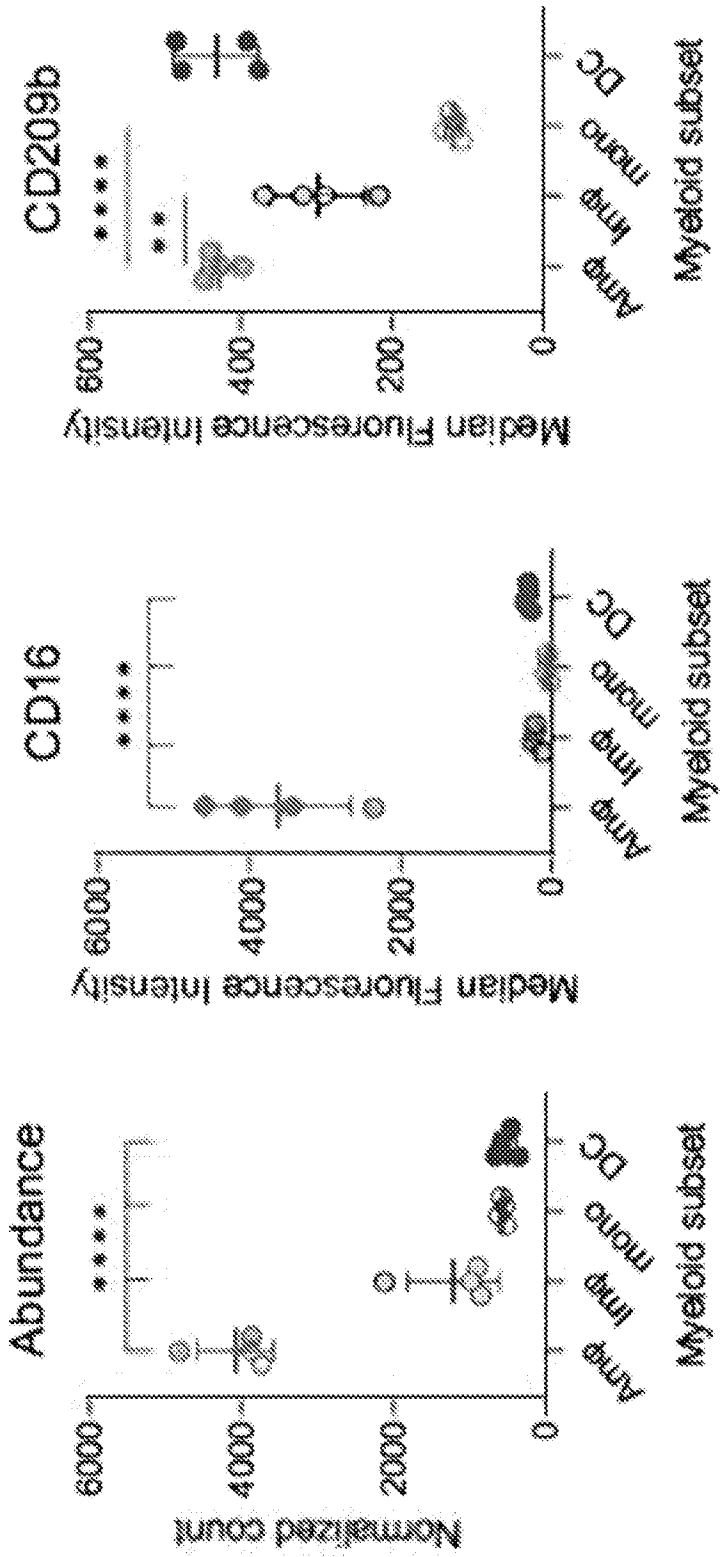

Abundance
Normalized count
6000
4000
2000
0
****
Myeloid subset
Anna
Inna
mono
DC
CD16
Median Fluorescence Intensity
6000
4000
2000
0
****
Myeloid subset
Anna
Inna
mono
DC
CD209b
Median Fluorescence Intensity
600
400
200
0
****
**
Myeloid subset
Anna
Inna
mono
DC

FIG. 21B

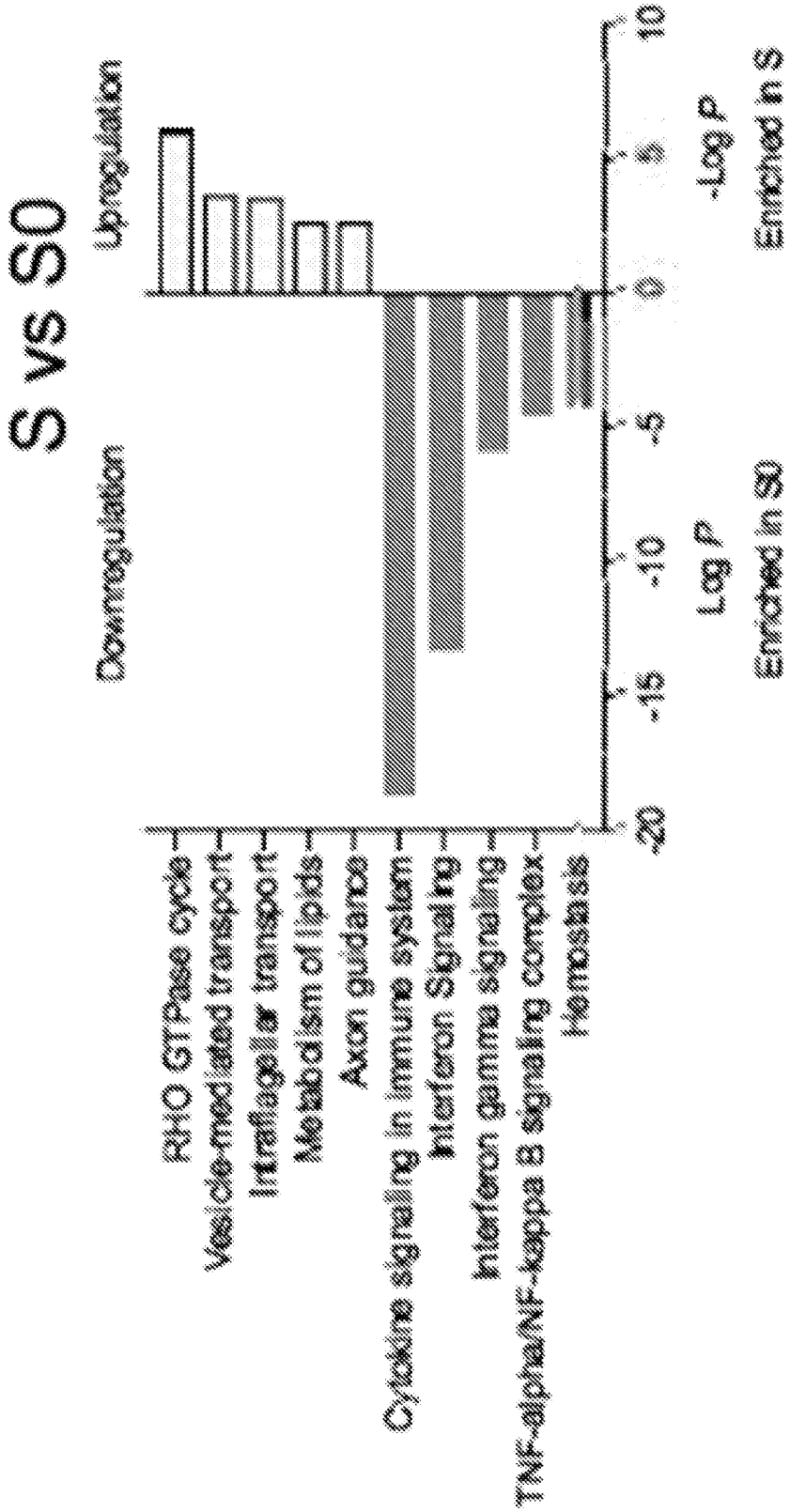

S vs S0
Upregulation
Downregulation
RHO GTPase cycle
Vesicle-mediated transport
Intraflagellar transport
Metabolism of lipids
Axon guidance
Cytokine signaling in immune system
Interferon Signaling
Interferon gamma signaling
TNF-alpha/NF-kappa B signaling complex
Hemostasis
-20
-15
-10
-5
0
5
10
Log P
Enriched in S0
-Log P
Enriched in S

FIG. 22A

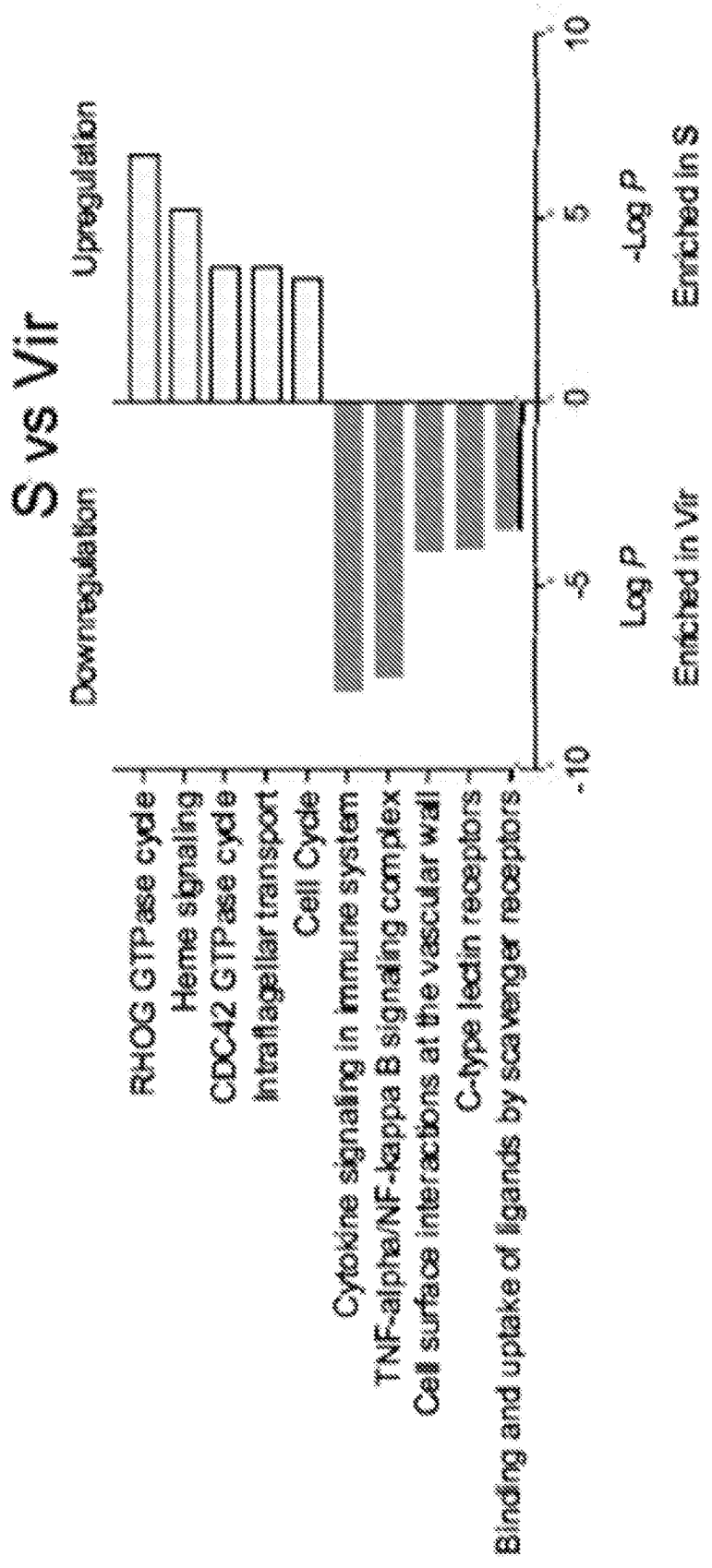
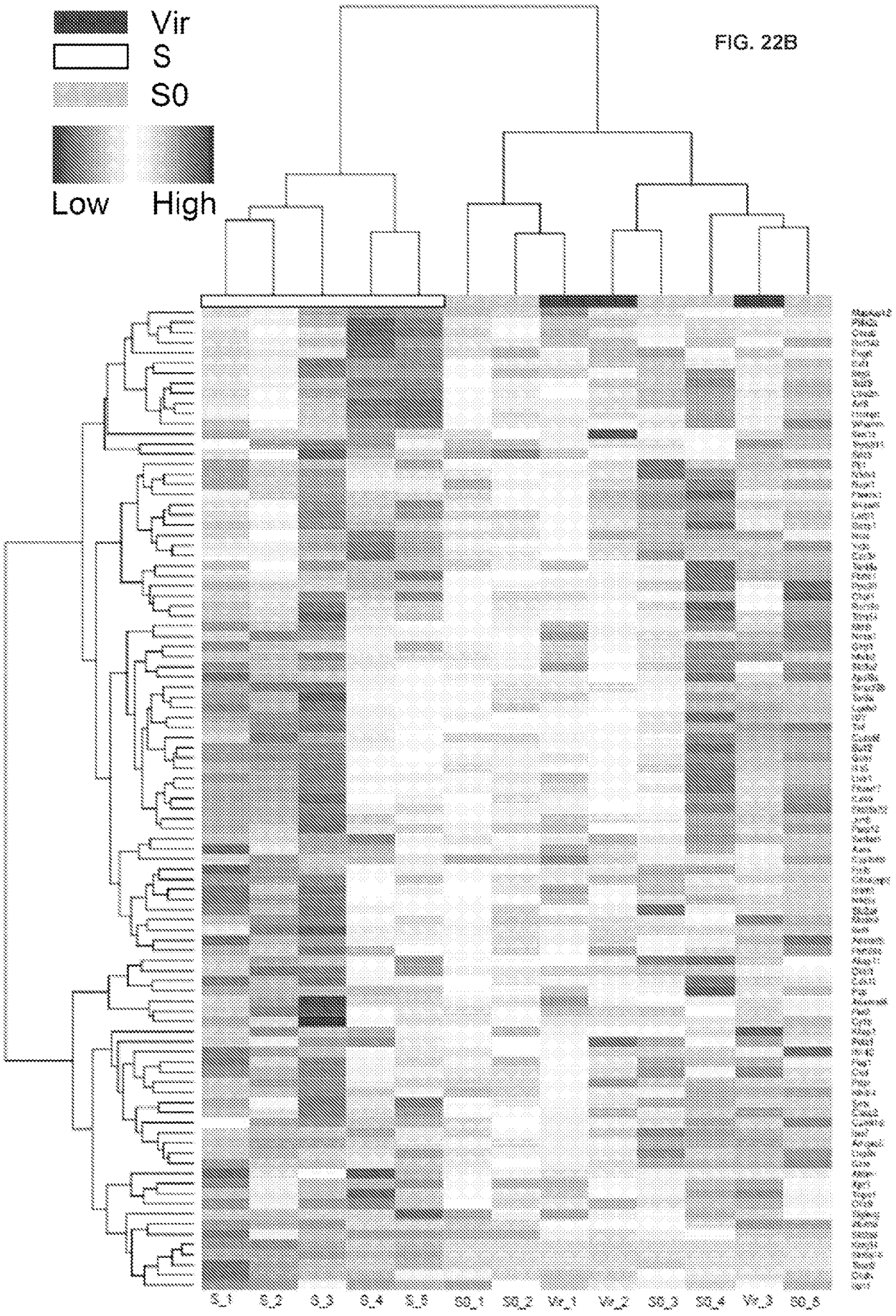

S vs Vir
Upregulation
Downregulation
RHOG GTPase cycle
Heme signaling
CDC42 GTPase cycle
Intraflagellar transport
Cell Cycle
Cytokine signaling in immune system
TNF-alpha/NF-kappa B signaling complex
Cell surface interactions at the vascular wall
C-type lectin receptors
Binding and uptake of ligands by scavenger receptors
10
5
0
-5
-10
-Log p
Enriched in S
Log p
Enriched in Vir

FIG. 22A (cont.)

FIG. 22B


Vir
S
S0
Low
High
S_1
S_2
S_3
S_4
S_5
S0_1
S0_2
Vir_1
Vir_2
S0_3
S0_4
Vir_3
S0_5

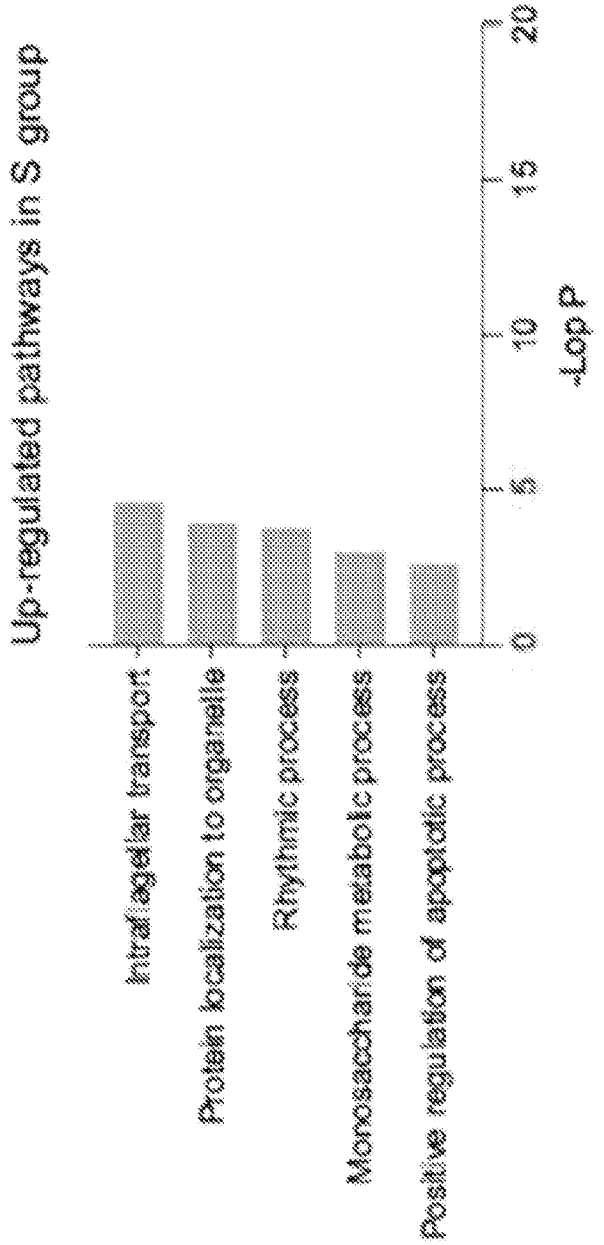

Up-regulated pathways in S group
Intraflagelar transport
Protein localization to organelle
Rhythmic process
Monosaccharide metabolic process
Positive regulation of apoptotic process
0
5
10
15
20
-Log P

FIG. 22C

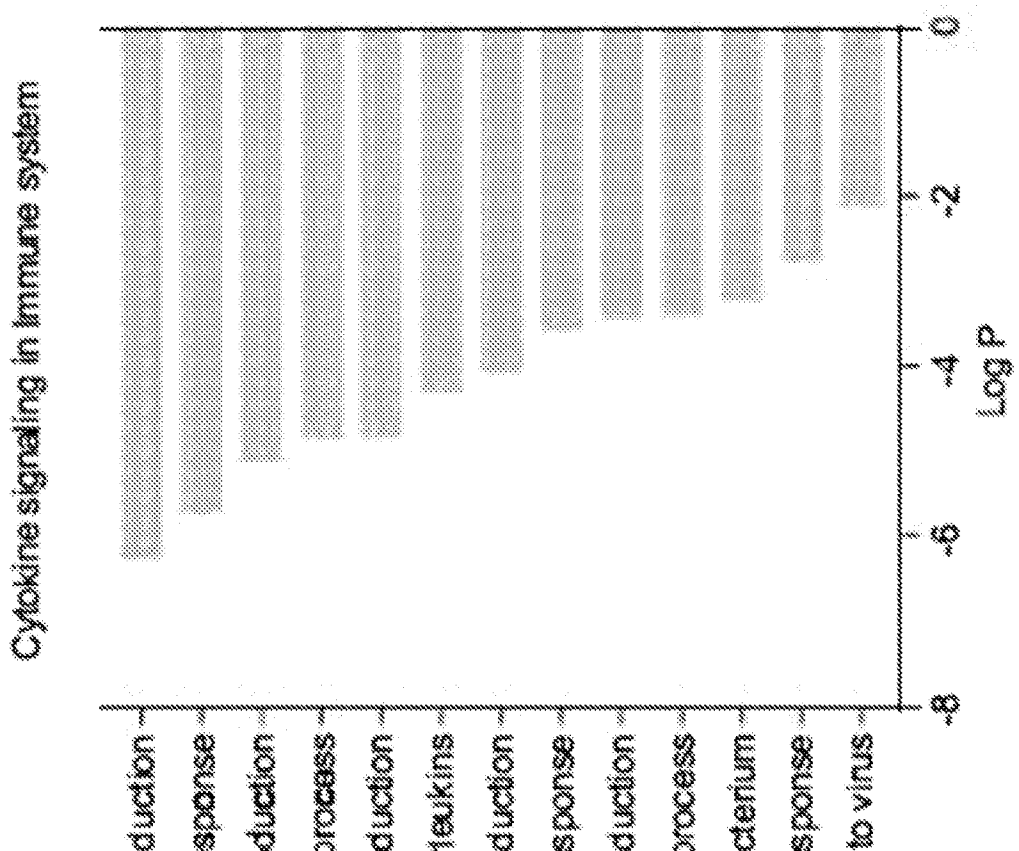

Cytokine signaling in immune system
Positive regulation of type II interferon production
Inflammatory response
Positive regulation of cytokine production
Regulation of immune effector process
Positive regulation of chemokine production
Signaling by Interleukins
Regulation of non-canonical NF-kappaB signal transduction
Positive regulation of inflammatory response
canonical NF-kappaB signal transduction
Regulation of viral process
Response to bacterium
regulation of inflammatory response
Response to virus
0
-2
-4
-6
-8
Log P

FIG. 22D

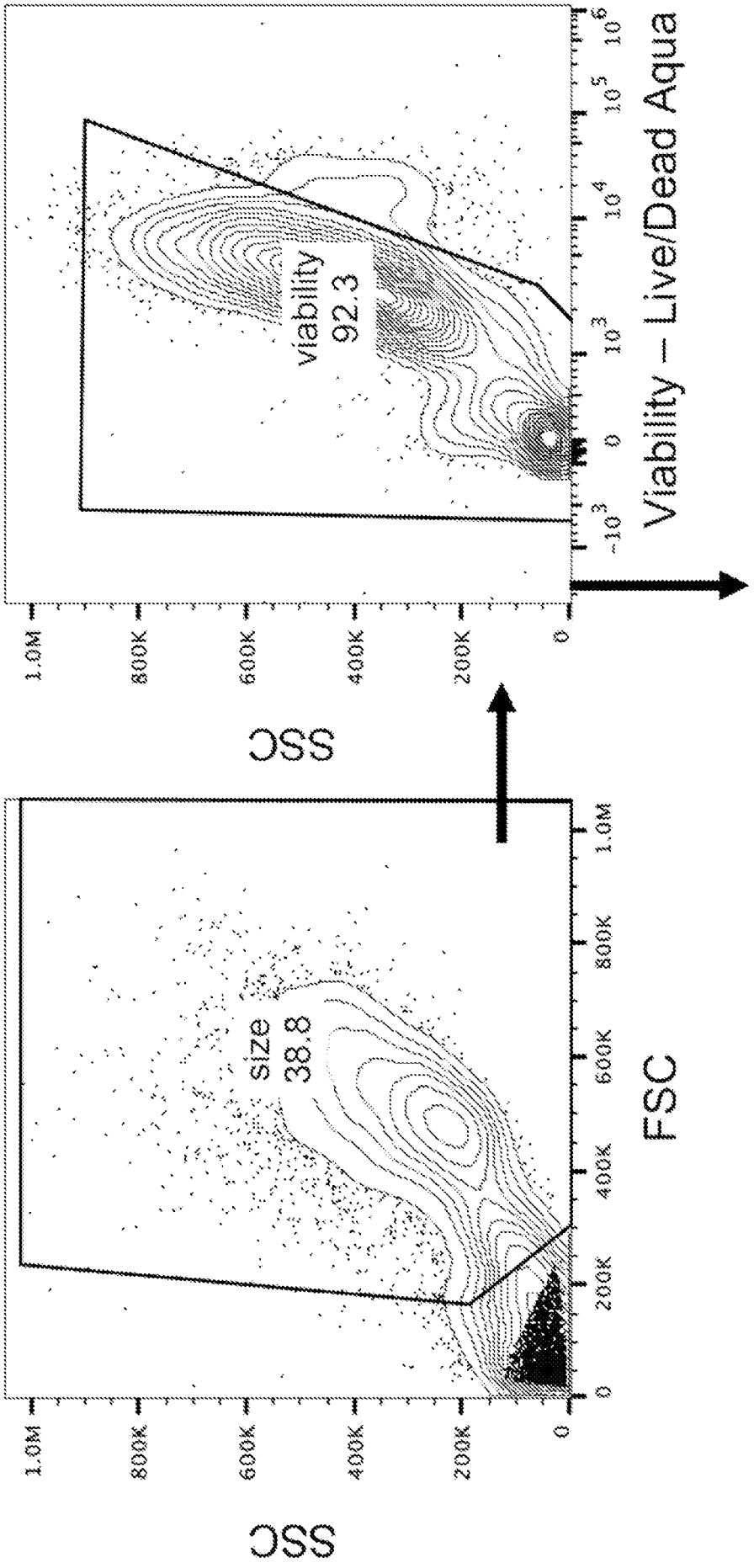

SSC
1.0M
800K
600K
400K
200K
0
FSC
0
200K
400K
600K
800K
1.0M
size
38.8
SSC
1.0M
800K
600K
400K
200K
0
Viability – Live/Dead Aqua
-10^3
0
10^3
10^4
10^5
10^6
viability
92.3

FIG. 23A

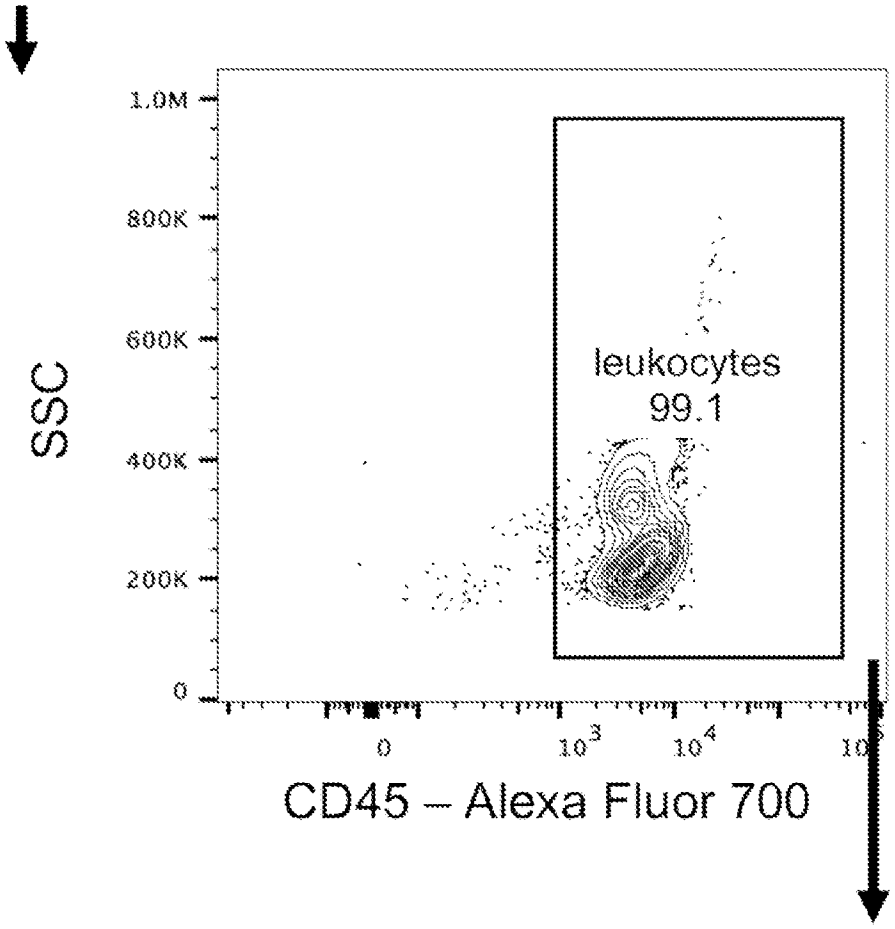

1.0M
800K
600K
400K
200K
0
SSC
leukocytes
99.1
0
10^3
10^4
CD45 – Alexa Fluor 700

FIG. 23A (cont.)

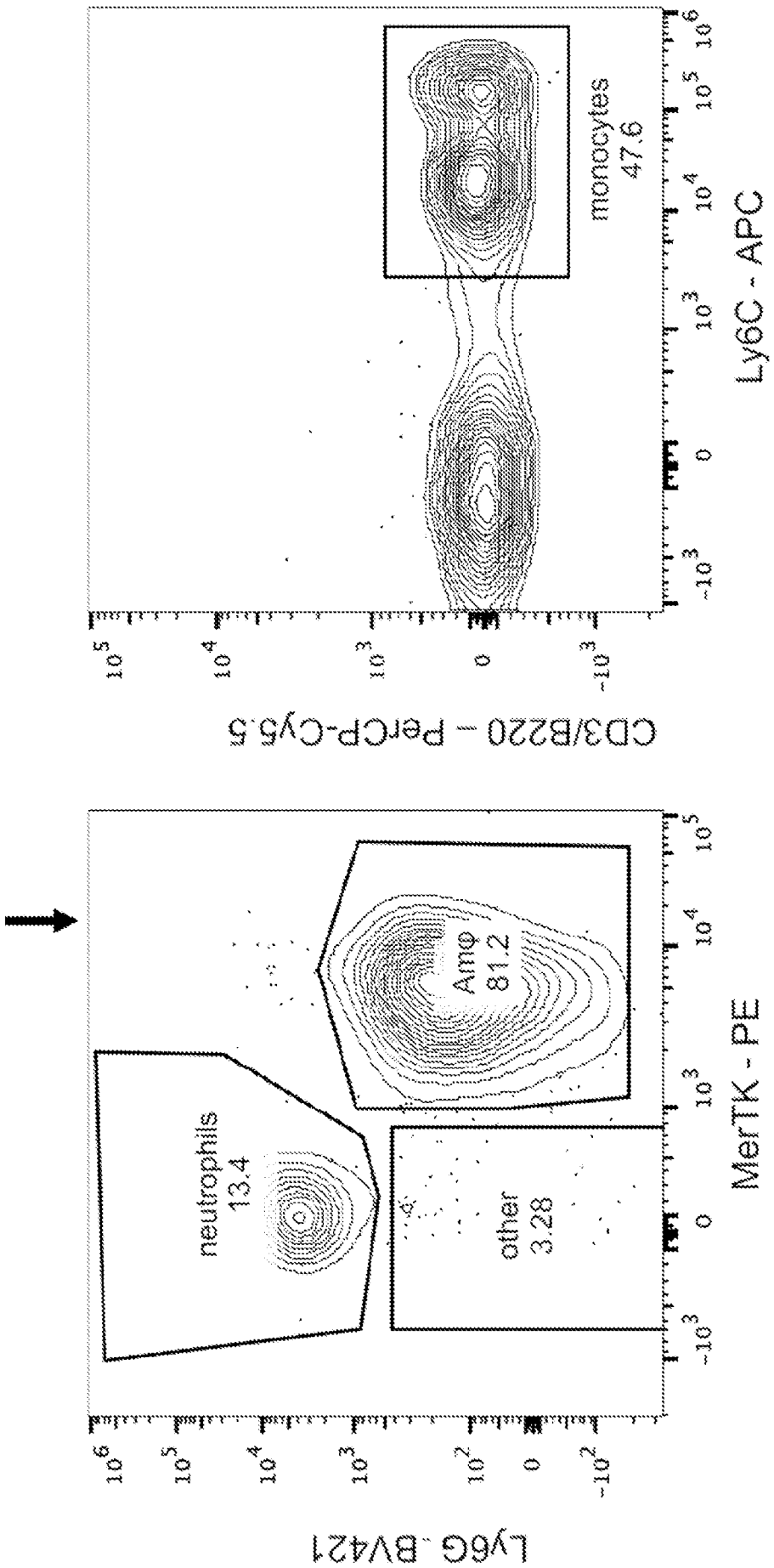

Ly6G - BV421
MerTK - PE
neutrophils
13.4
Amφ
81.2
other
3.28
CD3/B220 – PerCP-Cy5.5
Ly6C - APC
monocytes
47.6

FIG. 23A (cont.)

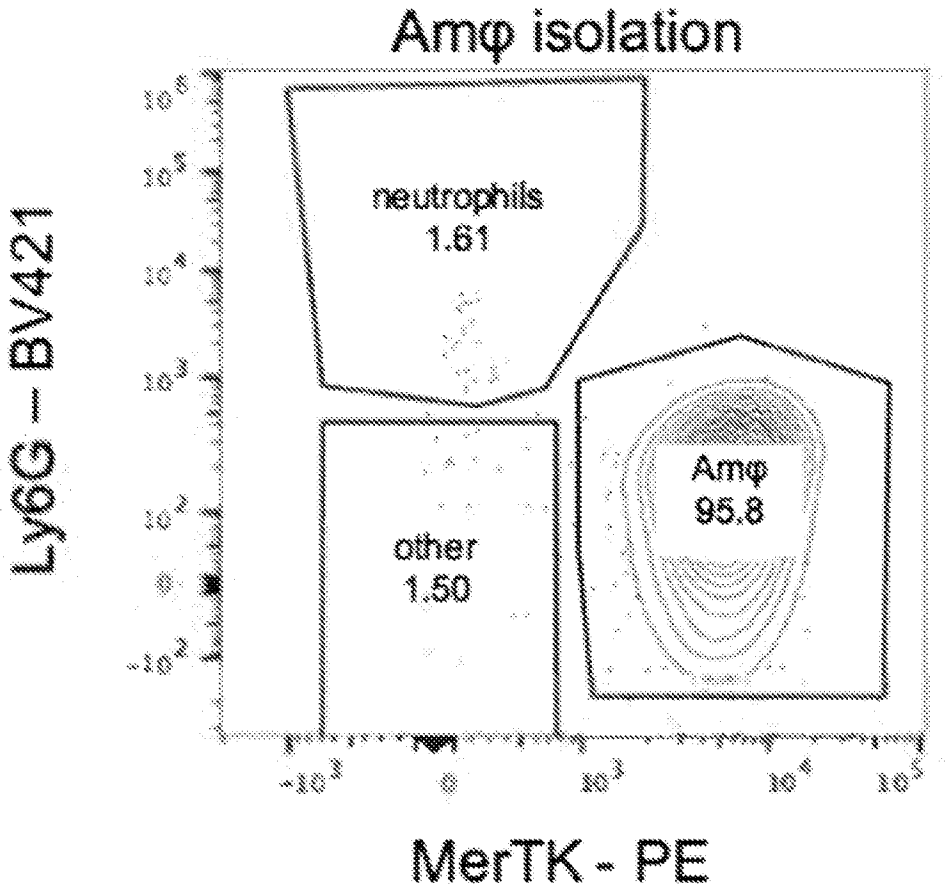

Amφ isolation
neutrophils
1.61
other
1.50
Amφ
95.8
Ly6G – BV421
MerTK - PE

FIG. 23B

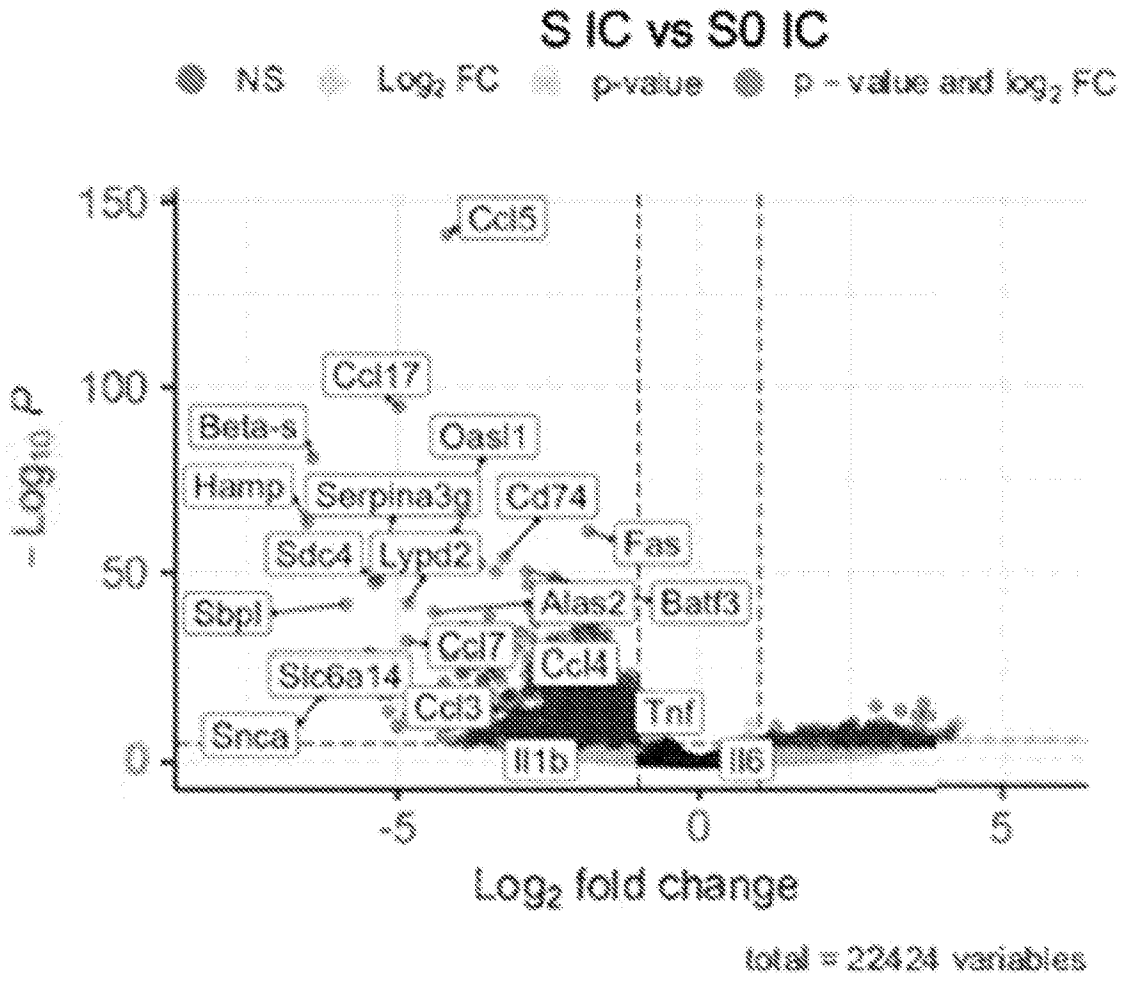

S IC vs S0 IC
NS
Log2 FC
p-value
p - value and log2 FC
150
100
50
0
-Log10 p
Ccl5
Ccl17
Beta-s
Oasl1
Hamp
Serpina3g
Cd74
Fas
Sdc4
Lypd2
Alas2
Batf3
Sbpl
Ccl7
Ccl4
Slc6a14
Ccl3
Tnf
Snca
Il1b
Il6
-5
0
5
Log2 fold change
total = 22424 variables

FIG. 24A

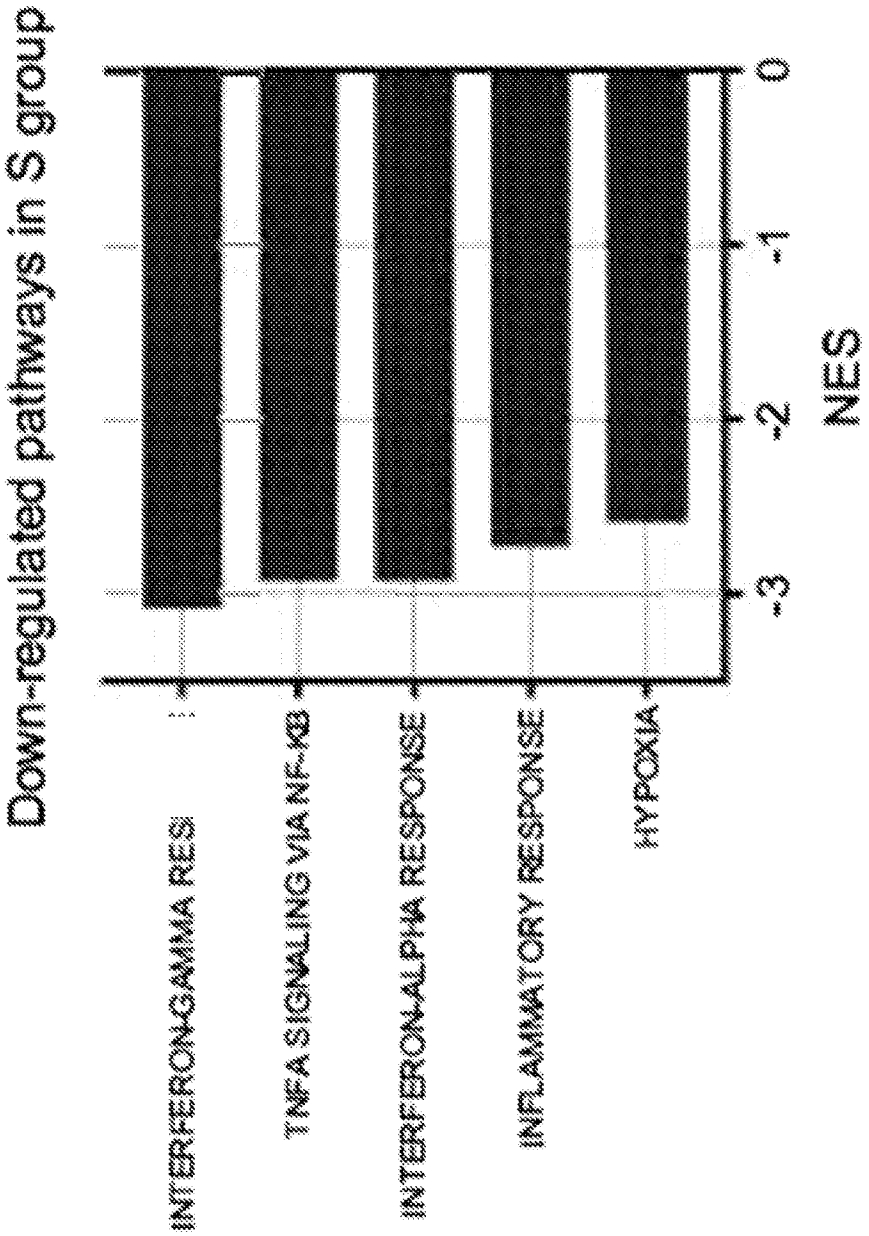

Down-regulated pathways in S group
INTERFERON-GAMMA RESI
TNFA SIGNALING VIA NF-KB
INTERFERON-ALPHA RESPONSE
INFLAMMATORY RESPONSE
HYPOXIA
0
-1
-2
-3
NES

FIG. 24B

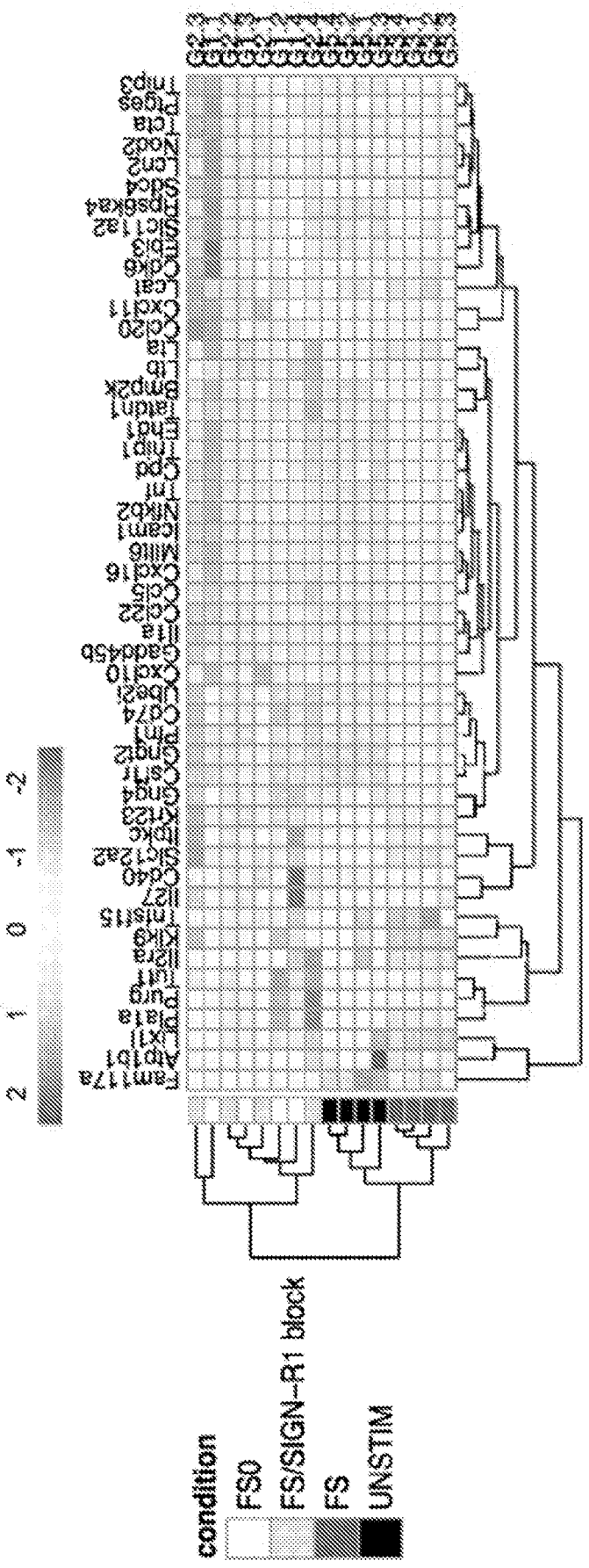


FIG. 24C

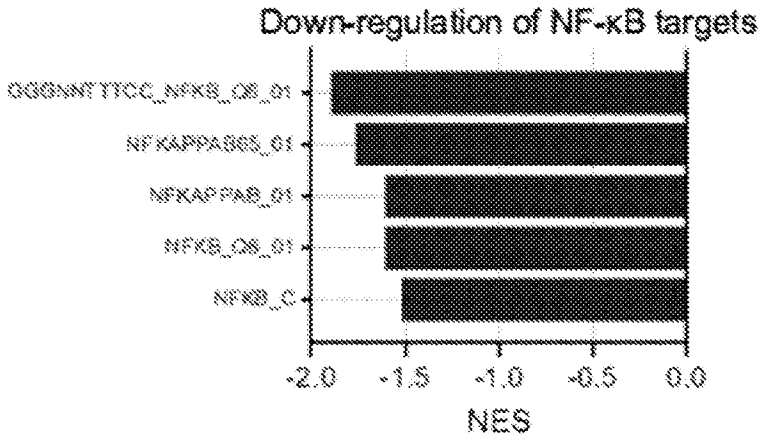


FIG. 24D

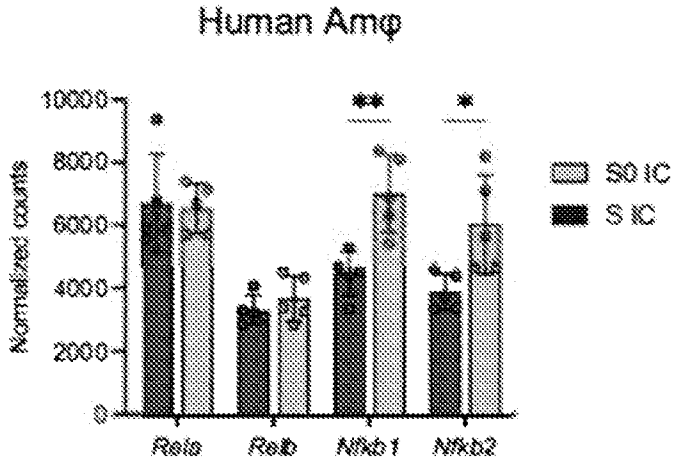


FIG. 24E

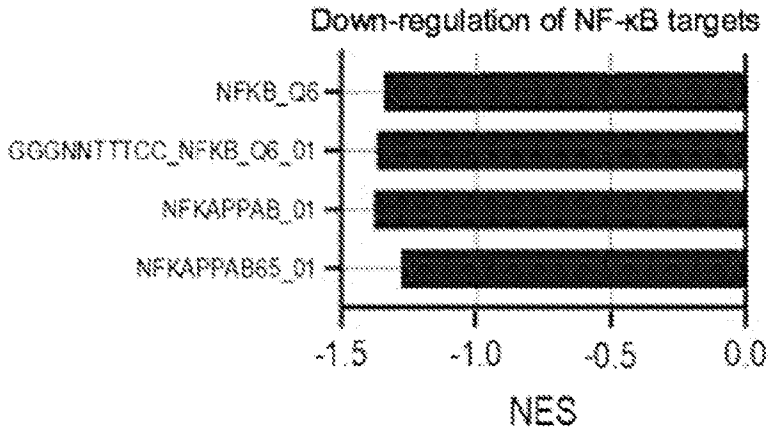


FIG. 24F

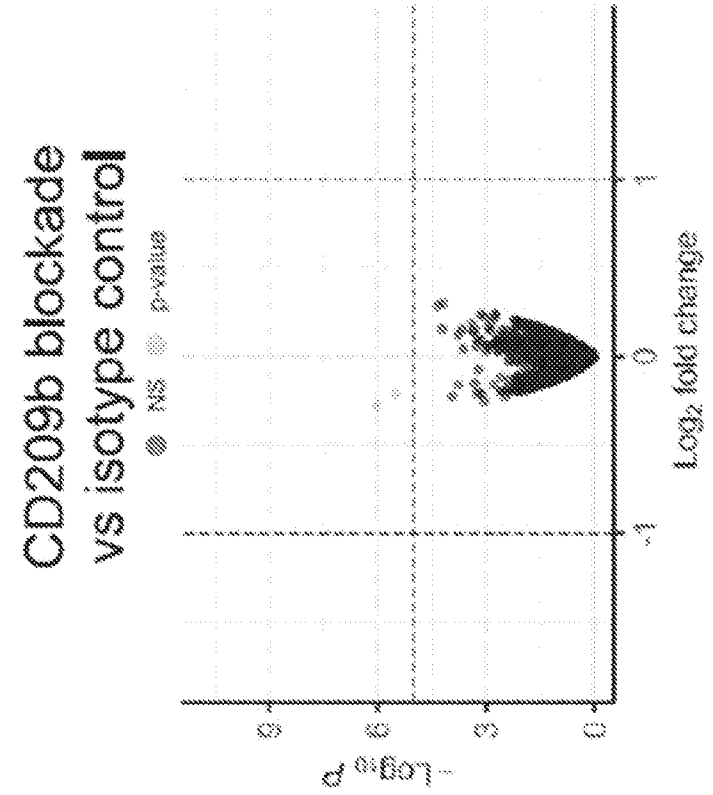


FIG. 25B

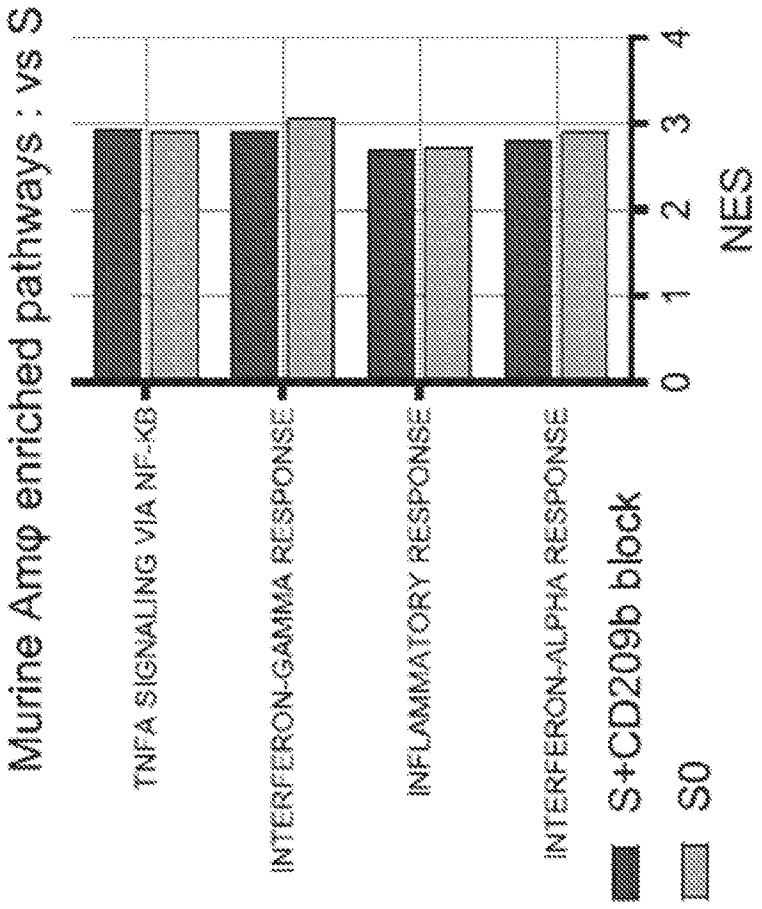


FIG. 25A

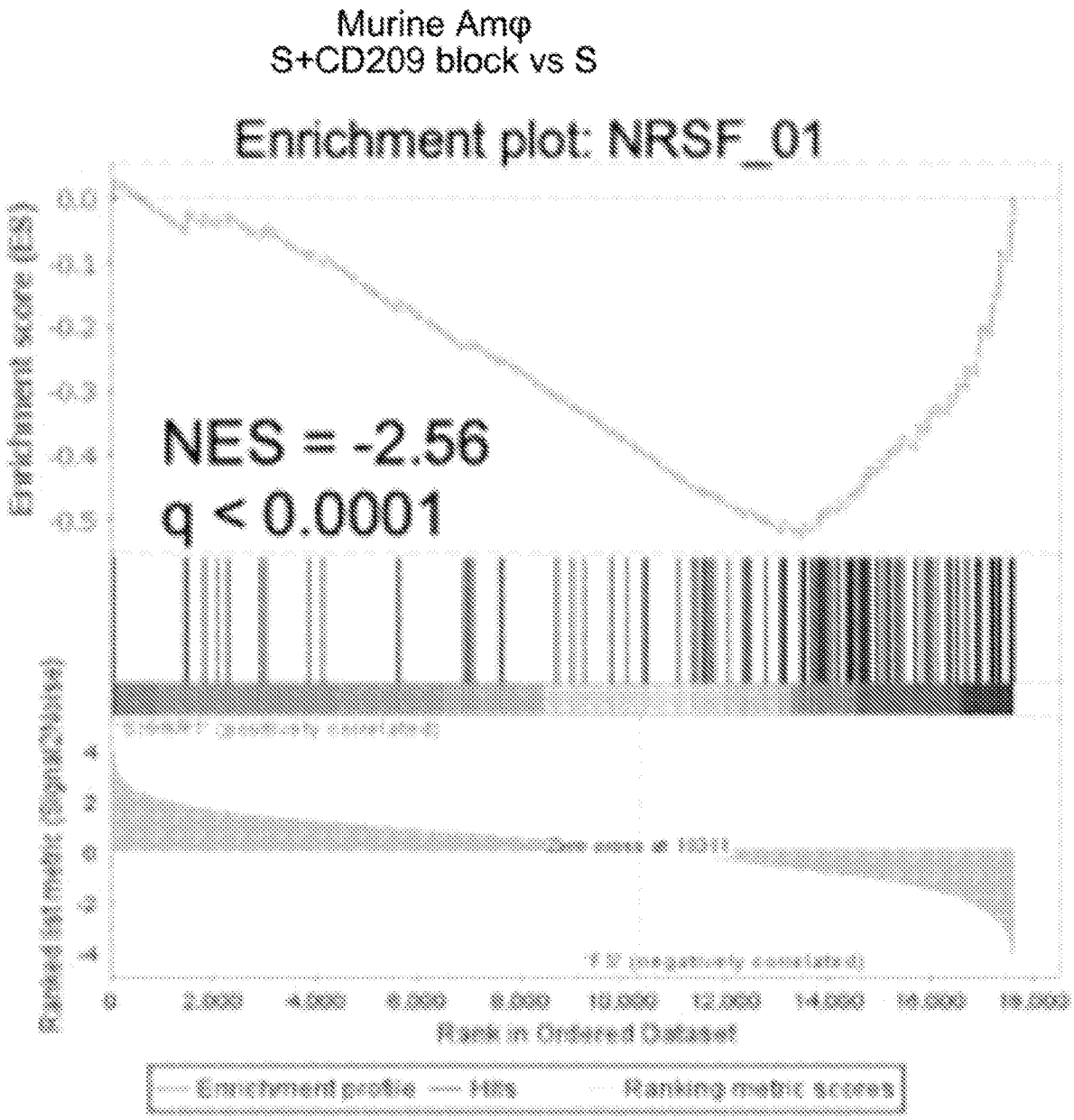

Murine Amφ
S+CD209 block vs S
Enrichment plot: NRSF_01
NES = -2.56
q < 0.0001
Enrichment score (ES)
Ranked list metric (Signal2Noise)
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

FIG. 25C

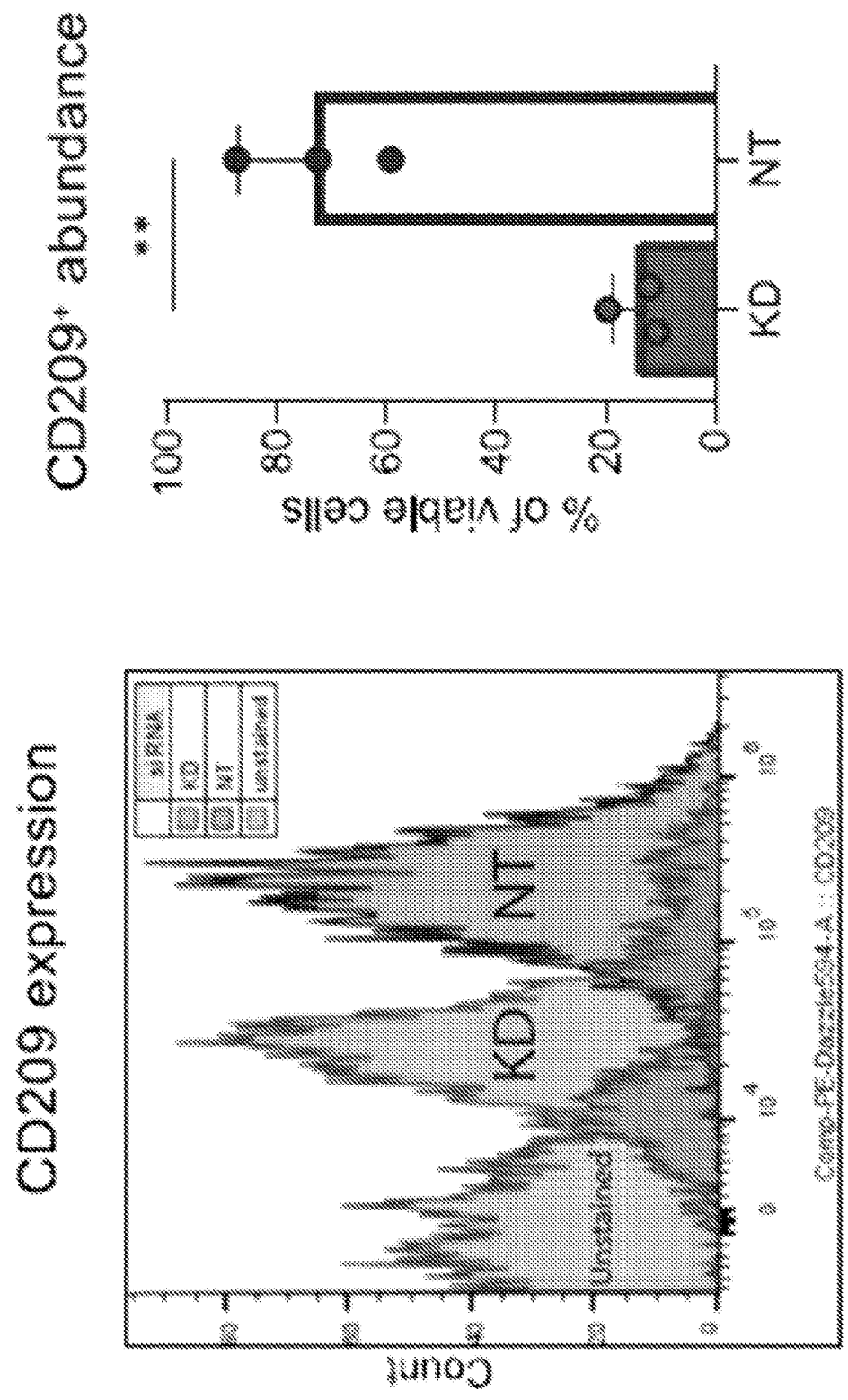

CD209 expression
siRNA
KD
NT
Unstained
Count
KD
NT
Cano-FE-Dectin2-A :: CD209
% of viable cells
CD209⁺ abundance
**
KD
NT

FIG. 25D

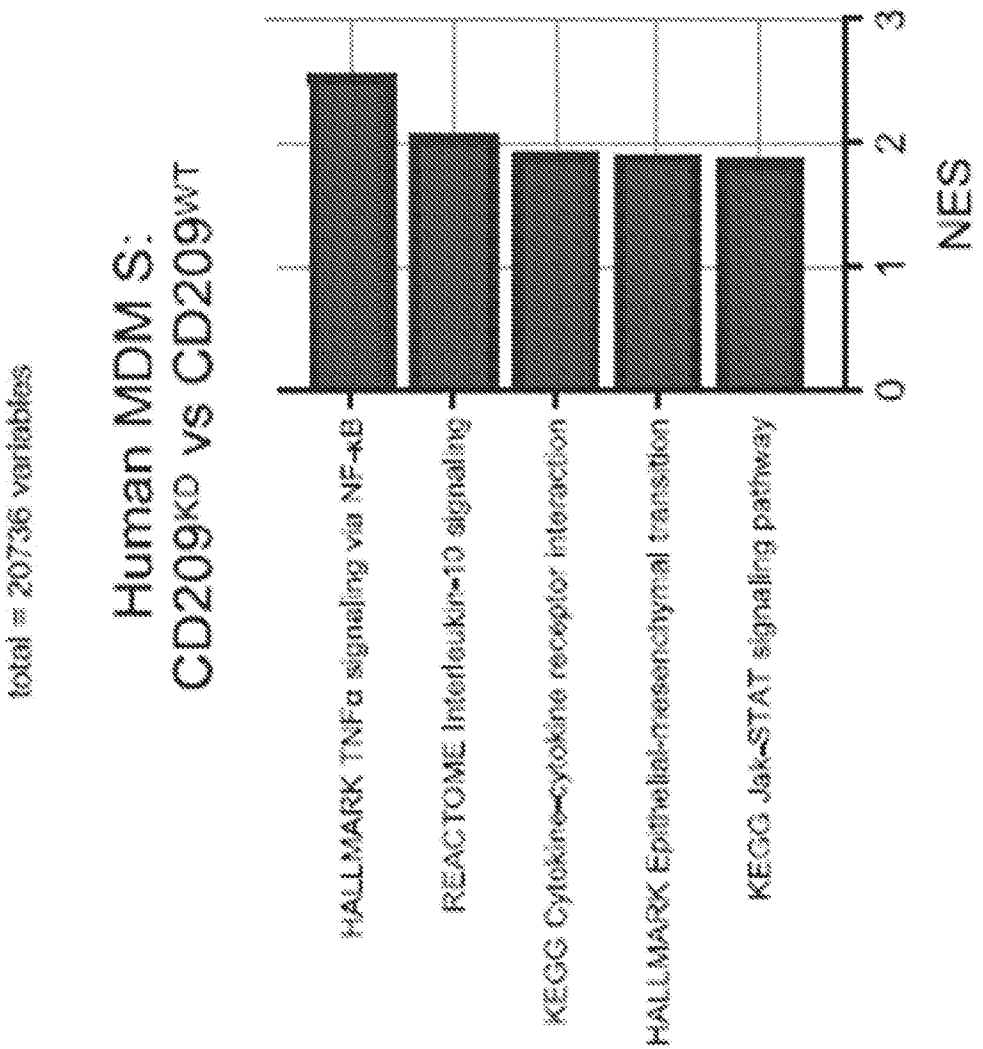

total = 20736 variables
Human MDM S:
CD209KD vs CD209WT
HALLMARK TNFa signaling via NF-kB
REACTOME Interleukin-10 signaling
KEGG Cytokine-cytokine receptor interaction
HALLMARK Epithelial-mesenchymal transition
KEGG JakSTAT signaling pathway
0
1
2
3
NES

FIG. 25E

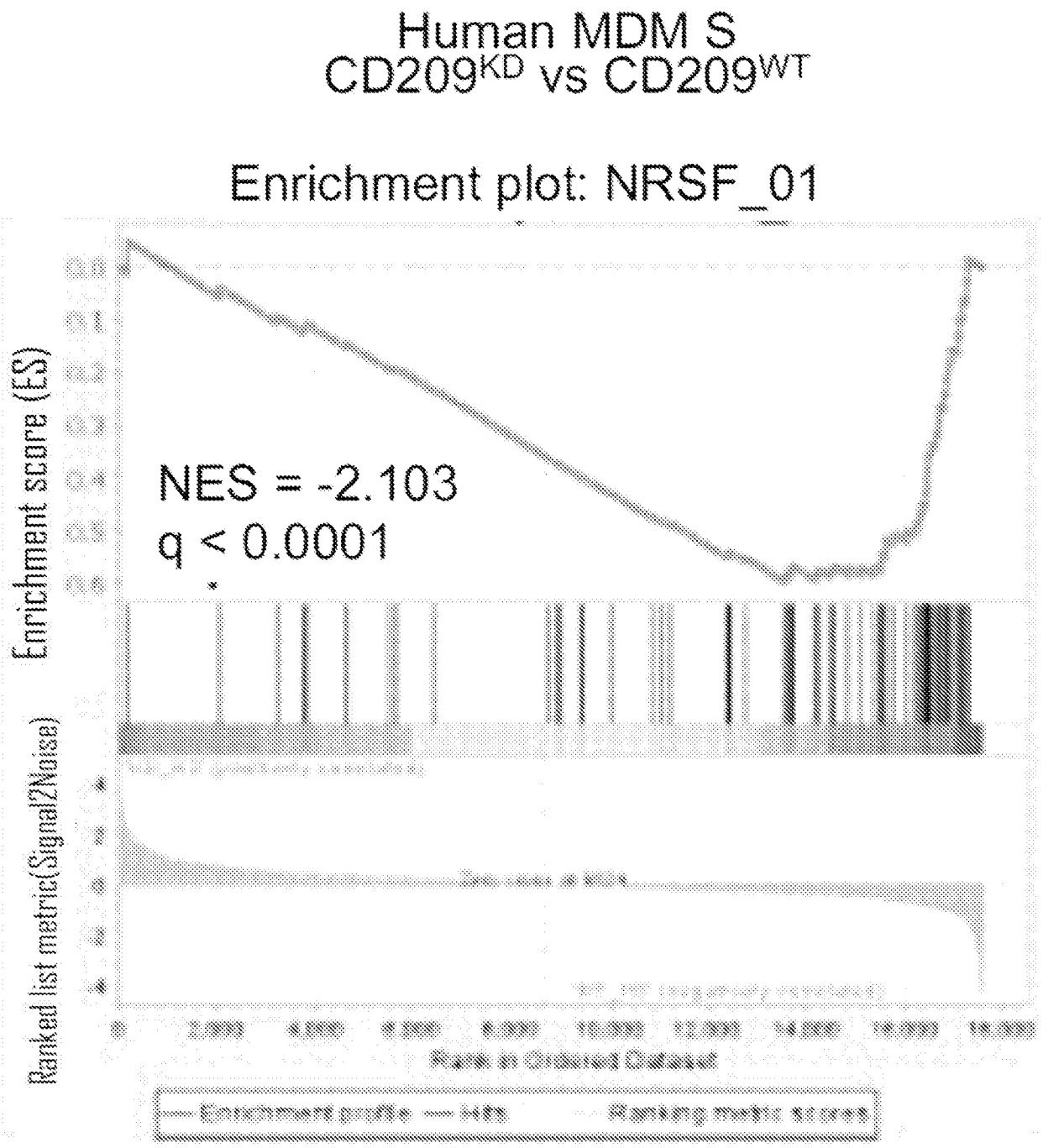

Human MDM S
CD209KD vs CD209WT
Enrichment plot: NRSF_01
NES = -2.103
q < 0.0001
Enrichment score (ES)
Ranked list metric(Signal2Noise)

FIG. 25F

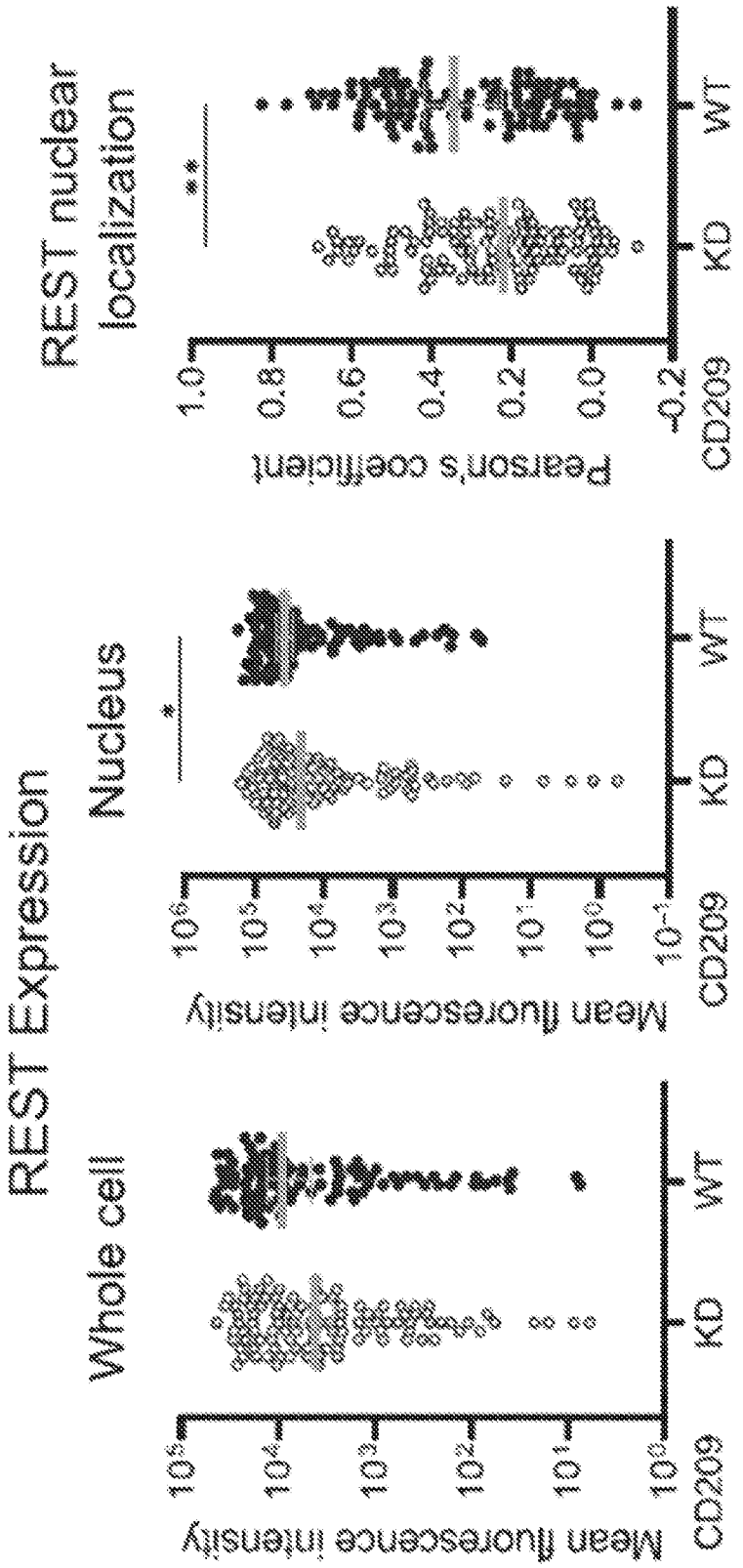

REST Expression
Whole cell
Nucleus
REST nuclear localization
Mean fluorescence intensity
Pearson's coefficient
CD209
KD
WT
*
**

FIG. 25G

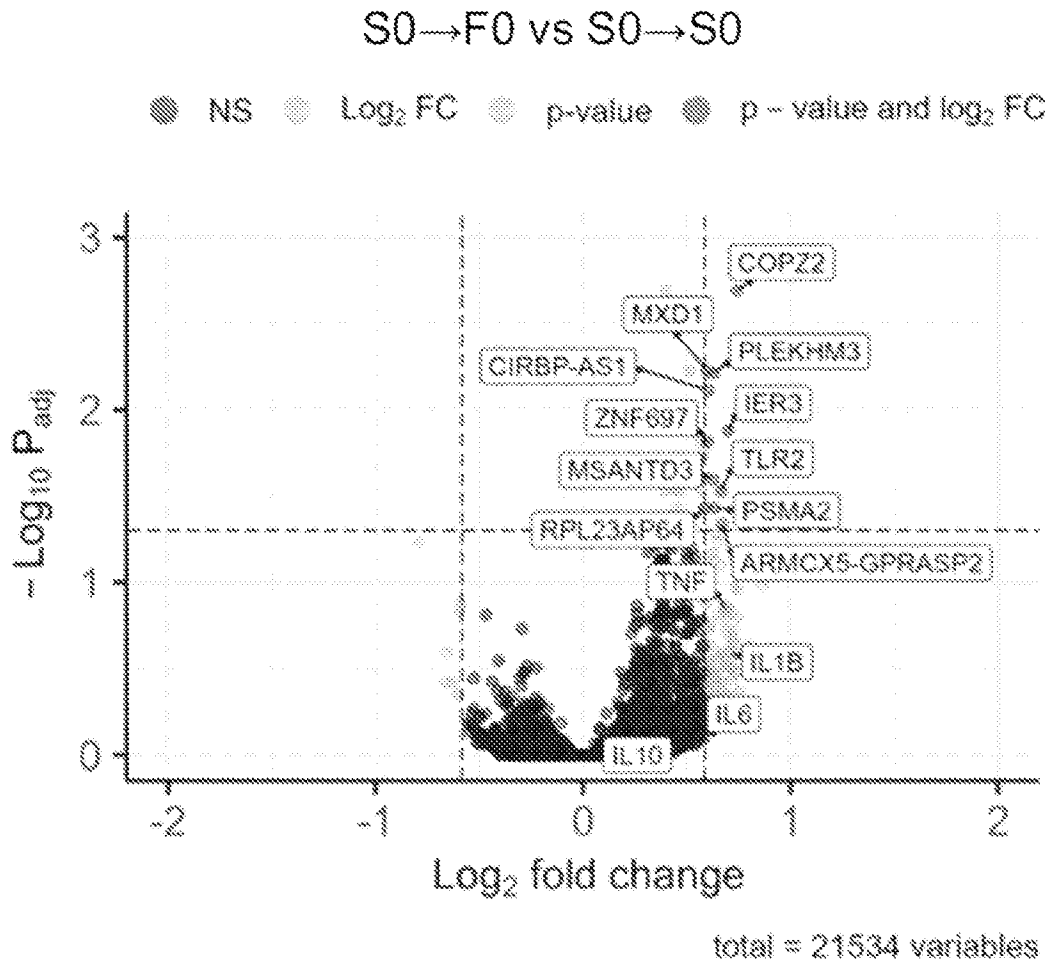

S0→F0 vs S0→S0
NS
Log2 FC
p-value
p – value and log2 FC
COPZ2
MXD1
PLEKHM3
CIRBP-AS1
IER3
ZNF697
TLR2
MSANTD3
PSMA2
RPL23AP64
ARMCX5-GPRASP2
TNF
IL1B
IL6
IL10
-Log10 Padj
Log2 fold change
total = 21534 variables

FIG. 26A

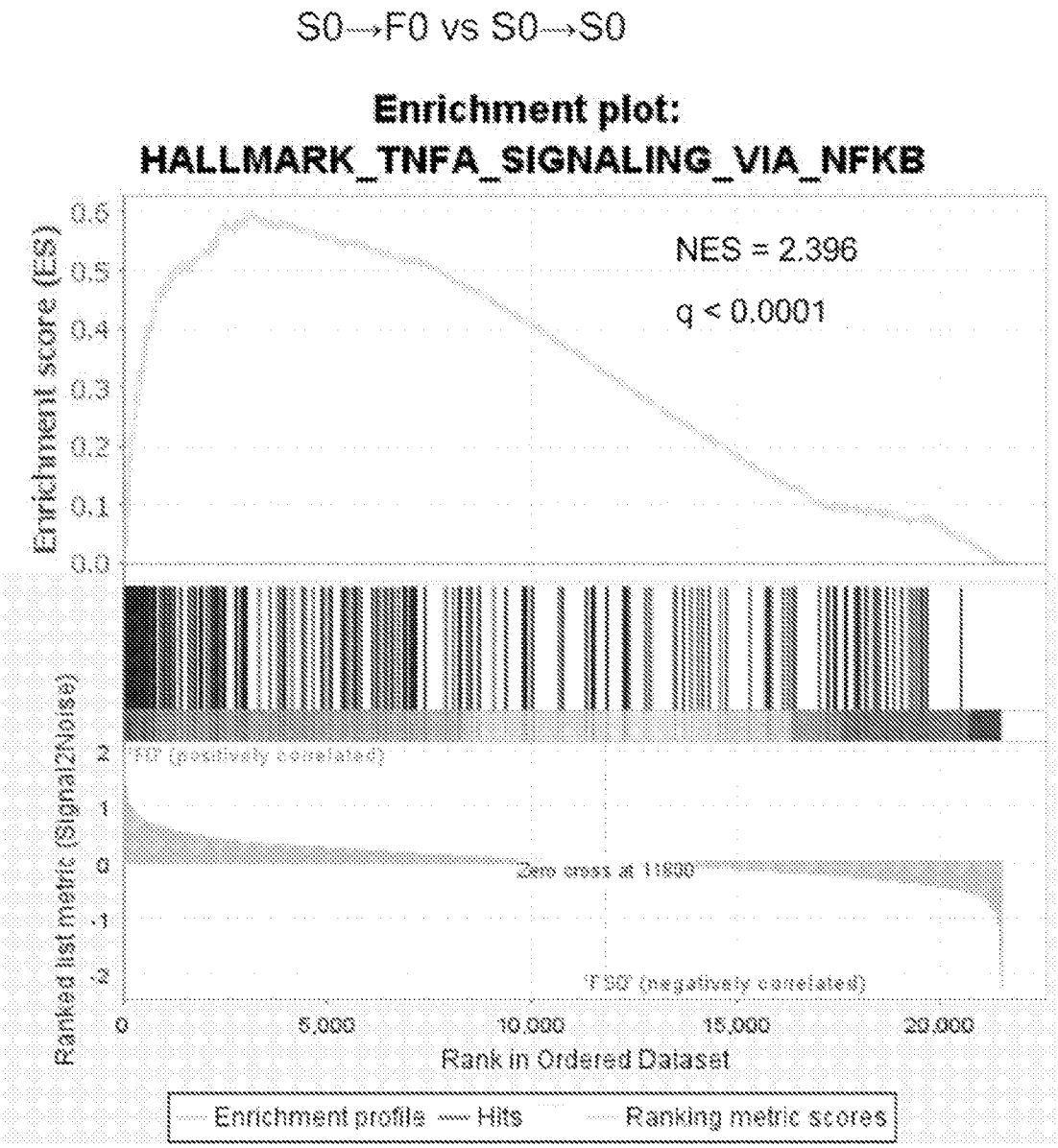

S0→F0 vs S0→S0
Enrichment plot:
HALLMARK_TNFA_SIGNALING_VIA_NFKB
NES = 2.396
q < 0.0001
Enrichment score (ES)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Ranked list metric (Signal2Noise)
2
1
0
-1
-2
'F0' (positively correlated)
Zero cross at 11800
'F30' (negatively correlated)
0
5,000
10,000
15,000
20,000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

FIG. 26B

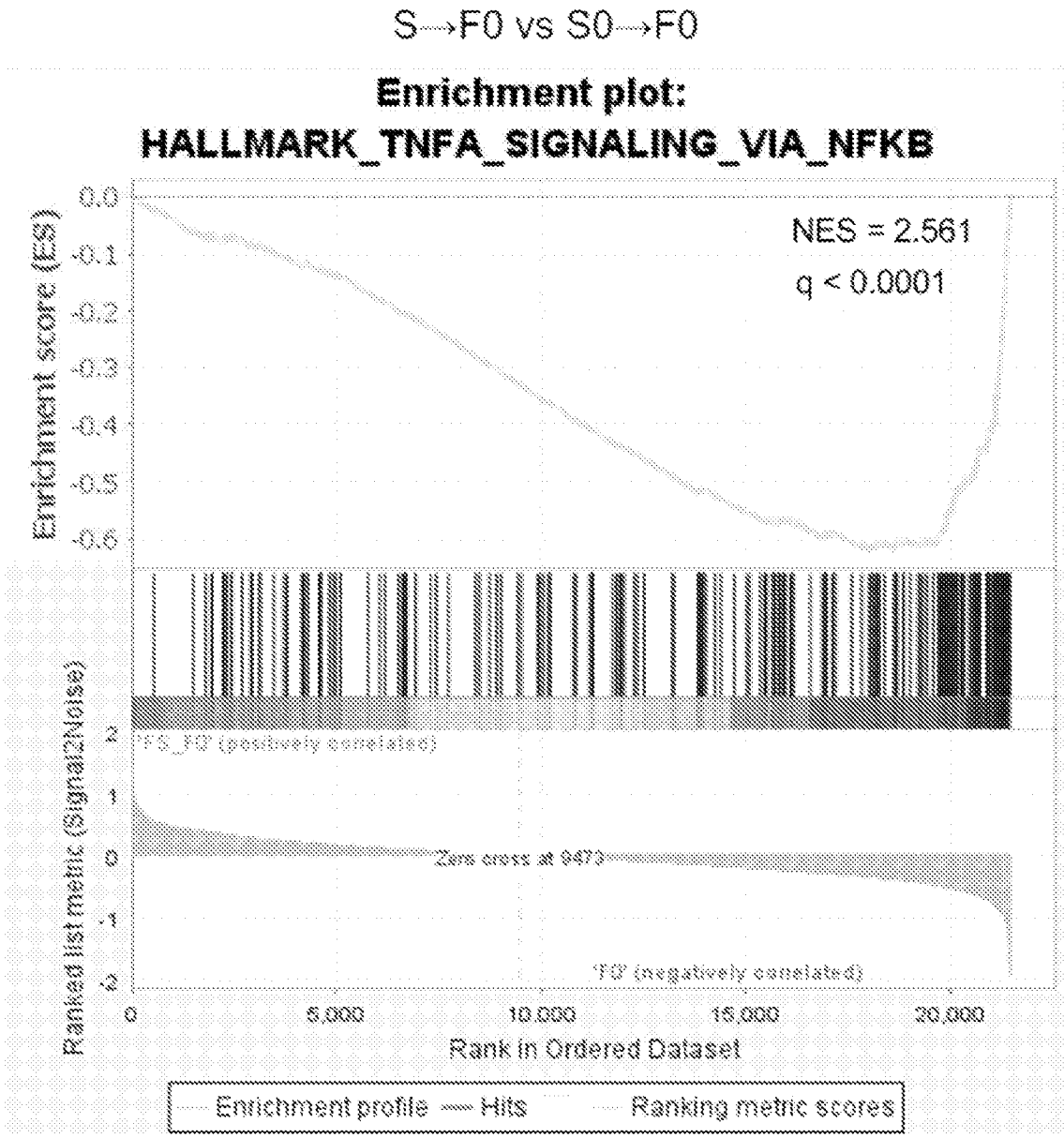

S→F0 vs S0→F0
Enrichment plot:
HALLMARK_TNFA_SIGNALING_VIA_NFKB
NES = 2.561
q < 0.0001
Enrichment score (ES)
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
'FS_F0' (positively correlated)
Zero cross at 9473
'F0' (negatively correlated)
Ranked list metric (Signal2Noise)
2
1
0
-1
-2
0
5,000
10,000
15,000
20,000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

FIG. 26C

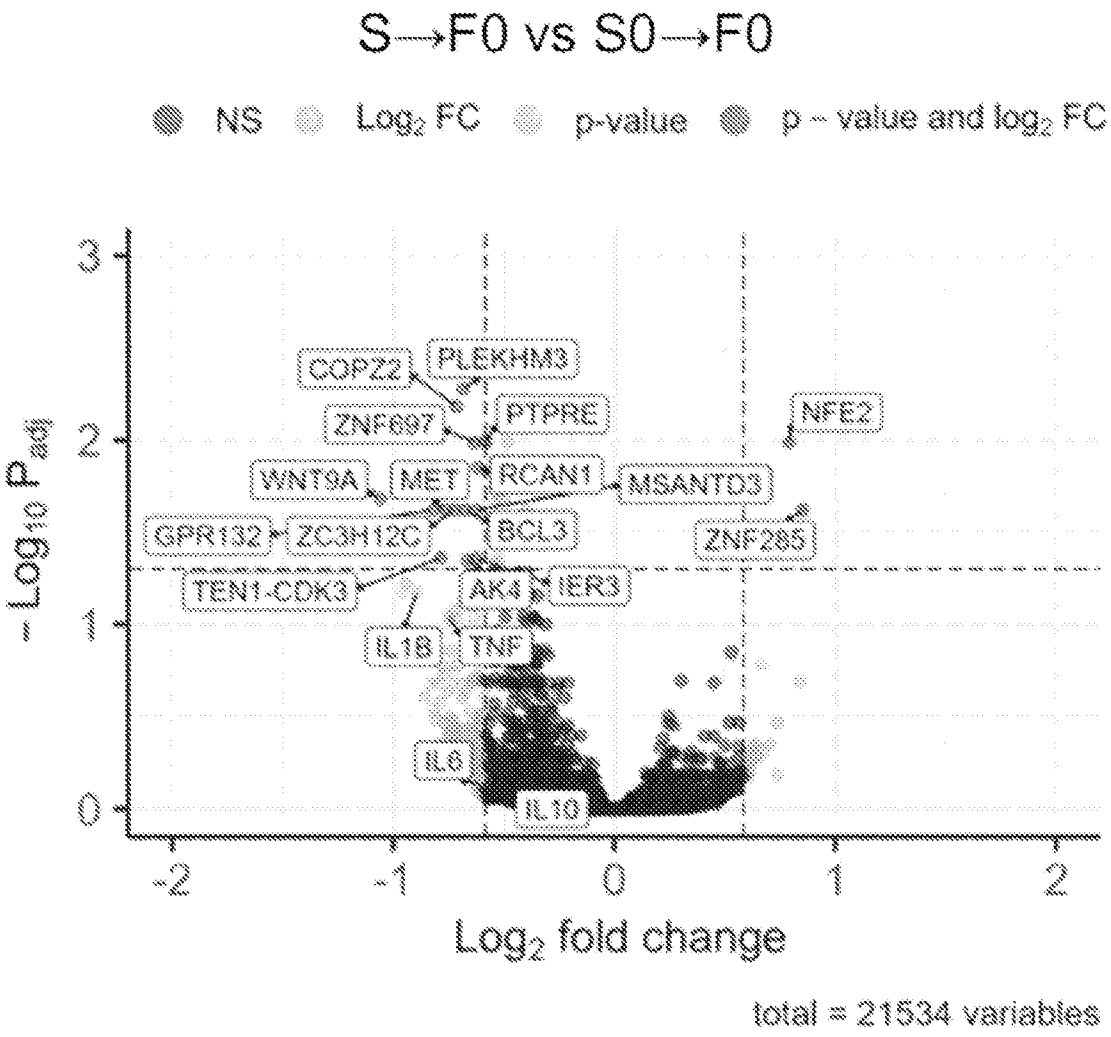

S→F0 vs S0→F0
NS
Log2 FC
p-value
p – value and log2 FC
COPZ2
PLEKHM3
ZNF697
PTPRE
NFE2
WNT9A
MET
RCAN1
MSANTD3
GPR132
ZC3H12C
BCL3
ZNF285
TEN1-CDK3
AK4
IER3
IL1B
TNF
IL6
IL10
3
2
1
0
-2
-1
0
1
2
Log2 fold change
total = 21534 variables

FIG. 26D

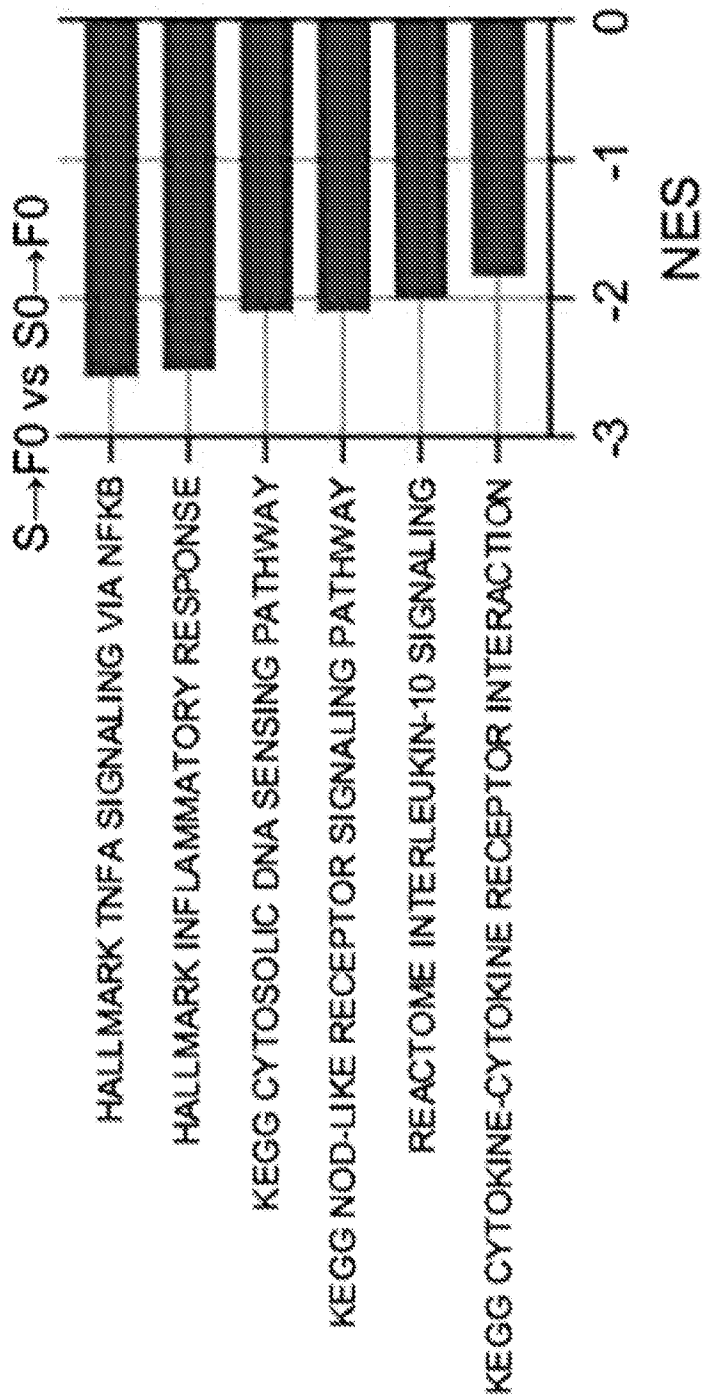

S→F0 vs S0→F0
HALLMARK TNFA SIGNALING VIA NFKB
HALLMARK INFLAMMATORY RESPONSE
KEGG CYTOSOLIC DNA SENSING PATHWAY
KEGG NOD-LIKE RECEPTOR SIGNALING PATHWAY
REACTOME INTERLEUKIN-10 SIGNALING
KEGG CYTOKINE-CYTOKINE RECEPTOR INTERACTION
-3
-2
-1
0
NES

FIG. 26E

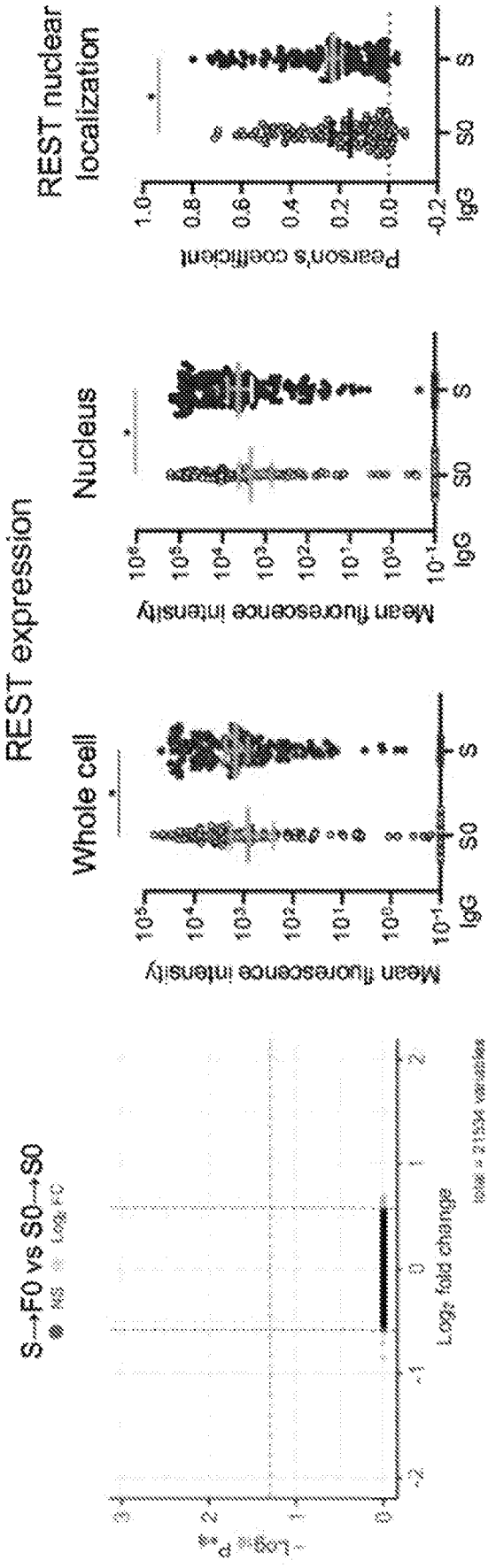


FIG. 26G

FIG. 26F

Table 1. REST-binding RE-1 motifs within NF-κB-related and subunit genes

																	Position		
	RE-1	t	t	C	A	G	c	A	C	C	a	c	G	G	A	C	A	G	c	g	c	c	p-value	chr	Start	End
References	*Grin1*	T	T	C	A	G	C	A	C	C	G	C	G	G	A	C	A	G	C	G	C	C	1.03E-10	9	140033712	140033732
	Grin1	C	T	G	A	G	C	A	C	C	T	G	G	G	C	C	A	G	C	T	C	C	1.38E-08	9	140041154	140041174
	Grin1	T	G	C	A	G	T	A	C	C	C	C	T	G	A	G	A	G	C	G	A	C	3.36E-06	9	140051727	140051747
	Nfkb2	G	T	C	A	G	C	A	C	C	C	C	T	G	G	A	G	A	G	G	G	A	8.07E-07	10	104160924	104160944
NF-κB genes	*Rela*	C	A	C	A	G	C	A	C	C	A	C	A	G	G	A	C	A	G	T	G	C	G	1.11E-06	11	65429275	65429295
	Rela	C	A	C	A	G	G	A	C	C	A	G	A	G	G	A	C	A	G	T	G	C	G	2.27E-06	11	65422542	65244562
	Tnfaip3	T	T	C	G	G	C	C	C	C	A	C	C	C	G	A	C	A	G	C	A	C	C	2.55E-06	6	138199956	138199976
	Tnfaip3	T	T	C	A	G	T	C	C	C	A	G	A	G	G	A	C	A	G	C	T	T	C	3.95E-06	6	138189154	138189174
	Il1b	T	T	C	A	A	C	A	C	G	C	A	G	G	A	C	A	G	G	T	A	C	C	3.68E-06	2	113588897	113588917
	Tnfaip2	T	C	C	G	C	C	A	C	C	A	C	G	G	C	C	A	G	C	G	C	C	C	3.53E-07	14	103593565	103593585
	Ifi6	T	T	T	G	G	G	A	C	A	T	T	G	G	A	C	A	G	C	A	C	C	C	6.12E-07	7	22768978	22768998

FIG. 27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/055127

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 39/395*** (2024.01); ***A61P 31/14*** (2024.01); ***C07K 16/18*** (2024.01); *C07K 14/705* (2024.01)

CPC: ***A61K 39/395; A61P 31/14; C07K 16/18;*** *C07K 14/70596; C07K 2317/41; C07K 2317/52*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/0110807 A1 (THE ROCKEFELLER UNIVERSITY et al.) 23 April 2015 (23.04.2015) entire document	1-4, 11, 12, 14, 15, 53-56, 63, 64, 66, 67
A	WO 2023/205659 A2 (AUGMENT BIOLOGICS INC.) 26 October 2023 (26.10.2023) entire document	1-4, 11, 12, 14, 15, 53-56, 63, 64, 66, 67
A	US 2014/0046032 A1 (BLANCHE et al.) 13 February 2014 (13.02.2014) entire document	1-4, 11, 12, 14, 15, 53-56, 63, 64, 66, 67
A	US 2023/0338505 A1 (THE ROCKEFELLER UNIVERSITY) 26 October 2023 (26.10.2023) entire document	1-4, 11, 12, 14, 15, 53-56, 63, 64, 66, 67

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2024 (20.12.2024)	**10 February 2025 (10.02.2025)**

Name and mailing address of the ISA/US	Authorized officer
COMMISSIONER FOR PATENTS **MAIL STOP PCT, ATTN: ISA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** **UNITED STATES OF AMERICA**	**TAINA MATOS**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/055127

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☑ forming part of the international application as filed.
   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/055127

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☑ Claims Nos.: **8-10, 16-52, 60-62, 68-101**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-4, 11, 12, 53-56, 63, 64 and also claims 14, 15, 66, and 67 (in part) are drawn to methods comprising the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN.

Group II: claims 5-7, 13, 57-59, 65 and also claims 14, 15, 66, and 67 (in part) are drawn to methods comprising wherein the IgG Fc region-containing protein induces REST.

The inventions listed in Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, methods comprising the IgG Fc region-containing protein each induce and/or repress transcription of one or more genes dependent on DC-SIGN, are not present in Group II; and the special technical features of Group II, methods comprising wherein the IgG Fc region-containing protein induces REST, are not present in Group I.

Additionally, even if Groups I and II were considered to share the technical features of a method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids; A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids; A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids; A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids; A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region; A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region; A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region; and A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2015/0110807 A1 to The Rockefeller University et al. teaches a method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]); A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]; "treating" or "treatment" refers to administration of a compound or agent to a subject who has a disorder with the purpose to cure, alleviate, relieve, remedy, delay the onset of, prevent, or ameliorate the disorder, the symptom of the disorder, the disease state secondary to the disorder, or the predisposition toward the disorder, Para. [0081]); A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]; "treating" or "treatment" refers to administration of a compound or agent to a subject who has a disorder with the purpose to cure, alleviate, relieve, remedy, delay the onset of, prevent, or ameliorate the disorder, the symptom of the disorder, the disease state secondary to the disorder, or the predisposition toward the disorder, Para. [0081]); A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject hypersialylated intravenous immunoglobulin (IVIg) or an IgG Fc region-containing protein comprising a hypersialylated IgG Fc region, wherein the hypersialylated IVIg and the IgG Fc region-containing protein each include a2,6-linked sialic acids (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]; "treating" or "treatment" refers to administration of a compound or agent to a subject who has a disorder with the purpose to cure, alleviate, relieve, remedy, delay the onset of, prevent, or ameliorate the disorder, the symptom of the disorder, the disease state secondary to the disorder, or the predisposition toward the disorder, Para. [0081]); A method for treating moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]); A method for improving lung function or preserving lung function in a human subject with a moderate to severe respiratory virus disease, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]; "treating" or "treatment" refers to administration of a compound or agent to a subject who has a disorder with the purpose to cure, alleviate, relieve, remedy, delay the onset of, prevent, or ameliorate the disorder, the symptom of the disorder, the disease state secondary to the disorder, or the predisposition toward the disorder, Para. [0081]); A method for reducing inflammation associated with moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]; "treating" or "treatment" refers to administration of a compound or agent to a subject who has a disorder with the purpose to cure, alleviate, relieve, remedy, delay the onset of, prevent, or ameliorate the disorder, the symptom of the disorder, the disease state secondary to the disorder, or the predisposition toward the disorder, Para. [0081]); and A method for preventing moderate to severe respiratory virus disease in a human subject, comprising administering to the subject an IgG Fc region-containing protein comprising a modified IgG Fc region (a method for treating an inflammatory disorder, e.g., an autoimmune disease, in a subject in need thereof. The method includes, among others, a step of administering to the subject the protein or composition described above. The first polypeptide or the protein can have an N-linked, complex biantennary glycan terminating with an α2,6 linked sialic acid, Para. [0011]; Accordingly, one aspect of this invention features an isolated protein containing a first polypeptide chain that has the sequence of… (SEQ ID NO: 1)…. The just mentioned sequence corresponds to aa. 261-300 of human IgG1 Fc, Para. [0007]; This immunomodulating activity suggests that the immunogenic or vaccine composition of the invention is useful in treating conditions such as, but not limited to:… a coronavirus (e.g., SARS), Para. [0074]; "treating" or "treatment" refers to administration of a compound or agent to a subject who has a disorder with the purpose to cure, alleviate, relieve, remedy, delay the onset of,

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

prevent, or ameliorate the disorder, the symptom of the disorder, the disease state secondary to the disorder, or the predisposition toward the disorder, Para. [0081]).

The inventions listed in Groups I and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-4, 11, 12, 14, 15, 53-56, 63, 64, 66, 67**

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.