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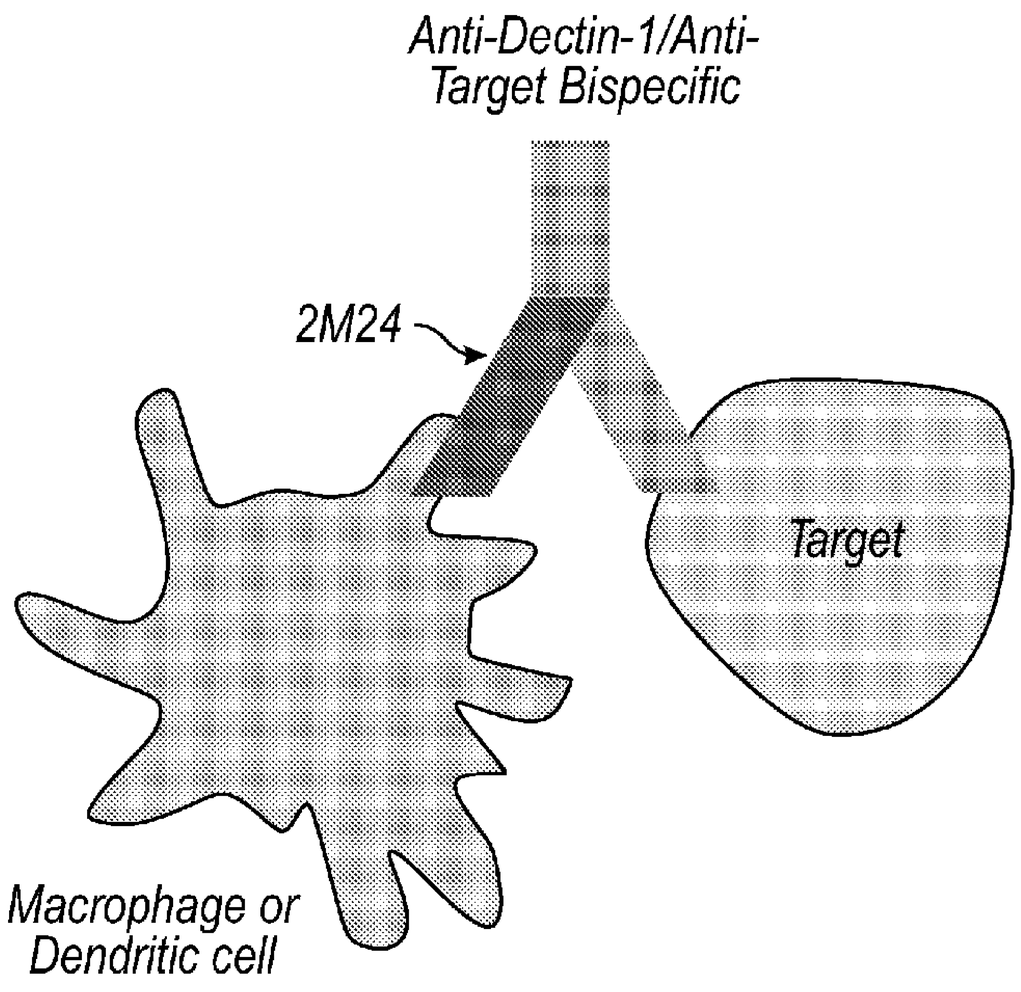


FIG. 29B

(57) Abstract: The present invention relates to anti-human dectin-1 antibody clone 2M24 (hIgG4) or 15E2 and multi-specific binding molecules comprising them, and method of producing and using them.

[Continued on next page]

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ANTI-DECTIN-1 ANTIBODIES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial Nos. 63/088,895, filed October 7, 2020, and 63/174,439, filed April 13, 2021, the disclosures of each of which are incorporated herein by reference in their entirety.

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 186542000440SEQLIST.TXT, date recorded: October 6, 2021, size: 108,547 bytes).

FIELD

[0003] The present disclosure relates to antibodies that bind human Dectin-1, multispecific (*e.g.*, bispecific) binding molecules, and methods of use and production related thereto.

BACKGROUND

[0004] Phagocytosis is a major mechanism used to remove pathogens and cell debris. Professional phagocytes, such as monocytes, macrophages, dendritic cells, and granulocytes, specifically recognize and engulf host or foreign agents that are aberrant or cause disease. The engulfed material is destroyed through the endo-lysosomal pathway in the phagocytes. Moreover, dendritic cells and macrophages can present antigens to the cells of the adaptive immune system to further promote the elimination of the disease-causing agents.

[0005] Dectin-1 is a C-type lectin receptor that recognizes beta-glucans and promotes anti-fungal phagocytic activities. It is expressed on phagocytes and has been clearly shown to be sufficient for activating phagocytosis. Dectin-1 can be exploited for antibody-targeted phagocytosis and elimination of disease-causing agents.

[0006] It would be beneficial to develop targeted removal and degradation of accumulated disease-causing agents without boosting overall phagocytosis. This disclosure provides a solution for the problems and describes other advantages.

[0007] All references cited herein, including patent applications, patent publications, and scientific literature, are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

BRIEF SUMMARY

[0008] The present disclosure relates to antibodies that bind human Dectin-1, multispecific (*e.g.*, bispecific) binding molecules, and methods of use and production related thereto. Described herein are methods of targeted phagocytosis to remove disease-causing agents, including host cells/host cell products, microbes or their products, etc., upon administration of multispecific (*e.g.*, bispecific) binding molecules comprising a Dectin-1 binding arm and a second arm that specifically binds to the agent. The multispecific (*e.g.*, bispecific) binding molecules allow the phagocyte to engage the target agent and form a synapse between it and promote clustering of Dectin-1 on the phagocyte. This stimulates phagocytosis of the target agent and at the same time cytokine secretion via the Dectin-1/Syk/NfkB pathway by the phagocyte. Moreover, antigens from the engulfed material are presented on the surface of dendritic cells/macrophages to boost an adaptive immune response against the disease-causing agent. Overall, it is thought that the Dectin-1 agonistic, multispecific (*e.g.*, bispecific) binding molecules promote immune stimulation, targeted phagocytosis, and neo-antigen presentation/activation of the adaptive immune system to eliminate the disease-causing agent.

[0009] As such, the present disclosure describes, *inter alia*, the generation and functional characterization of an agonistic anti-human Dectin-1 antibody that exhibits high affinity binding to Dectin-1 and can promote immune stimulation. Further described is the generation of bispecific antibody formats including the anti-human Dectin-1 antibody with antibodies targeting antigens on disease-causing agents, with data supporting target engagement, immune stimulation, phagocytosis, and antigen presentation.

[0010] In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD

TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and wherein the VL domain comprises a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the VH domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or the VL domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the VH domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or the VL domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment binds to human Dectin-1 expressed on the surface of a cell with an EC50 of less than 2nM, less than 1nM, or less than 0.5nM. In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment is capable of binding human or

cynomolgus Dectin-1. In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment does not compete (*e.g.*, for binding to human Dectin-1) with a native ligand of Dectin-1, *e.g.*, human Dectin-1. In some embodiments, the antibody or fragment competes for binding to human Dectin-1 with a reference antibody that comprises: (a) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6); (b) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6); or (c) a heavy chain variable (VH) domain comprising the sequence

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7) and a light chain variable (VL) domain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the antibody or fragment binds the same epitope of human Dectin-1 as a reference antibody that comprises (a) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6); (b) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the

sequence QQAYSFPFT (SEQ ID NO:6); or (c) a heavy chain variable (VH) domain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7) and a light chain variable (VL) domain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the antibody or fragment is a human, humanized, or chimeric antibody or fragment. In some embodiments, the antibody or fragment binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, and/or granulocyte. In some embodiments, the antigen-binding antibody fragment is a Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibody, nanobody, or scFv fragment. In some embodiments, the antibody further comprises an Fc region. In some embodiments, the antibody or fragment is a multispecific antibody or fragment. In some embodiments, the antibody or fragment is a bispecific antibody, fragment, or diabody comprising a first antigen binding domain comprising the VH and VL domains that bind to human Dectin-1 and a second antigen binding domain that binds to a target of interest or comprising a first antigen binding domain that binds to a target of interest and a second antigen binding domain comprising the VH and VL domains that bind to human Dectin-1. In some embodiments, the bispecific antibody comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising the VH and VL domains that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises the VH domain of the second antigen binding domain in association with an antibody light chain that comprises the VL domain of the second antigen binding domain and a second Fc region connected to the VH domain of the second antigen binding domain. In some embodiments, the second antigen-binding domain binds to CD20 and comprises a VH domain comprising the sequence of SEQ ID NO:24 and a VL domain comprising the sequence of SEQ ID NO:25. In some embodiments, the second antigen-binding domain binds to Trop-2 and comprises a VH domain comprising the sequence of SEQ ID NO:42 and a VL domain comprising the sequence of SEQ ID NO:43. In some embodiments, the second antigen-binding domain binds to light chain amyloid and comprises a VH domain comprising the sequence of SEQ ID NO:44 and a VL domain comprising the sequence of SEQ ID NO:45. In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or wherein the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or

more cognate hole-forming mutations. In some embodiments, the first Fc region comprises a T366W substitution, and the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering. In some embodiments, the first antibody arm comprises a first linker between the VH and VL domains, and a second linker between the VL domain and the first Fc region. In some embodiments, the first linker comprises one or more repeats of the sequence GGGGS (SEQ ID NO:26). In some embodiments, the first linker comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:27) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:28). In some embodiments, the second linker comprises the sequence EPKRSDKTHTCPPC (SEQ ID NO:29) or SATHTCPPC (SEQ ID NO:30). In some embodiments, the bispecific antibody comprises a first IgG antibody comprising the first antigen binding domain covalently linked to a second IgG antibody comprising the second antigen binding domain. In some embodiments, the bispecific antibody comprises a first antibody arm comprising a first antibody heavy chain that comprises the VH domain of the first antigen binding domain and a first Fc region and a second antibody arm comprising a second antibody heavy chain that comprises the VH domain of the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the first Fc region comprises a T366W substitution, and the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering. In some embodiments, the bispecific antibody comprises a first antibody arm comprising a first antibody heavy chain that comprises the VH domain of the first antigen binding domain and a first Fc region and a second antibody arm comprising a second antibody heavy chain that comprises the VH domain of the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more hole-forming mutations, and the second Fc region comprises one or more cognate knob-forming mutations. In some embodiments, the first Fc region comprises T366S, L368A, and Y407V substitutions, and the second Fc region comprises a T366W substitution, according to EU numbering. In some embodiments, the bispecific antibody comprises a first IgG antibody comprising the first antigen binding domain coupled to biotin or an avidin-binding derivative thereof, and a second IgG antibody comprising the second antigen binding domain coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, wherein the biotin or avidin-binding derivative thereof is bound to the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof. In some embodiments, the bispecific antibody comprises a first IgG antibody comprising the first antigen binding domain coupled to avidin, streptavidin, neutravidin, or a

biotin-binding derivative thereof, and a second IgG antibody comprising the second antigen binding domain coupled to biotin or an avidin-binding derivative thereof, wherein the biotin or avidin-binding derivative thereof is bound to the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof. In some embodiments, the target of interest is a disease-causing agent. In some embodiments, the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate (*e.g.*, amyloid beta, or lambda or kappa light chain amyloids), LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is a surface antigen of the virus. In some embodiments, the target of interest is an antigen expressed on the surface of a cancer cell. In some embodiments, the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR. In some embodiments, the target of interest is CD20; the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and the VH domain of the second antigen-binding domain comprises the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24) and/or the VL domain of the second antigen-binding domain comprises the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25). In some embodiments, the antibody comprises two antibody heavy chains, and wherein each of the antibody heavy chains comprises an amino acid substitution at one or more of positions 234, 235, and 237, according to EU numbering. In some embodiments, each of the antibody heavy chains comprises L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the antibody comprises two antibody heavy chains, and wherein only one of the antibody heavy chains comprises H435R and Y436F substitutions, according to EU numbering. In some embodiments, the antibody comprises two arms, and only one of the antibody arms comprises a heavy chain comprising F126C and C220V substitutions and a light chain comprising S121C and C214V substitutions, according to EU numbering. In some embodiments, the bispecific antibody comprises a first and a second antibody heavy chain, wherein the VH domain of the first antibody heavy chain forms an antigen binding domain with the VL domain of the first antibody light chain, wherein the VH domain of the second antibody heavy chain

forms an antigen binding domain with the VL domain of the second antibody light chain, wherein the first antibody heavy chain comprises F126C, C220V, and T366W substitutions, wherein the first antibody light chain comprises S121C and C214V substitutions, and wherein the second antibody heavy chain comprises T366S, L368A, Y407V, H435R, and Y436F substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains further comprise L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains comprise human IgG1 Fc domains. In some embodiments, the antibody comprises a first and a second antibody heavy chain, wherein at least one or two of the first and second antibody heavy chains is/are non-fucosylated. In some embodiments, the antibody may be produced in a cell line having an alpha1,6-fucosyltransferase (Fut8) or alpha-1,3-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltranferase (MGAT1) knockout. In some embodiments, the antibody may be produced in a cell line overexpressing β1,4-N-acetylglucosaminyltransferase III (GnT-III). In further embodiments, the cell line additionally overexpresses Golgi μ-mannosidase II (ManII). In some embodiments, the antibody may be produced in a cell line treated with an inhibitor of mannosidase I, *e.g.*, kifunensine.

[0011] In some embodiments, provided herein is a multispecific binding molecule, comprising: (a) a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to human Dectin-1; and (b) a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a target of interest. In some embodiments, the target of interest is a disease-causing agent. In some embodiments, the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate (*e.g.*, amyloid beta, or lambda or kappa light chain amyloids), LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is a surface antigen of the virus. In some embodiments, the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR. In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW

(SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the VH domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or the VL domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the VH domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the first antigen-binding domain: binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, or granulocyte; binds to human Dectin-1 expressed on the surface of a cell with an EC50 of less than 2nM; is capable of binding human or cynomolgus Dectin-1; and/or does not compete with a native ligand of human Dectin-1. In some embodiments, the second antigen-binding domain binds to CD20 and comprises a VH domain comprising the sequence of SEQ ID NO:24 and a VL domain comprising the sequence of SEQ ID NO:25. In some embodiments, the second antigen-binding domain binds to Trop-2 and

comprises a VH domain comprising the sequence of SEQ ID NO:42 and a VL domain comprising the sequence of SEQ ID NO:43. In some embodiments, the second antigen-binding domain binds to light chain amyloid and comprises a VH domain comprising the sequence of SEQ ID NO:44 and a VL domain comprising the sequence of SEQ ID NO:45. In some embodiments, one or both of the first and second antibodies or fragments are human or humanized antibodies or fragments. In some embodiments, one or both of the first and second antibodies or fragments are Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibodies, nanobodies, or scFv fragments. In some embodiments, one or both of the first and second antibodies or fragments further comprise an Fc domain. In some embodiments, the first antibody or fragment is a Fab fragment, and wherein the second antibody or fragment is a full-length antibody, *e.g.*, that comprises an antibody heavy chain and an antibody light chain. In some embodiments, the first and the second antibodies or fragments are both full-length antibodies, *e.g.*, that each comprise an antibody heavy chain and an antibody light chain. In some embodiments, the multispecific binding molecule comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising the VH and VL domains that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises the VH domain of the second antigen binding domain in association with an antibody light chain that comprises the VL domain of the second antigen binding domain and a second Fc region connected to the VH domain of the second antigen binding domain. In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or wherein the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the first Fc region comprises a T366W substitution, and the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering. In some embodiments, the first antibody arm comprises a first linker between the VH and VL domains, and a second linker between the VL domain and the first Fc region. In some embodiments, the first linker comprises one or more repeats of the sequence GGGGS (SEQ ID NO:26). In some embodiments, the first linker comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:27) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:28). In some embodiments, the second linker comprises the sequence EPKRSDKTHTCPPC (SEQ ID NO:29) or SATHTCPPC (SEQ ID NO:30). In some embodiments, the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or wherein the second antibody or

fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; and wherein the first antibody or fragment is bound to the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof. In some embodiments, the first antibody or fragment is a Fab fragment coupled to monomeric streptavidin (mSA), and wherein the second antibody or fragment is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain. In some embodiments, the first antibody or fragment is a full-length antibody coupled to monomeric streptavidin (mSA), and wherein the second antibody or fragment is a biotinylated full-length antibody. In some embodiments, the multispecific binding molecule comprises a first IgG antibody comprising the first antigen binding domain covalently linked to a second IgG antibody comprising the second antigen binding domain. In some embodiments, the multispecific binding molecule comprises a first antibody arm comprising a first antibody heavy chain that comprises the VH domain of the first antigen binding domain and a first Fc region and a first antibody light chain comprising the VL domain of the first antigen binding domain, and a second antibody arm comprising a second antibody heavy chain that comprises the VH domain of the second antigen binding domain and a second Fc region and a second antibody light chain comprising the VL domain of the second antigen binding domain, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the first Fc region comprises a T366W substitution, and wherein the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering. In some embodiments, the multispecific binding molecule comprises a first antibody arm comprising the VH domain of the first antigen binding domain and a first Fc region and a second antibody arm comprising the VH domain of the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more hole-forming mutations, and the second Fc region comprises one or more cognate knob-forming mutations. In some embodiments, the first Fc region comprises T366S, L368A, and Y407V substitutions, and wherein the second Fc region comprises a T366W substitution, according to EU numbering. In some embodiments, the multispecific binding molecule comprises two antibody Fc regions, and wherein each of the antibody heavy chains comprises an amino acid substitution at one or more of positions 234, 235, and 237, according to EU numbering. In some embodiments, each of the antibody Fc regions comprises L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the multispecific binding molecule comprises two antibody heavy chains, and wherein only one of

the antibody heavy chains comprises H435R and Y436F substitutions, according to EU numbering. In some embodiments, only one of the antibody arms comprises a heavy chain comprising F126C and C220V substitutions and a light chain comprising S121C and C214V substitutions, according to EU numbering. In some embodiments, the multispecific binding molecule comprises a first antibody heavy chain and a first antibody light chain and a second antibody heavy chain and a second antibody light chain, wherein the VH domain of the first antibody heavy chain forms a first antigen binding domain with the VL domain of the first antibody light chain, wherein the VH domain of the second antibody heavy chain forms a second antigen binding domain with the VL domain of the second antibody light chain, wherein the first antibody heavy chain comprises F126C, C220V, and T366W substitutions, wherein the first antibody light chain comprises S121C and C214V substitutions, and wherein the second antibody heavy chain comprises T366S, L368A, Y407V, H435R, and Y436F substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains further comprise L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains comprise human IgG1 Fc domains. In some embodiments, at least one or two of the heavy chains of the antibody is non-fucosylated. In some embodiments, the antibody may be produced in a cell line having an alpha1,6-fucosyltransferase (Fut8) or alpha-1,3-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltranferase (MGAT1) knockout. In some embodiments, the antibody may be produced in a cell line overexpressing β1,4-N-acetylglucosaminyltransferase III (GnT-III). In further embodiments, the cell line additionally overexpresses Golgi μ-mannosidase II (ManII). In some embodiments, the antibody may be produced in a cell line treated with an inhibitor of mannosidase I, *e.g.*, kifunensine.

[0012] In some embodiments, provided herein is a multispecific binding molecule, comprising: (a) a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to a first target of interest; and (b) a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a second target of interest; wherein: (i) the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or (ii) the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; and wherein the first antibody or fragment is bound to the second antibody or fragment via an interaction between the avidin,

streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof. In some embodiments, the first target of interest is human Dectin-1. In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and wherein the VL domain comprises a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the VH domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or the VL domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS

RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the VH domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, provided herein is a multispecific binding molecule, comprising a first polypeptide chain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31), a second polypeptide chain comprising the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVS KLTVDKSRWQQGNVFSCSVMHEALHNRFTQKSLSLSPG (SEQ ID NO:32), and a third polypeptide chain comprising the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:33). In some embodiments, provided herein is a multispecific binding molecule comprising a first arm comprising a first antigen-binding domain and a second arm comprising a second antigen-binding domain; wherein the first antigen-binding domain binds to human Dectin-1 and the second antigen-binding domain

binds to a target of interest; and wherein the first arm comprises a polypeptide chain comprising the sequence
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the first antigen-binding domain binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, or granulocyte. In some embodiments, one or both of the first and second antibodies or fragments are human or humanized antibodies or fragments. In some embodiments, one or both of the first and second antibodies or fragments are Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibodies, nanobodies, or scFv fragments. In some embodiments, one or both of the first and second antibodies or fragments further comprise an Fc domain. In some embodiments, the first antibody or fragment is a Fab fragment, and wherein the second antibody comprises an antibody heavy chain and an antibody light chain. In some embodiments, the first antibody or fragment is a Fab fragment coupled to monomeric streptavidin (mSA), and wherein the second antibody is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain. In some embodiments, the first antibody or fragment is a full-length antibody coupled to monomeric streptavidin (mSA), and wherein the second antibody is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain. In some embodiments, the second target of interest is a disease-causing agent. In some embodiments, the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate (*e.g.*, amyloid beta, or lambda or kappa light chain amyloids), LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is a surface antigen of the virus. In some embodiments, the target of interest is an antigen expressed on the surface of a cancer cell. In some embodiments, the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR. In some embodiments, the target of interest is CD20; the second antigen-binding domain comprises a

heavy chain variable (VH) domain and a light chain variable (VL) domain; and the VH domain of the second antigen-binding domain comprises the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24) and/or the VL domain of the second antigen-binding domain comprises the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25). In some embodiments, the second antigen-binding domain binds to Trop-2 and comprises a VH domain comprising the sequence of SEQ ID NO:42 and a VL domain comprising the sequence of SEQ ID NO:43. In some embodiments, the second antigen-binding domain binds to light chain amyloid and comprises a VH domain comprising the sequence of SEQ ID NO:44 and a VL domain comprising the sequence of SEQ ID NO:45.

[0013] In some embodiments, provided herein is a polynucleotide encoding the antibody or multispecific binding molecule of any one of the above embodiments. In some embodiments, provided herein is a vector (*e.g.*, an expression vector) comprising the polynucleotide of any one of the above embodiments. In some embodiments, provided herein is a host cell (*e.g.*, an isolated host cell or cell line) comprising the polynucleotide or vector of any one of the above embodiments. In some embodiments, provided herein is a method of producing an antibody or multispecific binding molecule, comprising culturing the host cell of any one of the above embodiments under conditions suitable for production of the antibody or multispecific binding molecule. In some embodiments, the method further comprises recovering the antibody or multispecific binding molecule. In some embodiments, provided herein is a pharmaceutical composition comprising the antibody or multispecific binding molecule of any one of the above embodiments and a pharmaceutically acceptable carrier.

[0014] In some embodiments, provided herein is a method of generating a multispecific binding molecule, comprising: (a) providing a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to a first target of interest; (b) providing a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a second target of interest; wherein: (i) the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or (ii) the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof,

and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; and (c) contacting the first antibody or fragment with the second antibody or fragment under conditions suitable for binding between the first antibody or fragment and the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof, thereby generating a multispecific binding molecule. In some embodiments, provided herein is a method of identifying a multispecific binding molecule that binds a first and a second target of interest, comprising: (a) providing a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to a first target of interest; (b) providing a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a second target of interest; wherein: (i) the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or (ii) the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; (c) contacting the first antibody or fragment with the second antibody or fragment under conditions suitable for binding between the first antibody or fragment and the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof, thereby generating a multispecific binding molecule; and (d) measuring binding between the multispecific binding molecule and at least one of the first and the second target of interest. In some embodiments, the first target of interest is human Dectin-1. In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV

SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and wherein the VL domain comprises a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the VH domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or the VL domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the VH domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the first antigen-binding domain binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, or granulocyte. In some embodiments, one or both of the first and second antibodies or fragments are human or humanized antibodies or fragments. In some embodiments, one or both of the first and second antibodies or fragments are Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibodies, nanobodies, or scFv fragments. In some embodiments, one or both of the first and second antibodies or fragments further comprise an Fc domain. In some embodiments, the first antibody or fragment is a Fab fragment,

and wherein the second antibody or fragment is a full-length antibody, *e.g.*, that comprises an antibody heavy chain and an antibody light chain. In some embodiments, the first and the second antibodies or fragments are both full-length antibodies, *e.g.*, that each comprise an antibody heavy chain and an antibody light chain. In some embodiments, the first antibody or fragment is a Fab fragment coupled to monomeric streptavidin (mSA), and wherein the second antibody is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain. In some embodiments, the first antibody or fragment is a full-length antibody coupled to monomeric streptavidin (mSA), and wherein the second antibody or fragment is a biotinylated full-length antibody. In some embodiments, the second target of interest is a disease-causing agent. In some embodiments, the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate (*e.g.*, amyloid beta, or lambda or kappa light chain amyloids), LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is a surface antigen of the virus. In some embodiments, the target of interest is an antigen expressed on the surface of a cancer cell. In some embodiments, the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR. In some embodiments, the target of interest is CD20, the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, and the VH domain of the second antigen-binding domain comprises the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24) and/or the VL domain of the second antigen-binding domain comprises the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25). In some embodiments, the antibody comprises two antibody Fc regions, and wherein each of the antibody Fc regions comprises an amino acid substitution at one or more of positions 234, 235, and 237, according to EU numbering. In some embodiments, each of the antibody heavy chains comprises L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the antibody comprises two antibody heavy chains, and wherein only one of the antibody heavy chains comprises H435R and Y436F substitutions, according to EU numbering. In some embodiments, only one of the antibody arms comprises a heavy chain comprising F126C

and C220V substitutions and a light chain comprising S121C and C214V substitutions, according to EU numbering. In some embodiments, the bispecific antibody comprises two antibody heavy chains and two antibody light chains, wherein the VH domain of the first antibody heavy chain forms an antigen binding domain with the VL domain of the first antibody light chain, wherein the VH domain of the second antibody heavy chain forms an antigen binding domain with the VL domain of the second antibody light chain, wherein the first antibody heavy chain comprises F126C, C220V, and T366W substitutions, wherein the first antibody light chain comprises S121C and C214V substitutions, and wherein the second antibody heavy chain comprises T366S, L368A, Y407V, H435R, and Y436F substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains further comprise L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains comprise human IgG1 Fc domains. In some embodiments, at least one or two of the heavy chains of the antibody is non-fucosylated. In some embodiments, the antibody may be produced in a cell line having an alpha1,6-fucosyltransferase (Fut8) or alpha-1,3-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltranferase (MGAT1) knockout. In some embodiments, the antibody may be produced in a cell line overexpressing β1,4-N-acetylglucosaminyltransferase III (GnT-III). In further embodiments, the cell line additionally overexpresses Golgi μ-mannosidase II (ManII). In some embodiments, the antibody may be produced in a cell line treated with an inhibitor of mannosidase I, *e.g.*, kifunensine.

[0015] In some embodiments, provided herein is a method of treating a disease or disorder, comprising administering an effective amount of the antibody, multispecific binding molecule, or composition of any one of the above embodiments to an individual in need thereof. In some embodiments, the first target of interest is human Dectin-1, and wherein the second target of interest is a disease-causing agent. In some embodiments, the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate (*e.g.*, amyloid beta, or lambda or kappa light chain amyloids), LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is a surface antigen of the virus. In some embodiments, the disease or disorder is cancer, a bacterial infection, a fungal infection, a viral infection, a mast cell disease or disorder, systemic mastocytosis, amyloidosis (*e.g.*, light chain amyloidosis or Alzheimer's disease), or an aging-related disease or disorder. In some embodiments, the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2,

Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR. In some embodiments, the individual is a human.

[0016] In some embodiments, provided herein is a method of treating cancer, comprising administering an effective amount of a composition comprising a multispecific binding molecule to an individual in need thereof, wherein the multispecific binding molecule comprises: (a) a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to human Dectin-1; and (b) a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR. In some embodiments, the second antigen binding domain binds to human CD70, human HER2, human DLL3, human NECTIN-4, human TROP-2, human Mesothelin, human LIV-1, human C-MET, human FOLR1, human CD20, human CCR8, human CD33, or human EGFR, *e.g.*, as expressed on the surface of a cancer cell. In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGDTNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTVSS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and wherein the VL domain comprises a CDR-L1 comprising

the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the VH domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or the VL domain comprises a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the VH domain of the first antigen-binding domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain of the first antigen-binding domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, the second antigen binding domain binds to CD20; wherein the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and wherein the VH domain of the second antigen-binding domain comprises the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24) and/or wherein the VL domain of the second antigen-binding domain comprises the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25). In some embodiments, the multispecific binding molecule comprises a first antibody arm comprising the first antigen binding domain and a first Fc region and a second antibody arm comprising the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the first Fc region comprises a

T366W substitution, and the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering. In some embodiments, the multispecific binding molecule comprises a first antibody arm comprising the first antigen binding domain and a first Fc region and a second antibody arm comprising the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more hole-forming mutations, and the second Fc region comprises one or more cognate knob-forming mutations. In some embodiments, the first Fc region comprises T366S, L368A, and Y407V substitutions, and the second Fc region comprises a T366W substitution, according to EU numbering. In some embodiments, the antibody comprises two antibody Fc regions, and wherein each of the antibody Fc regions comprises an amino acid substitution at one or more of positions 234, 235, and 237, according to EU numbering. In some embodiments, each of the antibody heavy chains comprises L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the antibody comprises two antibody heavy chains, and wherein only one of the antibody heavy chains comprises H435R and Y436F substitutions, according to EU numbering. In some embodiments, only one of the antibody arms comprises a heavy chain comprising F126C and C220V substitutions and a light chain comprising S121C and C214V substitutions, according to EU numbering. In some embodiments, the bispecific antibody comprises two antibody heavy chains and two antibody light chains, wherein the VH domain of the first antibody heavy chain forms an antigen binding domain with the VL domain of the first antibody light chain, wherein the VH domain of the second antibody heavy chain forms an antigen binding domain with the VL domain of the second antibody light chain, wherein the first antibody heavy chain comprises F126C, C220V, and T366W substitutions, wherein the first antibody light chain comprises S121C and C214V substitutions, and wherein the second antibody heavy chain comprises T366S, L368A, Y407V, H435R, and Y436F substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains further comprise L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains comprise human IgG1 Fc domains. In some embodiments (*e.g.*, wherein the second antigen binding domain binds to CD20), the antibody comprises three polypeptide chains: a first polypeptide chain comprising the sequence

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31), a second polypeptide chain comprising the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVS KLTVDKSRWQQGNVFSCSVMHEALHNRFTQKSLSLSPG (SEQ ID NO:32), and a third polypeptide chain comprising the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:33). In some embodiments, at least one or two of the heavy chains of the antibody is non-fucosylated. In some embodiments, the antibody may be produced in a cell line having an alpha1,6-fucosyltransferase (Fut8) or alpha-1,3-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltranferase (MGAT1) knockout. In some embodiments, the antibody may be produced in a cell line overexpressing β1,4-N-acetylglucosaminyltransferase III (GnT-III). In further embodiments, the cell line additionally overexpresses Golgi μ-mannosidase II (ManII). In some embodiments, the antibody may be produced in a cell line treated with an inhibitor of mannosidase I, *e.g.*, kifunensine. In some embodiments, the individual is a human.

[0017] In some embodiments, provided herein is a kit or article of manufacture comprising the antibody, multispecific binding molecule, or composition of any one of the above embodiments and instructions for using the antibody, multispecific binding molecule, or composition according to the method of any one of the above embodiments.

[0018] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present disclosure. These and other aspects of the present disclosure will become apparent to one of skill in the art. These and other embodiments of the present disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIGs. 1A-1C show the binding analysis of the anti-human Dectin-1 antibody (clone 2M24) in human and monkey monocytes derived from peripheral blood mononuclear cells (PBMC) by flow cytometry. Single, live and CD14+ cells were gated to identify monocytes. The cells were incubated with 2M24 anti-Dectin-1 primary antibody or a mIgG1 isotype control antibody, followed by incubation with a fluorescent anti-mouse secondary antibody. The primary antibodies were used in a serial dose titration. **FIG. 1A** shows the binding analysis for anti-human Dectin-1 clone 2M24 in human monocytes. **FIG. 1B** shows the binding analysis for anti-human Dectin-1 clone 2M24 antibody in cynomolgus monocytes. **FIG. 1C** depicts a comparison of binding to human monocytes, HEK cells overexpressing human Dectin-1 and cynomolgus monocytes between the 2M24 clone and other Dectin-1 antibodies identified from the ATX-Gx Alloy transgenic mice immunization as well as commercial anti-Dectin-1 antibodies. Anti-human Dectin-1 clone 2M24 antibody demonstrated high affinity to both human and cynomolgus monkey Dectin-1 expressed in monocytes, and exhibited superior affinity as compared to other anti-Dectin-1 antibodies, including commercial antibodies.

[0020] FIGs. 2A-2B show the phagocytosis of pHrodo-labeled polystyrene anti-mouse Fc IgG beads conjugated with anti-Dectin-1 antibody 2M24 or isotype control antibody by HEK-Blue hDectin-1a cells and human monocytes. Polystyrene anti-mouse Fc IgG beads (~ 3.4 μm) were labeled with a pH-sensitive fluorescent dye (pHrodo Red) and conjugated with Dectin-1 antibody 2M24 or isotype control. The beads were then incubated with cultured HEK-Blue hDectin-1a cells or human monocytes at a ratio of 1:2 (cells: beads). HEK-Blue hDectin-1a cells were labeled with the cell-permeant dye Calcein AM. The phagocytosis of the beads was monitored by IncuCyte live cell imaging. Phagocytosis was quantified using the IncuCyte analysis software and expressed as overlap of red object count (pHrodo) to calcein-positive cells. **FIG. 2A** shows the phagocytosis of beads over 2.5 hours in HEK-Blue hDectin-1a cells (top) and representative images of pHrodo positive cells at 2.5 hours of phagocytosis (bottom). **FIG. 2B** shows the phagocytosis of beads over 4 hours in human monocytes (top), as well as representative images of pHrodo positive cells at 2.5 hours of phagocytosis (bottom). In the representative images, engulfed beads fluoresce brightly in phagosomes.

[0021] FIGs. 3A-3B show the binding of the fully human 2M24 anti-Dectin-1 antibody (hIgG4) or isotype control antibody in HEK-Blue hDectin-1a cells and primary human monocytes. **FIG. 3A** shows the binding analysis of the fully human 2M24 anti-Dectin-1 antibody to HEK cells, while **FIG. 3B** shows the binding to primary human monocytes. The primary antibodies were used in a serial dose titration followed by a fluorescent secondary antibody against the primary

antibody. The fully human 2M24 anti-Dectin-1 hIgG4 antibody bound with high affinity to Dectin-1 expressing cells.

[0022] FIG. 4 shows the targeted phagocytosis of pHrodo-labeled polystyrene biotin beads conjugated with the fully human 2M24 anti-Dectin-1 antibody (hIgG4) or isotype control antibody by Dectin-1 expressing cells. Polystyrene biotin beads were labeled with pHrodo Red and conjugated via streptavidin to anti-Dectin-1 antibody 2M24 or an isotype control. The conjugated beads were mixed with cells at a ratio of 1:3, and phagocytosis of the beads was monitored by IncuCyte live cell imaging. The phagocytosis of phrodo-biotin beads conjugated to streptavidin 2M24 anti-Dectin-1 hIgG4 antibody is shown for HEK-Blue hDectin-1a cells (top left), human monocytes (top right) and human macrophages (bottom). The fully human 2M24 anti-Dectin-1 antibody (hIgG4) promoted phagocytosis in Dectin-1 expressing cells.

[0023] FIGs. 5A-5B show the results of a secreted alkaline phosphatase reporter assay of Dectin-1 in HEK-Blue hDectin-1a cells. **FIG. 5A** shows the results for a secreted alkaline phosphatase assay performed using immobilized fully human 2M24 anti-Dectin-1 antibody. The fully human 2M24 (hIgG4) anti-Dectin-1 antibody or an isotype control antibody were immobilized overnight in U-bottomed polypropylene microtiter plates at quantities ranging from 0.1 – 10 μg per well, followed by culture of HEK-Blue hDectin-1a cells for 22 hours and evaluation of alkaline phosphatase secretion at OD 630 nm in the supernatant. **FIG. 5B** shows the results for a secreted alkaline phosphatase assay performed using bead-conjugated fully human 2M24 anti-Dectin-1 antibody. Biotin beads of 3, 10 and 16.5 μm in size were conjugated to streptavidin 2M24 (hIgG4) anti-Dectin-1 antibody. Antibody-conjugated beads were mixed with HEK-Blue hDectin-1a cells for 22 hours, and the supernatant was evaluated for alkaline phosphatase secretion at OD 630 nm. Bars represent mean ± s.d.; n = 2 replicates. The 2M24 (hIgG4) anti-Dectin-1 antibody induced alkaline phosphatase secretion in HEK-Blue hDectin-1a cells both in an immobilized form and conjugated to beads.

[0024] FIGs. 6A-6B show the cytokine secretion by human primary macrophages stimulated with anti-Dectin-1 (15E2) antibody in solution. Primary human macrophages and primary monocytes were stimulated with 10 μg/ml of the 15E2 anti-Dectin-1antibody or isotype antibody in solution for 24 hours, and secretion of TNFa and IL6 was assessed by ELISA analysis of the supernatant. Zymosan was used as positive controls for cytokine secretion. Bars represent mean ± s.d.; n = 2 replicates **FIG. 6A** shows the results for primary human monocytes stimulated with soluble 15E2 anti-Dectin-1antibody, while **FIG. 6B** shows the results for stimulated primary human macrophages. Soluble 15E2 anti-Dectin-1 antibody did not induce cytokine secretion in primary human monocytes and macrophages.

[0025] **FIGs. 7A-7B** show the cytokine secretion by human primary monocytes and PBMCs stimulated with immobilized 2M24 or 15E2 anti-Dectin-1 antibody. The anti-Dectin-1 antibodies or isotype control antibodies were immobilized overnight in U-bottomed polypropylene microtiter plates at 10 μg per well, followed by culture of human monocytes or human PBMCs for 24 hours. The secretion of TNFa, IL6 and IFNg was evaluated by ELISA analysis of the supernatant. **FIG. 7A** shows the cytokine secretion by human monocytes following stimulation with immobilized anti-Dectin-1 antibodies, while **FIG. 7B** shows the cytokine secretion by cultured human PBMCs after stimulation. Bars represent mean ± s.d.; n = 2 replicates. The 2M24 anti-Dectin-1 antibody induced cytokine secretion in both primary human monocytes and PBMCs and exhibited superior immune stimulation to the 15E2 Dectin-1 agonistic antibody

[0026] **FIG. 8** shows the results of a competition assay performed using the 12M4 anti-Dectin-1 antibody clone and natural ligands for Dectin-1. HEK-Blue hDectin-1a cells were incubated in a 1/3 serial dose titration of 2M24 (hIgG4) anti-Dectin-1 antibody or the 15E2, 259931, GE2 anti-Dectin-1 commercial antibodies starting at 300 nM and in the presence of 8 ug/ml of biotin-laminarin for 30 minutes on ice. Binding of laminarin to Dectin-1 was assessed by flow cytometry using Streptavidin-Alexa fluor 647. The 2M24 (hIgG4) anti-Dectin-1 antibody did not compete with natural ligand for binding to Dectin-1.

[0027] **FIG. 9** depicts a summary of the functional characterization of the 2M24 and 15E2 anti-Dectin-1 antibodies.

[0028] **FIGs. 10A-10B** show a schematic illustration of bispecific antibody generation by click chemistry. **FIG. 10A** depicts the differential labeling of antibodies with MTA or FOL reagents **FIG. 10B** depicts the covalent crosslinking of antibodies via specific MTA-FOL interactions.

[0029] **FIG. 11A** illustrates the potential modes of activity deployed by anti-Dectin-1 agonistic bispecific antibodies to eliminate target cancer cells. These include immune stimulation, phagocytosis, neo-antigen presentation and activation of T and B lymphocytes of the adaptive immune system.

[0030] **FIG. 11B** shows a list of potential targets for cancer cell depletion.

[0031] **FIGs. 12A-12B** show the characterization of click chemistry-conjugated bispecifics comprising anti-Dectin-1 (clone 2M24) and anti-hCD70 arms. **FIG. 12A** shows an SDS-PAGE analysis of covalently conjugated antibody pairs (2M24/anti-hCD20, 2M24/anti-hCD70, and isotype controls) under non-reducing and reducing conditions. **FIG. 12B** shows a flow cytometry-based characterization of bispecific (2M24/anti-hCD70 or isotype control) binding to Dectin-1-expressing HEK293 cells (top left) and two renal carcinoma cell lines – A498 (top right) and 786-0 (bottom left). **FIG. 12B** also depicts the EC50 concentration (nM) based on a

non-linear regression fitting (bottom right). Anti-Dectin-1/anti-hCD70 bispecific binds Dectin-1- or CD70-expressing cells with an affinity of 1.8 nM or 12.34 nM, respectively.

[0032] FIG. 13 shows coupling of Dectin-1-expressing HEK293 cell line and A498 renal carcinoma cell line induced by 2M24/anti-hCD70 bispecific. Shown are a flow cytometry analysis of co-cultures of HEK293 cells (labeled with calcein green) and A498 cells (labeled with calcein red) in the presence of 2M24/anti-hCD70 bispecific or isotype control (left). Coupling of HEK293 and A498 cells is indicated by a double-positive signal (green+ red+, square box). Also shown is coupling efficiency, which is quantified as the percentage of total target cells (A498) that forms doublets with HEK293 cells (right). Bars represent mean ± s.d.; n = 3 replicates. The 2M24/anti-hCD70 bispecific antibody induced coupling of Dectin-1-expressing HEK293 cell line and A498 renal carcinoma cell line

[0033] FIGs. 14A-14B shows the coupling of Dectin-1-expressing cells and B cells induced by anti-Dectin-1/anti-hCD20 bispecific antibody. **FIG. 14A** shows the coupling of Dectin-1-expressing HEK293 cells and B cells induced by anti-Dectin-1/anti-hCD20 bispecific antibody. Shown are a flow cytometry analysis of co-cultures of HEK293 cells (labeled with calcein green) and Raji cells (labeled with calcein red) in the presence of 2M24/anti-hCD70 bispecific or isotype control (left). Coupling of HEK293 and Raji cells is indicated by a double-positive signal (green+ red+; square box). Also shown is the coupling efficiency, which is quantified as the percentage of total target cells (Raji) that forms doublets with HEK293 cells (right). Bars represent mean ± s.d.; n = 2 replicates. **FIG. 14B** shows the results of similar experiments performed to assess the coupling of human M0 macrophages and Raji cells induced by anti-Dectin-1/anti-hCD20 bispecific. Bars represent mean ± s.d.; n = 2 replicates. The 2M24/anti-hCD20 bispecific induced coupling of Dectin-1-expressing cells and CDC20-positive B cells (Raji cells).

[0034] FIG. 15 shows the results of a secreted alkaline phosphatase reporter assay by Dectin-1 in HEK-Blue hDectin-1a cells using an anti-Dectin-1/anti-CD20 bispecific in the presence of Raji cells. A 2M24 (hIgG4)/a-CD20 bispecific antibody was incubated with Raji cells, after which it was washed twice to remove unbound bispecific antibody. The Raji cells were then mixed with HEK-Blue hDectin-1a cells at a ratio of 200.000 Raji cells to 100.000 HEK cells for 22 hours. Secreted alkaline phosphatase was evaluated at OD 630 nm in the supernatant. Bars represent mean ± s.d.; n = 2 replicates. Raji cells coated with an anti-Dectin-1/anti CD20 bispecific induced alkaline phosphatase secretion in HEK-Blue hDectin-1a cells.

[0035] FIG. 16 shows the induction of Raji cell phagocytosis by Dectin-1-expressing HEK 293 cells by anti-Dectin-1/anti-hCD20 bispecific antibodies. Representative Incucyte images

illustrating phagocytosis of Raji cells by HEK cells (arrowhead) at 16h versus 0h are shown (left). Co-localization is indicated by yellow fluorescence. Reduction in calcein red signal of Raji cells at 16h indicates phagocytosis-mediated cell death. Quantification of overlap or co-localization of HEK (calcein green) and Raji (calcein red) in different treatment groups are shown (right). Pre-incubation of HEK cells with ADCP inhibitor Latrunculin A blocks phagocytosis mediated by 15E2/anti-hCD20 bispecific antibody. (n = 2 replicates).

[0036] FIG. 17 shows coupling of Dectin-1- and HER2-expressing cells induced by anti-Dectin-1/anti-hHER2 bispecific antibodies. Shown are a flow cytometry analysis of co-cultures of Dectin-1-expressing HEK 293 cells (labeled with calcein green) and HER2-expressing SKBR3 cells (labeled with pHrodo red) in the presence of 15E2/anti-hHER2 bispecific or isotype control (left). Coupling of HEK 293 and SKBR3 cells is indicated by a double-positive signal (green+ red+; square box). Also shown is the coupling efficiency, which is quantified as the percentage of total target cells (SKBR3) that forms doublets with the Dectin-1 expressing cells (right). Bars represent mean ± s.d.; n = 2 replicates. Anti-Dectin-1/anti-hHER2 bispecific induces coupling of Dectin-1- and HER2-positive cancer cells.

[0037] FIG. 18 shows coupling of Dectin-1-expressing HEK293 cells and CD94-expressing BaF3 cells induced by anti-Dectin-1/anti-hCD94 bispecific induces. Shown are a flow cytometry analysis of co-cultures of HEK293 cells (labeled with calcein green) and BaF3 cells (labeled with pHrodo red) in the presence of 2M24/anti-hCD94 bispecific or isotype control (left). Coupling of HEK293 and BaF3 cells is indicated by a double-positive signal (green+ red+; square box). Also shown is the coupling efficiency, which is quantified as the percentage of total target cells (BaF3) that forms doublets with HEK293 cells (right). Bars represent mean ± s.d.; n = 2 replicates. Anti-Dectin-1/anti-hCD94 bispecific induced coupling of Dectin-1- and CD94-expressing cells.

[0038] FIGs. 19A-19B show a schematic illustration of Fab 2M24-mSA or full length 2M24-mSA bound to a biotinylated target antibody. **FIG. 19A** shows chimeric fusions of monomeric Streptavidin (mSA) and Fab 2M24 or full length 2M24. mSA is genetically fused to either Fab 2M24 or full length 2M24. **FIG. 19B** shows the coupling of Fab 2M24-mSA or 2M24-mSA to biotinylated target antibodies. The chimeric fusions are incubated with biotinylated target antibodies to generate a bispecific comprising a Dectin-1-binding arm and a second arm binding a target receptor or protein of interest.

[0039] FIGS. 20A-20C show the biochemical and functional characterization of Fab 2M24-mSA fusion protein. **FIG. 20A** shows an HPLC characterization of recombinant Fab 2M24-mSA. **FIG. 20B** shows an SDS-PAGE analysis of purified Fab 2M24-mSA under reducing conditions. **FIG. 20C** shows a flow cytometry characterization of Fab 2M24-mSA binding to

HEK 293 cells stably overexpressing human Dectin-1 (EC_{50} = 1.45 nM). Fab 2M24 fusion to monomeric streptavidin binds to Dectin-1-expressing cells with an affinity of 1.45 nM.

[0040] FIGs. 21A-21B shows the phagocytosis of pHrodo-labeled polystyrene biotin beads conjugated with a Fab-2M24 anti-Dectin-1 antibody tagged with monomeric streptavidin (Fab-2M24-mSA). **FIG. 21A** shows duplet formation of HEK-Blue hDectin-1a cells with Fab-2M24-mSA conjugated to biotin beads and phagocytosis of the beads, assessed by flow cytometry. **FIG. 21B** shows the phagocytosis of phrodo biotin beads (~ 3 μm) conjugated to Fab-2M24-mSA assessed by IncuCyte live imaging (top), as well as representative images of pHrodo positive cells at 3 hours of phagocytosis (engulfed beads fluoresce brightly red in phagosomes) vs. no bead controls (bottom). Fab 2M24-mSA fusion induced binding and phagocytosis of beads by Dectin-1-expressing HEK 293 cells.

[0041] FIGS. 22A-22D show bispecific complexes comprising Fab 2M24-mSA and target biotinylated antibodies. Depicted are the HPLC analyses of Fab 2M24-mSA in complex with biotinylated anti-hCD20 (**FIG. 22A**), biotinylated anti-hCD19 (**FIG. 22B**), biotinylated anti-hCD70 (**FIG. 22C**), or biotinylated anti-Amyloid β 1-42 (**FIG. 22D**). Each panel contains superposition of A280 traces including Fab 2M24-mSA alone, target biotinylated antibody alone, and Fab 2M24-mSA in complex with biotinylated target antibody.

[0042] FIG. 23 shows coupling of Dectin-1-expressing HEK293 cells and CD20-expressing Raji cells induced by Fab 2M24-mSA/biotin anti-hCD20 bispecific antibodies. Shown are the flow cytometry analysis of co-cultures of HEK293 (labeled with calcein green) and Raji (labeled with calcein red) in the presence of Fab 2M24-mSA/biotin anti-hCD20 bispecific or isotype bispecific control (left). Co-cultures were incubated at 4 °C or 37 °C. Coupling of HEK293 and Raji cells is indicated by a double-positive signal (green+ red+; dotted-square). Also shown is the coupling efficiency, which is quantified as the percentage of total target cell (Raji) that forms doublets (right). Bars represent mean ± s.d.; n = 4 replicates. Fab 2M24-mSA/biotin anti-hCD20 bispecific induced coupling of Dectin-1-expressing HEK293 cells and Raji cells.

[0043] FIG. 24 is a schematic of targeted phagocytosis of amyloid deposits in amyloidosis using Dectin-1 agonistic bispecific antibodies.

[0044] FIGs. 25A-25B show strategies for targeted depletion of mast cells using Dectin-1 agonistic bispecific antibodies. **FIG. 25A** is a schematic of depletion of mast cells by Dectin-1 agonistic bispecific antibodies. **FIG. 25B** shows a list of potential targets for mast cell depletion.

[0045] FIG. 26 shows the phagocytosis of large (~ 16.2 μm) phrodo-labelled beads by human dendritic cells. **FIG. 26** shows the quantification of phagocytosis of beads over 12 hours (left), and representative images of pHrodo positive cells at 3 hours of phagocytosis (engulfed beads

fluoresce brightly red in phagosomes; right). Dectin-1 antibody promoted the directed phagocytosis of beads in cultured monocyte-derived dendritic cells.

[0046] **FIG. 27** is a schematic of targeted depletion of microbes by Dectin-1 agonistic bispecific antibodies. Bispecific antibodies with a Dectin-1-binding arm and a microbial agent-binding arm are generated to target bacteria, viruses or fungi (top). The Dectin-1 bispecific antibodies deploy Dectin-1-expressing phagocytes to eliminate bacterial, viral or fungal pathogens (bottom).

[0047] **FIGs. 28A-28B** show binding of bispecific antibodies comprised of Dectin-1 antibody (15E2 clone) conjugated to anti-H3N2 Hemagglutinin antibody (12CA5 clone) to the H3N2 flu virus and to Dectin-1-expressing cells. **FIG. 28A** shows the binding analysis of an anti-Dectin-1/anti-Hemagglutinin bispecific antibody to the H3N2 flu virus as assessed by ELISA. 96 well microtiter plates were coated with the H3N2 flu viral particles followed by incubation of single antibodies, bispecific antibodies and isotype controls. After extensive washing, the primary antibodies were detected with a secondary anti-mouse FcgR HRP antibody. **FIG. 28B** shows the binding analysis of an anti-Dectin-1/anti-Hemagglutinin bispecific antibody to HEK cells expressing Dectin-1 by flow cytometry. HEK cells were incubated with the primary antibodies followed by detection with a secondary fluorescent antibody against the anti-Dectin-1 antibody (anti-mIgG2a APC) or the Hemagglutinin antibody (anti-mIgG2b PB). The anti-Dectin-1/anti-Hemagglutinin bispecific antibody bound efficiently to both the H3N2 flu virus and to HEK cells expressing Dectin-1.

[0048] **FIGs. 29A-29B** show schematic diagrams using anti-Dectin-1 antibodies to deliver antigens for vaccine development, using anti-Dectin-1 antibodies fused to target antigens for delivery to APCs (**FIG. 29A**), or anti-Dectin-1 bispecific antibodies for targeted delivery of disease-causing agents (*e.g.*, cells, microbes, proteins, etc.) to APCs **(FIG. 29B).**

[0049] **FIG. 30** shows the phagocytosis of pHrodo-labeled polystyrene anti-mouse Fc IgG beads (~ 3.4 μm) conjugated with Dectin-1antibody (15E2) or isotype control antibody by human dendritic cells. Polystyrene anti-mouse Fc IgG beads were labeled with a pH-sensitive fluorescent dye (pHrodo Red) and conjugated with a Dectin-1 antibody or isotype control. The beads were then incubated with cultured monocyte-derived dendritic cells at a ratio of 1:3 (cells: beads). Bead phagocytosis was monitored by IncuCyte live cell imaging. Phagocytosis was quantified using the IncuCyte analysis software and expressed as total integrated intensity (total sum fluorescent intensity) of red objects (pHrodo) in the image. **FIG. 30** shows the quantification of phagocytosis of beads over 9 hours (top) and representative images of pHrodo positive cells at 3 hours of phagocytosis (engulfed beads fluoresce brightly red in phagosomes; bottom).

[0050] **FIGs. 31A-31C** show the phagocytosis of SARS-CoV-2 Spike protein-coated beads by Dectin-1-expressing HEK 293 cells. **FIG. 31**A is a schematic illustration of the experiment. Beads coated with the Spike protein from SARS-CoV-2 are coupled to Dectin-1-expressing HEK 293 cells by an anti-Dectin-1 bispecific antibody comprising a Dectin-1 protein binding arm and a Spike protein binding arm. **FIG. 31B** shows a flow cytometry characterization of effector (HEK 293 cells) and target (Spike-coated beads) engagement by the bispecific and isotype controls (panel A), as well as a quantification of coupling efficiency based on doublet population (panel B). **FIG. 31C** shows the phagocytosis of SARS-CoV-2 Spike protein-coated beads by HEK 293 cells in a co-culture experiment. Phagocytosis of pHrodo-labeled beads was monitored by the change in pHrodo fluorescence as a result of acidic pH in phagosomes. **FIG. 31C** shows quantification of phagocytosis (left), which was quantified by the Incucyte analysis software and expressed as overlap of red object count (pHrodo) to calcein-positive cells, as well as representative images of pHrodo-positive cells at 2 hours of phagocytosis (engulfed beads fluoresce brightly red in phagosomes; right).

[0051] **FIGS. 32A & 32B** show a bispecific antibody design for human bispecific antibodies (*e.g.*, human IgG1 bispecific antibodies) targeting Dectin-1 and a disease target or antigen. **FIG. 32A** provides a diagram of the design. One arm (2M24A.X) with VH domain A and VL domain B targets human Dectin-1, while the other arm (2M24B.X) with VH domain C and VL domain D targets a disease target or antigen. **FIG. 32B** provides a diagram of an exemplary mechanism of action for an anti-Dectin-1 bispecific antibody with an active Fc domain, which targets hDectin-1 (via the first arm) on myeloid cells, an antigen on a target cell/disease-causing agent (via the second arm), and Fc receptors on myeloid and NK cells, eliciting robust immune stimulation and phagocytosis.

[0052] **FIGS. 33A & 33B** show that a bispecific antibody with one arm targeting hDectin-1 and the other arm targeting hCD20 (using the variable domains of rituximab) binds to cells expressing human Dectin-1 or human CD20. **FIG. 33A (top panel)** shows binding of the bispecific antibody targeting hDectin-1 and hCD20 (2M24/CD20), or a bispecific antibody targeting hDectin-1 and RSV (2M24/RSV), to HEK293 cells stably expressing human Dectin-1, as assessed by flow cytometry. **FIG. 33A (bottom panel)** shows binding of the bispecific antibody 2M24/RSV hIgG1-FITC conjugated and 2M24 bivalent hIgG1-FITC conjugated to PBMCs, as assessed by flow cytometry. **FIG. 33B** shows binding of rituximab (human IgG1), 2M24/CD20 with active human IgG1 Fc, 2M24/CD20 with inert human IgG1 Fc, 2M24/RSV with active human IgG1 Fc, or 2M24/RSV with inert human IgG1 Fc to CD20-expressing B cell lymphoma Raji cell line.

[0053] FIGS. 34A & 34B show that bispecific antibody targeting hDectin-1 and hCD20 (2M24/CD20) induces coupling of Dectin-1- and CD20-expressing cells. **FIG. 34A**: To assess coupling of Dectin-1-expressing HEK293 cells (effector) and CD20-expressing Raji cells (target), cells were differentially labeled with calcein green (effector) or calcein red (target) dyes. Labeled cells were co-cultured and treated with hIgG1 inert 2M24/CD20 or 2M24/RSV (control) bispecific antibody to induce effector: target coupling. Successful coupling of effector: target cells is indicated by the double-positive staining (Calcein green+, calcein red+, square box). **FIG. 34B**: Dose-titration of bispecifics in co-cultures of effector: target cells. Coupling efficiency is quantified as the percentage of total target cells that binds or couples to effector cells.

[0054] FIGS. 35A & 35B show that bispecific antibody targeting hDectin-1 and hCD20 (2M24/CD20) with an active hIgG1 Fc does not induce monocyte depletion by antibody dependent-cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP). PBMCs from two healthy donors – donor 76 (**FIG. 35A**) and donor 77 (**FIG. 35B**) were treated with increasing concentrations of 2M24/CD20 bispecific antibody (hIgG1 active or inert isotypes) and rituximab for 24 h, and subsequently analyzed by flow cytometry to quantify the levels of live, CD14+ monocytes remaining (as a % of isotype controls).

[0055] FIGS. 36A & 36B show that bispecific antibody targeting hDectin-1 and hCD20 (2M24/CD20) with an active hIgG1 Fc elicits superior B cell depletion compared to Rituximab. PBMCs from two healthy donors – donors 83 (**FIG. 36A**) and 84 (**FIG. 36B**) – were treated with increasing concentrations of the indicated antibodies for 24 h, and subsequently analyzed by flow cytometry to quantify the levels of remaining live, CD19+ B cells (reported as a % of B cells in isotype control-treated PBMCs).

[0056] FIGS. 37A & 37B show that Rituximab induces higher B cell shaving (CD19 downregulation) compared to 2M24/CD20 active IgG1 bispecific antibody. Expression of CD19+ on B cells from two healthy donors – donor 83 (**FIG. 37A**) and donor 84 (**FIG. 37B**) – was quantified by flow cytometry following a 24-hour incubation with increasing concentration of 2M24/CD20 hIgG1 (active isotype) bispecific antibody, Rituximab, or isotype controls. The mean fluorescent intensity (MFI) for CD19 staining using anti-CD19 (BV605 conjugated) was used to evaluate the effect of 2M24/CD20 bispecific and Rituximab on CD19 expression on B cells. EC50 values were calculated based on non-linear regression analysis.

[0057] FIG. 38 shows differential cytokine release induced by 2M24/CD20 active IgG1 bispecific antibody as compared to rituximab. ELISA-based (mesoscale discovery) quantification of cytokines was undertaken in supernatants isolated from healthy donor PBMCs treated with 2M24/CD20 active hIgG1 bispecific, Rituximab, or isotype controls. PBMCs were

stimulated with antibodies overnight, and supernatants were subsequently analyzed by MSD. Cytokines tested were IFNγ, IL-12p70, IL-6, TNFα, IL-1β, IL-4, IL-13, IL-10, and IL-8. Each plot shows cytokine secretion (in pg/mL) as a function of antibody used for treatment (from left to right: 2M24/CD20 hIgG1 bispecific, 2M24/RSV hIgG1 bispecific, rituximab hIgG1, and isotype control hIgG1).

[0058] FIGS. 39A & 39B show that 2M24/CD20 hIgG1 (active isotype) bispecific antibody induces superior B-cell depletion and lower CD19 shaving compared to Rituximab in co-cultures of human macrophages and GFP-expressing Raji B cells. **FIG. 39A**: Flow cytometry analysis of co-cultures of human macrophages and Raji-GFP cells (3:1 ratio) in the presence of 2M24/CD20 hIgG1 (active isotype) bispecific, 2M24/RSV control, fucosylated Rituximab or isotype hIgG1 control. Co-cultures were incubated at 37ºC for 24 hours and then stained with a PE a-CD206 Ab to label macrophages and a BV-605 a-CD19 antibody to label Raji cells. The number of the remaining live/Raji-GFP+ cells was assessed in the end of the experiment. The primary antibodies were used in a serial dose titration. **FIG. 39B**: Assessment of CD19 on Raji-GFP cells after 24 hours. B-cell receptor shaving is shown as the reduction in the CD19 MFI in the presence of a-Dectin-1/a-hCD20 bispecific or Rituximab.

[0059] FIGS. 40A-40C show that 2M24/CD20 active IgG1 bispecific antibody induces superior tissue B cell depletion as compared to Rituximab in single cell suspension of kidney cancer biopsies. Single cell suspensions from two Kidney cancer tissue biopsies were analyzed by flow cytometry in the presence of 2M24/CD20 hIgG1 (active or inert) bispecific antibody, 2M24/RSV hIgG1 controls, fucosylated Rituximab, and respective isotype controls. Kidney cancer tissue biopsies were dissociated to single cell suspensions and treated with primary antibodies (2 μg/ml) for 24 hours at 37ºC. Immune cell populations were analyzed by flow cytometry. Cells were initially gated for live cells, further separated into CD45+ cells (immune cells) and CD45- cells (non-immune cells), and then CD19+ (B cells) and CD3+ (T Cells) cells were identified within the CD45+ population (**FIGS. 40A & 40B**). The number of the remaining B cells was assessed by an anti-CD19 antibody and expressed as percentage of the CD45+ immune cell population (**FIG. 40C**).

[0060] FIGS. 41A-41C show that Anti-Dectin 1 antibody (clone 2M24) induces Dectin 1-clustering and TNFα secretion from human macrophages. Cytokine secretion by cultured macrophages and single cell suspension of kidney cancer biopsies stimulated with immobilized anti-Dectin-1 antibody (clone 2M24) or 2M24/CD20 bispecific antibody was tested. The anti-Dectin-1 antibody (clone 2M24), isotype control or the 2M24/CD20 bispecific antibody were immobilized overnight in U-bottomed polypropylene microtiter plates at 10 ug per well, followed

by culture of human monocyte-derived macrophages (**FIGS. 41A & 41B**) or single cell suspension from kidney cancer biopsy (**FIG. 41C**). The cells were cultured for 24 hours and evaluation of TNFα secretion in the supernatant was assessed by ELISA. As a positive control, cells were stimulated with zymosan.

[0061] FIG. 42 shows that immobilized anti-Dectin 1 antibody (clone 2M24) promotes immune stimulation in single cell suspension of kidney cancer biopsies. Single-cell suspensions from kidney cancer biopsies were treated with immobilized anti-Dectin-1 antibody (clone 2M24) or isotype control hIgG4 antibody for 24 h. Supernatants were analyzed by ELISA for the release of various cytokines, including IFNγ, IL-6, TNFα, IL-23, IL-12p70, IL-10, and IL-13. Each plot shows amount of cytokine (pg/mL) as a function of antibody treatment. Shown are results from treatment with anti-Dectin-1 antibody (clone 2M24) or isotype control hIgG4 antibody using kidney cancer donor 3 (left) or donor 4 (right).

[0062] FIG. 43 shows the effect of 2M24/CD20 bispecific antibody on CD16 expression in human NK cells, as compared to rituximab or isotype control (RSV). Results indicate that CD16 antigen levels on NK cells are better maintained in PBMCs treated with the 2M24/CD20 bispecific compared to rituximab.

[0063] FIG. 44 shows the effect of 2M24/CD20 bispecific antibody on CD19 expression in human B cells, as compared to rituximab or isotype control (2M24/RSV bispecific). Results indicate that CD19 antigen levels are better maintained on B cells treated with the 2M24/CD20 bispecific compared to rituximab.

[0064] FIG. 45 shows depletion of human B cells by 2M24/CD20 bispecific antibody derived from rituximab or 2M24/CD20 bispecific antibody derived from obinutuzumab. Results indicate that the 2M24/CD20 bispecific derived from the rituximab arm is better at depleting B cells compared to the bispecific derived from obinutuzumab.

[0065] FIG. 46 shows the design of an exploratory study on safety and efficacy of 2M24/CD20 bispecific antibody in non-human primates.

[0066] FIGS. 47 & 48 show depletion of circulating B cells in cynomolgus monkeys by 2M24/CD20 hIgG1 bispecific antibody generated in cells treated with kifunensine (KIF). **FIG. 47**: B cell depletion in monkeys treated with 5mg/kg 2M24/CD20 hIgG1 KIF (upper) or 2M24/CD20 hIgG1 inert (lower). **FIG. 48**: B cell depletion in monkeys treated with 5mg/kg rituximab hIgG1 KIF.

[0067] FIGS. 49A & 49B show depletion of tissue-resident B cells in cynomolgus monkeys by 2M24/CD20 hIgG1 bispecific antibody generated in cells treated with kifunensine (KIF). **FIG. 49A**: B cell depletion in bone marrow of monkeys treated with 5mg/kg 2M24/CD20 hIgG1 KIF

or rituximab hIgG1 KIF. **FIG. 49B**: B cell depletion in lymph nodes of monkeys treated with 5mg/kg 2M24/CD20 hIgG1 KIF or rituximab hIgG1 KIF.

[0068] **FIG. 50** shows depletion of B cells from cynomolgus monkey PBMCs *ex vivo*.

[0069] **FIG. 51** shows the format of a bispecific molecule that uses knobs-into-holes technology to pair an anti-CD20 conventional half-antibody with an anti-Dectin-1 single chain variable fragment (scFv) Fc fusion arm (2M24 scFv/CD20). H: 2M24 VH domain; L: 2M24 VL domain.

[0070] **FIGS. 52A-52C** show purification and functional characterization of the 2M24/CD20 bispecific antibody. **FIG. 52A** shows purification of the molecule by size exclusion chromatography (SEC). **FIG. 52B** shows that purified bispecific antibody promoted targeted immune stimulation, as assessed in an NFκB reporter assay. **FIG. 52C** shows human B cell depletion by the 2M24 scFv/CD20 bispecific antibody.

[0071] **FIGS. 53A-53C** show development and characterization of an anti-Dectin-1 (2M24)/anti-Trop-2 bispecific antibody. **FIG. 53A** shows the purification of 2M24/Trop-2 bispecific antibody by SEC (left). Purified antibody was analyzed by SDS-PAGE under non-reducing (NR) or reducing (R) conditions (right). **FIGS. 53B & 53C** show high affinity binding of the molecule to Dectin-1-expressing HEK cells (**FIG. 53B**) and moderate affinity binding to the Trop-2 expressing A431 cancer cell line (**FIG. 53C**).

[0072] **FIG. 54** shows Trop-2 expression levels on cancer cells.

[0073] **FIGS. 55A-55D** show binding of 2M24/Trop-2 bispecific antibody to Trop-2-expressing cell lines HeLa (**FIG. 55A**), BxPC-3 (**FIG. 55B**), SiHa (**FIG. 55C**), and Capan-2 (**FIG. 55D**). Binding EC50, as determined using four-parameter logistic (4PL) non-linear regression, is shown for each cell line.

[0074] **FIGS. 56A & 56B** show depletion of Trop-2-expressing cell lines (SKBR3 cells in **FIG. 56A**; A431 cells in **FIG. 56B**) using 2M24/Trop-2 bispecific antibody.

[0075] **FIGS. 57A & 57B** show Trop-2 and Dectin-1 expression in a lung cancer biopsy.

[0076] **FIG. 58** shows depletion of Trop-2-positive cancer cells in a lung cancer biopsy.

[0077] **FIG. 59A** shows activity of 2M24/Trop-2 bispecific antibody in an NFκB reporter assay.

[0078] **FIGS. 59B-59E** show that 2M24/Trop-2 bispecific antibody promotes antigen presentation and T cell activation. **FIG. 59B** provides a schematic representation of the assay set up. In **FIG. 59C**, macrophages and SKBR3 breast cancer cells were co-incubated in the presence of 2M24/Trop-2 hIgG1 or control 2M24/RSV hIgG1 bispecific antibody. Phagocytosis or depletion of SKBR3 cells was assessed by flow cytometry by staining for EPCAM expression on SKBR3 cells. Data are reported as relative to the control bispecific 2M24/RSV. In **FIG. 59D**, IFN gamma levels in the supernatants were quantified using the BD OptiEIA Kit. In **FIG. 59E**,

expression of CD69, an early activation marker, on T cells was assessed by flow cytometry. Data are reported as relative to total CD3+ T cells.

[0079] FIGS. 60A & 60B show design and production of a 2M24/Nectin-4 bispecific antibody. **FIG. 60A** shows a diagram of the bispecific molecule. **FIG. 60B** shows purification of the bispecific antibody using Protein A chromatography.

[0080] FIGS. 61A & 61B show Nectin-4 expression on cancer cell lines (**FIG. 61A**) and cancer cells from primary tumor biopsies (**FIG. 61B**).

[0081] FIG. 62 shows binding of 2M24/Nectin-4 bispecific antibody to Dectin-1-expressing HEK cells (upper) or Nectin-4-expressing A431 cells (lower).

[0082] FIG. 63 shows stimulation of Dectin-1 in the NFκB reporter assay by 2M24/Nectin-4 bispecific antibody. Upper panel shows a diagram of the assay. Lower panel shows the results, as quantified based on SEAP levels in media.

[0083] FIGS. 64A & 64B show depletion of Nectin-4-expressing cancer cells by the 2M24/Nectin-4 bispecific antibody. **FIG. 64A** shows detection of phagocytosis/depletion by flow cytometry. **FIG. 64B** shows depletion relative to RSV control.

[0084] FIGS. 65A-65C show that 2M24/11-1F4 bispecific antibody binds to light chain amyloids. **FIG. 65A** shows purification of parental anti-amyloid antibody 11-1F4 (upper) and 2M24/11-1F4 bispecific antibody (lower) by SEC. **FIGS. 65B & 65C** show binding of 11-1F4 parental antibody (**FIG. 65B**) or 2M24/11-1F4 bispecific antibody (**FIG. 65C**) to recombinant light chain amyloids from different patients (AL30, AL47, AL48, and AL55) by Octet.

[0085] FIG. 66 shows phagocytosis of light chain amyloid fibrils by monocytes.

DETAILED DESCRIPTION

[0086] Several aspects are described below with reference to example applications for illustration. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the features described herein. One having ordinary skill in the relevant art, however, will readily recognize that the features described herein can be practiced without one or more of the specific details or with other methods. The features described herein are not limited by the illustrated ordering of acts or events, as some acts can occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated acts or events are required to implement a methodology in accordance with the features described herein.

[0087] As used herein, the singular forms “a”, “an”, and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms “including”, “includes”, “having”, “has”, “with”, or variants thereof are used in either the

detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term "comprising". The term "comprising" as used herein is synonymous with "including" or "containing", and is inclusive or open-ended.

[0088] Any reference to "or" herein is intended to encompass "and/or" unless otherwise stated. As used herein, the term "about" with reference to a number refers to that number plus or minus 10% of that number. The term "about" with reference to a range refers to that range minus 10% of its lowest value and plus 10% of its greatest value.

I. Antibodies and Multispecific Binding Proteins

[0089] In certain aspects, the present disclosure provides antigen binding domains, antibodies, and antibody fragments that bind to human Dectin-1, as well as multispecific (*e.g.*, bispecific) binding molecules comprising the same.

[0090] In some embodiments, antibody and immunoglobulin are used interchangeably and herein are used in the broadest sense and encompass various antibody structures, including but not limited to monoclonal antibodies (e.g., full length or intact monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), antibody fragments and single domain antibody (as described in greater detail herein), so long as they exhibit the desired antigen binding activity.

[0091] In some embodiments, antibodies (immunoglobulins) refer to a protein having a structure substantially similar to a native antibody structure, or a protein having heavy and light chain variable regions having structures substantially similar to native heavy and light chain variable region structures. Native antibodies refer to naturally occurring immunoglobulin molecules with varying structures. For example, native immunoglobulins of the IgG class are heterotetrameric glycoproteins of about 150,000 daltons, composed of two light chains and two heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3), also called a heavy chain constant region. Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain, also called a light chain constant region. The subunit structures and three-dimensional configurations of the different classes of immunoglobulins are well known and described generally, for example, in Abbas et al., 2000, Cellular and Mol, and Kindt et al., Kuby Immunology, 6th ed., W.H. Freeman and Co., page 91 (2007). Antibodies (immunoglobulins) are assigned to different classes, depending on the amino acid sequences of the heavy chain constant

domains. There are five major classes of antibodies: α (IgA), δ (IgD), ϵ (IgE), γ (IgG), or μ (IgM), some of which may be further divided into subtypes, e.g., γ1 (IgG1), γ2 (IgG2), γ3 (IgG3), γ4 (IgG4), α1 (IgA1) and α2 (IgA2). The light chain of an immunoglobulin may be assigned to one of two types, called kappa (κ) and lambda (λ), based on the amino acid sequence of its constant domain. An immunoglobulin essentially consists of two Fab molecules and an Fc domain, linked via the immunoglobulin hinge region.

[0092] In some embodiments, an Fc, Fc region, or Fc domain refers to the C-terminal region of an antibody heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. An Fc can refer to the last two constant region immunoglobulin domains (e.g., CH2 and CH3) of IgA, IgD, and IgG, the last three constant region immunoglobulin domains of IgE and IgM, and optionally, all or a portion of the flexible hinge N-terminal to these domains. For IgA and IgM, Fc may include the J chain. An IgG Fc region comprises an IgG CH2 and an IgG CH3 domain and in some cases, inclusive of the hinge. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. Human IgG Fc domains are of particular use in the present disclosure, and can be the Fc domain from human IgG1, IgG2 or IgG4.

[0093] Multiple definitions for the CDR sequences of antibody variable domains are known in the art; *see, e.g.,* Kabat (*Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-3242, Bethesda MD (1991), vols. 1-3) and Chothia. Unless otherwise specified, CDR sequences are described herein according to the definition of IMGT. *See, e.g.,* www.imgt.org/IMGTScientificChart/Nomenclature/IMGT-FRCDRdefinition.html.

[0094] In some embodiments, an antigen binding domain, antibody, or antibody fragment that binds to human Dectin-1 comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, an antigen binding domain, antibody, or antibody fragment that binds to human Dectin-1 comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

[0095] As noted above, the Kabat definition for CDR sequences can also be used. In some embodiments, an antigen binding domain, antibody, or antibody fragment that binds to human Dectin-1 comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and wherein the VL domain comprises a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

[0096] In some embodiments, an antigen binding domain, antibody, or antibody fragment that binds to human Dectin-1 comprises a VH domain comprising a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or a VL domain comprising a sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, an antigen binding domain, antibody, or antibody fragment that binds to human Dectin-1 comprises a VH domain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or a VL domain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8). In some embodiments, an antigen binding domain, antibody, or antibody fragment that binds to

human Dectin-1 comprises a VH domain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and a VL domain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

[0097] In some embodiments, the antigen binding domain, antibody, or antibody fragment is humanized.

[0098] In some embodiments, the antibody that binds to human Dectin-1 comprises a heavy chain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:11) and/or a light chain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIERTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:12). In some embodiments, the antibody that binds to human Dectin-1 comprises a heavy chain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:11) and a light chain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS

RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIERTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:12).

[0099] In some embodiments, the antigen binding domain, antibody, or antibody fragment binds to human Dectin-1. In some embodiments, the antigen binding domain, antibody, or antibody fragment binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, or granulocyte. In some embodiments, the antigen binding domain, antibody, or antibody fragment binds to human Dectin-1 isoform A and/or human Dectin-1 isoform B. In some embodiments, human Dectin-1 isoform A comprises the amino acid sequence MEYHPDLENLDEDGYTQLHFDSQSNTRIAVVSEKGSCAASPPWRLIAVILGILCLVILVIA VVLGTMAIWRSNSGSNTLENGYFLSRNKENHSQPTQSSLEDSVTPTKAVKTTGVLSSPCP PNWIIYEKSCYLFSMSLNSWDGSKRQCWQLGSNLLKIDSSNELGFIVKQVSSQPDNSFWI GLSRPQTEVPWLWEDGSTFSSNLFQIRTTATQENPSPNCVWIHVSVIYDQLCSVPSYSICE KKFSM (SEQ ID NO:9). In some embodiments, human Dectin-1 isoform B comprises the amino acid sequence MEYHPDLENLDEDGYTQLHFDSQSNTRIAVVSEKGSCAASPPWRLIAVILGILCLVILVIA VVLGTMGVLSSPCPPNWIIYEKSCYLFSMSLNSWDGSKRQCWQLGSNLLKIDSSNELGFI VKQVSSQPDNSFWIGLSRPQTEVPWLWEDGSTFSSNLFQIRTTATQENPSPNCVWIHVSV IYDQLCSVPSYSICEKKFSM (SEQ ID NO:10). In some embodiments, the antigen binding domain, antibody, or antibody fragment binds to human Dectin-1 expressed on the surface of a cell with an EC50 of less than 5nM, less than 2nM, less than 1nM, or less than 0.5nM. In some embodiments, the antigen binding domain, antibody, or antibody fragment is capable of binding to human Dectin-1 and monkey Dectin-1, *e.g.*, cynomolgus Dectin-1.

[0100] In some embodiments, the antigen binding domain, antibody, or antibody fragment competes for binding to human Dectin-1 with a reference antibody that comprises a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the antigen binding domain, antibody, or antibody fragment competes for binding to human Dectin-1 with a reference antibody that comprises a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ

ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the antigen binding domain, antibody, or antibody fragment competes for binding to human Dectin-1 with a reference antibody that comprises a heavy chain variable (VH) domain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7) and a light chain variable (VL) domain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

[0101] In some embodiments, the antigen binding domain, antibody, or antibody fragment binds the same epitope of human Dectin-1 as a reference antibody that comprises a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the antigen binding domain, antibody, or antibody fragment binds the same epitope of human Dectin-1 as a reference antibody that comprises a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6). In some embodiments, the antigen binding domain, antibody, or antibody fragment binds the same epitope of human Dectin-1 as a reference antibody that comprises a heavy chain variable (VH) domain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7) and a light chain variable (VL) domain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

[0102] Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments, Fab'-SH, F(ab')2, diabodies, linear antibodies, single chain antibodies, nanobodies, scFv fragments, VH, and multispecific (*e.g.*, bispecific) antibodies/fragments formed from antibody fragments.

[0103] A "Fab" (fragment antigen binding) is a portion of an antibody that binds to antigens and includes the variable region and CH1 of the heavy chain linked to the light chain via an inter-chain disulfide bond.

[0104] In some embodiments, an antibody of the present disclosure comprises an Fc region. An antibody may be of any class or subclass, including IgG and subclasses thereof (IgG1, IgG2, IgG3, IgG4), IgM, IgE, IgA, and IgD. An immunoglobulin Fc region of the molecule that causes targeted phagocytosis may have important role in the process by engaging Fc receptors and inducing additional phagocytosis. In some embodiments, the molecule has a modified Fc region that has reduced ADCC activity as compared to a wild type human IgG1 (*e.g.*, comprising one or more mutations reducing effector function as described herein).

[0105] In some embodiments, an antibody of the present disclosure comprises an Fc region wherein a carbohydrate structure attached to the Fc region has reduced fucose or lacks fucose, *e.g.*, at least one or two of the heavy chains of the antibody is non-fucosylated. In some embodiments, provided herein is a composition comprising an antibody of the present disclosure that comprises an Fc region wherein a carbohydrate structure attached to the Fc region has reduced fucose or lacks fucose, *e.g.*, at least one or two of the heavy chains of the antibody is non-fucosylated. In some embodiments, less than 50% of the N-glycoside-linked carbohydrate chains in the composition contain a fucose residue. In some embodiments, substantially none of the N-glycoside-linked carbohydrate chains contain a fucose residue. In some embodiments, an antibody with reduced fucose or lacking fucose has improved ADCC function.

[0106] In other embodiments, an antibody of the present disclosure (*e.g.*, an IgG1 antibody) or composition comprising an antibody of the present disclosure (*e.g.*, an IgG1 antibody) comprises wild-type glycosylation of the Fc region. In some embodiments, provided herein are fucosylated antibodies of the present disclosure (*e.g.*, an IgG1 antibody) or compositions comprising a fucosylated antibody of the present disclosure (*e.g.*, an IgG1 antibody).

[0107] Fucosylation or fucosylated antibodies can refer to the presence of fucose residues within the oligosaccharides attached to the peptide backbone of an antibody. Specifically, a fucosylated antibody comprises α (1,6)-linked fucose at the innermost N-acetylglucosamine (GlcNAc) residue in one or both of the N-linked oligosaccharides attached to the antibody Fc region, e.g., at position Asn 297 of the human IgG1 Fc region (EU numbering of Fc region

residues). Asn297 may also be located about + 3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in immunoglobulins. Non-fucosylated or fucose-deficient antibodies have reduced fucose relative to the amount of fucose on the same antibody produced in a cell line. Antibody fucosylation can be measured, *e.g.*, in an N-glycosidase F treated antibody composition assessed by matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI TOF MS).

[0108] In some embodiments, the Fc region comprises one or more mutations that reduce or eliminate fucosylation, *e.g.*, a substitution at Asn 297 of the human IgG1 Fc region (EU numbering of Fc region residues). Optionally, the Fc region further comprises one or more amino acid substitutions therein which further improve ADCC, for example, substitutions at positions 298, 333, and/or 334 of the Fc region (Eu numbering of residues). Examples of publications related to "defucosylated" or "fucose-deficient" antibodies include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; Okazaki et al. J. Mol. Biol. 336:1239-1249 (2004); Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004).

[0109] In some embodiments, the afucosylated or non-fucosylated antibody is produced in a cell line with a genetic modification that results in an afucosylated or non-fucosylated antibody. Examples of cell lines producing afucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. Arch. Biochem. Biophys. 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004)), cells overexpressing β1,4-N-acetylglucosaminyltransferase III (GnT-III) and Golgi μ-mannosidase II (ManII), and cells with a knockout in the mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltranferase (MGAT1; *see* Byrne, G. *et al.* (2018) *PLoS Biol.* 16:e2005817).

[0110] In some embodiments, the afucosylated or non-fucosylated antibody is produced in a cell line treated with an inhibitor of glycoprocessing enzyme(s), such as kifunensine, which is an inhibitor of mannosidase I (*see, e.g.,* Elbein, A.D. *et al.* (1990) *J. Biol. Chem.* 265:15599-15605). For example, cells can be centrifuged and resuspended in growth medium comprising kifunensine (*e.g.*, at 250μg/mL), then cultured and used for antibody production.

[0111] In certain aspects, the present disclosure provides multispecific (*e.g.*, bispecific) antibodies and antibody fragments comprising a first antigen-binding domain that binds to a first

target of interest and a second antigen-binding domain that binds to a second target of interest. In some embodiments, the present disclosure provides multispecific (*e.g.*, bispecific) antibodies and antibody fragments comprising a first antigen-binding domain that binds to human Dectin-1 and a second antigen-binding domain that binds to a target of interest.

[0112] In some embodiments, multispecific (*e.g.*, bispecific) antibodies and antibody fragments comprise a first antibody or antigen-binding fragment comprising the first antigen-binding domain and a second antibody or antigen-binding fragment comprising the second antigen-binding domain. In some embodiments, the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof. In some embodiments, the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof. In some embodiments, the first antibody or fragment is bound to the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof.

[0113] Exemplary avidins, streptavidins, neutravidins, or biotin-binding derivatives thereof are known in the art. In some embodiments, the streptavidin is monomeric streptavidin (mSA). Exemplary biotins or avidin-binding derivatives thereof are known in the art. In some embodiments, an antibody or antigen-binding fragment thereof of the present disclosure is biotinylated. Kits for biotinylating an antibody of interest are known in the art and commercially available. In some embodiments, mSA comprises the sequence EFASAEAGITGTWYNQHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGT KLEWRVEWNNSTENCHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFT KVKPSAASGS (SEQ ID NO:14).

[0114] In some embodiments, an antibody that binds human Dectin-1 and is coupled to mSA via a linker comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSEFASAEAGITGTWYN

QHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLEWRVEWNNSTEN CHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFTKVKPSAASGS (SEQ ID NO:15). In some embodiments, an antibody fragment that binds human Dectin-1 and is coupled to mSA via a linker comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVGGGSGGGSGGGSEFASAEA GITGTWYNQHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLEWRV EWNNSTENCHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFTKVKPSA ASGS (SEQ ID NO:16) or QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVGGGSGGGSGGGSEFASAEA GITGTWYNQHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLEWRV EWNNSTENCHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFTKVKPSA ASGSAAAGASHHHHHH (SEQ ID NO:17).

[0115] In some embodiments, one or both of the first and second antigen binding domain, antibody, or fragment is/are humanized.

[0116] In some embodiments, one or both of the first and second antigen binding domain, antibody, or fragment comprise(s) a tag, *e.g.*, for affinity purification. In some embodiments, the tag is a polyhistidine tag.

[0117] In some embodiments, one or both of the first and second antibodies or fragments are Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibodies, nanobodies, or scFv fragments. In some embodiments, one or both of the first and second antibodies or fragments further comprise an Fc domain. In some embodiments, the first antibody or fragment is a Fab fragment, and wherein the second antibody or fragment is a full-length antibody. In some embodiments, the first and the second antibodies or fragments are both full-length antibodies. In some embodiments, the first antibody or fragment is a Fab fragment coupled to monomeric streptavidin (mSA), and wherein the second antibody or fragment is a biotinylated full-length antibody. In some embodiments, the first antibody or fragment is a full-length antibody coupled to monomeric streptavidin (mSA), and wherein the second antibody or fragment is a biotinylated full-length antibody.

[0118] In some embodiments, an antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, or coupled to biotin or an avidin-binding derivative thereof, via a linker. Linkers for creating antibody fusion proteins are known in the art. In some embodiments, the linker comprises, consists of, or consists essentially of, glycine and/or serine residues. In some embodiments, the linker is 15-20 amino acids in length. In some embodiments, the linker comprises the sequence GGGSGGGSGGGS (SEQ ID NO:13). In some embodiments, the linker comprises one or more repeats of the sequence GGGGS (SEQ ID NO:26). In some embodiments, the linker comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:27) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:28). Additional linker sequences are described in Chen, X. *et al.* (2013) *Adv. Drug Deliv. Rev.* 65:1357-1369. In some embodiments (*e.g.,* in a scFv of the present disclosure), the scFv comprises one type of linker between the VH and VL domains, and another type of linker connecting the VL domain to the rest of the half-antibody, *e.g.*, to an Fc region. For example, in some embodiments, the linker between the VH and VL domains comprises glycine and/or serine residues, such as GGGSGGGSGGGS (SEQ ID NO:13), GGGGSGGGGSGGGGS (SEQ ID NO:27), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:28), or one or more repeats of the sequence GGGGS (SEQ ID NO:26); and/or the linker connecting the VL domain to the Fc region comprises EPKRSDKTHTCPPC (SEQ ID NO:29) or SATHTCPPC (SEQ ID NO:30). In some embodiments, the linker between the VH and VL domains comprises glycine and/or serine residues and is 15-20 amino acids in length.

[0119] In some embodiments, the first target of interest is human Dectin-1 (*e.g.*, isoform(s) A and/or B). In some embodiments, the second target of interest is a disease-causing agent. In some embodiments, the second target of interest is human Dectin-1 (*e.g.*, isoform(s) A and/or B). In some embodiments, the first target of interest is a disease-causing agent.

[0120] In certain aspects, the present disclosure provides multispecific (*e.g.*, bispecific) antibodies and antibody fragments comprising at least one antigen binding domain that binds to human Dectin-1. Any of the antigen binding domains that bind to human Dectin-1 of the present disclosure may find use in a multispecific (*e.g.*, bispecific) binding molecule, antibody, or antibody fragment. In some embodiments, the multispecific (*e.g.*, bispecific) binding molecule, antibody, or antibody fragment further comprises at least one antigen binding domain that binds to a target of interest, *e.g.*, as described herein. In some embodiments, the target of interest is a disease-causing agent.

[0121] In some embodiments, the multispecific (*e.g.*, bispecific) binding molecule comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL

domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain, and a second Fc region connected to the VH domain. In some embodiments, the scFv arm binds to Dectin-1, and the conventional antibody arm with VH and VL domains on separate polypeptides binds to a target of interest, *e.g.*, as described herein, such as a disease-causing agent. In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or wherein the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the first antibody arm comprises a first linker between the VH and VL domains (*e.g.*, of 15-20 amino acids in length), and a second linker between the VL domain and the first Fc region. In some embodiments, the first linker comprises one or more repeats of the sequence GGGGS (SEQ ID NO:26), *e.g.*, the sequence GGGGSGGGGSGGGGS (SEQ ID NO:27) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:28). In some embodiments, the second linker comprises the sequence EPKRSDKTHTCPPC (SEQ ID NO:29) or SATHTCPPC (SEQ ID NO:30). Additional linker sequences are described in Chen, X. *et al.* (2013) *Adv. Drug Deliv. Rev.* 65:1357-1369. A non-limiting example of this format is shown in **FIG. 51**.

[0122] In some embodiments, the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate, LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is a surface antigen of the virus. In some embodiments, the target of interest is a protein aggregate or monomer thereof, *e.g.*, amyloid beta (such as in Alzheimer's disease), or lambda or kappa light chain amyloid (such as in light chain amyloidosis). In some embodiments, *e.g.*, for oncology applications, the second target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR, *e.g.*, as expressed on the surface of a cancer cell.

[0123] In some embodiments, the target of interest is CD20, *e.g.*, human CD20. In some embodiments, the antigen binding domain that binds CD20 comprises a CDR-H1, CDR-H2, and CDR-H3 sequence from the VH domain sequence
QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD
TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG

TTVTVSA (SEQ ID NO:24) and/or a CDR-L1, CDR-L2, and CDR-L3 sequence from the VL domain sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25). In some embodiments, the antigen binding domain that binds CD20 comprises a VH domain that comprises the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24) and/or a VL domain that comprises the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25). In some embodiments, the antigen binding domain that binds CD20 comprises the VH and VL domain sequences from rituximab. In some embodiments, the antigen binding domain that binds CD20 comprises the VH and VL domain sequences from obinituzumab. In some embodiments, the antigen binding domain that binds CD20 comprises a VH domain that comprises the sequence of SEQ ID NO:46 and/or a VL domain that comprises the sequence of SEQ ID NO:47.

[0124] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to a target of interest (*e.g.*, a disease causing agent of the present disclosure). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF

GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31).

[0125] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to CD20 (*e.g.*, human CD20). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of SEQ ID NO:24 and a VL domain comprising the sequence of SEQ ID NO:25. In some embodiments, the second antibody arm comprises a second polypeptide comprising the sequence of

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD
TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG
TTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF

PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVS KLTVDKSRWQQGNVFSCSVMHEALHNRFTQKSLSLSPG (SEQ ID NO:32) and a third polypeptide comprising the amino acid sequence of QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:33).

[0126] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to HER2 (*e.g.*, human HER2). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTL VTVSS (SEQ ID NO:34) and a VL domain comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID NO:35). In some embodiments, the antigen binding domain that binds HER2 comprises the VH and VL domain sequences from trastuzumab.

[0127] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to Trop-2 (*e.g.*, human Trop-2). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTG EPTYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCARGGFGSSYWYFDVWGQGS LVTVSS (SEQ ID NO:42) and a VL domain comprising the sequence of

DIQLTQSPSSLSASVGDRVSITCKASQDVSIAVAWYQQKPGKAPKLLIYSASYRYTGVPD RFSGSGSGTDFTLTISSLQPEDFAVYYCQQHYITPLTFGAGTKVEIK (SEQ ID NO:43). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of

QIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNWVKQAPGKGLKWMGWINTKTGEP TYAEEFKGRFAFSLETSASTAYLQINNLKKEDTATYFCGRGGYGSSYWYFDVWGAGTT VTVSS (SEQ ID NO:56) and a VL domain comprising the sequence of

DIVMTQSHKFMSTSVGDRVSITCKASQDVSIAVAWYQQKPGQSPKVLIYSASYRYTGVP DRFTGSGSGTDFTFTISRVQAEDLAVYYCQQHYITPLTFGAGTKLELK (SEQ ID NO:57). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of

QVQLQQSGPELVRPGTSVRISCKASGYTFTIYWLGWVKQRPGHGLEWIGNIFPGSAYINY NEKFKGKATLTADTSSSTAYMQLSSLTSEDSAVYFCAREGSNSGYWGQGTTLTVSS (SEQ ID NO:58) and a VL domain comprising the sequence of

DIVMTQSPSSLSVSAGEKVTMTCKSSQSLLNSGNQQNYLAWYQQKPGQPPKLLIYGAST RESGVPDRFTGSGSGTDFTLTINSVQAEDLAVYYCQSDHIYPYTFGGGTKLEIK (SEQ ID NO:59). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYGVHWIRQPPGKGLEWIGVIWTGGSTDYN SALMSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGDYDRYTMDYWGQGTLVTV SS (SEQ ID NO:66) and a VL domain comprising the sequence of

DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNLES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQHSRELPYTFGQGTKLEIK (SEQ ID NO:67). In some embodiments, the antigen binding domain that binds Trop-2 comprises the VH and VL domain sequences from sacituzumab, AR47A6.4.2, h7E6, or Pr1E11.

[0128] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to light chain amyloids (*e.g.*, human light chain amyloids, *e.g.*, human kappa light chain amyloids, human lambda light chain amyloids, or both human kappa and lambda light chain amyloids). In some embodiments, the first Fc region

comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of

QVQLKESGPGLVAPSQSLSITCTVSGFSLSSYGVSWVRQPPGKGLEWLGVIWGDGSTNY KPNLMSRLSISKDISKSQVLFKLNSLQTDDTATYYCVTLDYWGQGTSVTVSS (SEQ ID NO:44) and a VL domain comprising the sequence of

DVVMTQTPLSLPVSLGDQASISCRSSQSLVHRNGNTYLHWYLQKPGQSPKLLIYKVSNR FSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYFCFQTTYVPNTFGGGTKLEIK (SEQ ID NO:45). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of

EVQLVESGGRLVQPKGSLKLSCAASGFTFNTYAMYWIRQAPGKGLEWVARIRSKSNNY AIYYADSVKDRFTIFRDDSQSMLYLQMNNLKTEDTAMYYCVRPYSDSFAYWGQGTLVT VSA (SEQ ID NO:52) and a VL domain comprising the sequence of

DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSTGNTYLHWYLQKPGQSPKLLIYKVSNRF SGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCSQSTHVPFTFGGGTKLEIK (SEQ ID NO:53). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of

EVQLVESGGRLVQPKGSLKLSCAASGFTFNTYAMYWIRQAPGKGLEWVARIRSKSNNY AIYYADSVKDRFTIFRDDSQSMLYLQMNNLKTEDTAMYYCVRPYSDSFAYWGQGTLVT VSA (SEQ ID NO:54) and a VL domain comprising the sequence of

DVVMTQTPLSLPVSLGDQASISCRSSLSLVHSTGNTYLHWYLQKPGQSPKLLIYKVSNRF SGVPDRFSGSGSGTYFTLKISRVEAEDLGVYFCSQSTHVPFTFGGGTKLEIK (SEQ ID NO:55). In some embodiments, the antigen binding domain that binds light chain amyloid comprises the VH and VL domain sequences from antibody 11-1F4, 2A4, or 7D8.

[0129] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to amyloid beta (*e.g.*, human amyloid beta). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAVIWFDGTK KYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGARRGPYYMDVW GKGTTVTVSS (SEQ ID NO:48) and a VL domain comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO:49). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence

of
EVQLVESGGGLVQPGGSLRLSCSASGFTFSSFGMHWVRQAPGKGLEWVAYISSGSSTIY
YGDTVKGRFTISRDNAKNSLFLQMSSLRAEDTAVYYCAREGGYYYGRSYYTMDYWGQ
GTTVTVSS (SEQ ID NO:50) and a VL domain comprising the sequence of
DVVMTQSPLSLPVTPGAPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRFS
GVPDRFSGSGSGTDFTLRISRVEAEDVGIYYCFQGSHVPPTFGPGTKLEIK (SEQ ID
NO:51). In some embodiments, the antigen binding domain that binds amyloid beta comprises the VH and VL domain sequences from aducanumab or lecanemab.

[0130] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to CD70 (*e.g.*, human CD70). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFTFSVYYMNWVRQAPGKGLEWVSDINNEGGTT
YYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCARDAGYSNHVPIFDSWGQGT

LVTVSS (SEQ ID NO:38) and a VL domain comprising the sequence of QAVVTQEPSLTVSPGGTVTLTCGLKSGSVTSDNFPTWYQQTPGQAPRLLIYNTNTRHSG VPDRFSGSILGNKAALTITGAQADDEAEYFCALFISNPSVEFGGGTQLTVL (SEQ ID NO:39). In some embodiments, the antigen binding domain that binds CD70 comprises the VH and VL domain sequences from 4ID12.

[0131] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to nectin-4 (*e.g.*, human nectin-4). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNWVRQAPGKGLEWVSYISSSSSTIY YADSVKGRFTISRDNAKNSLSLQMNSLRDEDTAVYYCARAYYYGMDVWGQGTTVTVS S (SEQ ID NO:40) and a VL domain comprising the sequence of DIQMTQSPSSVSASVGDRVTITCRASQGISGWLAWYQQKPGKAPKFLIYAASTLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGGGTKVEIK (SEQ ID NO:41). In

some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGSTDY
NAAFISRLSISKDTSKSQVFFKMNSLQADDTAIYYCARELIHAMDNWGQGTSVTVSS
(SEQ ID NO:60) and a VL domain comprising the sequence of
DIQMTQSPASLSVSVGETVTITCRASENIYSNLAWYQQKQGNSPQLLVFAATNLADGVP
SRFSGSGSGTQYSLKINSLQSEDFGTYYCQHFWGTPTFGGGTKLEIK (SEQ ID NO:61). In some embodiments, the antigen binding domain that binds nectin-4 comprises the VH and VL domain sequences from N41 or Ha22-2.

[0132] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to EGFR (*e.g.*, human EGFR). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTD

YNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTV
SA (SEQ ID NO:62) and a VL domain comprising the sequence of
DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFS
GSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELK (SEQ ID NO:63). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPPGKGLEWIGYIYYSGSTD
YNPSLKSRVTMSVDTSKNQFSLKVNSVTAADTAVYYCARVSIFGVGTFDYWGQGTLVT
VSS (SEQ ID NO:64) and a VL domain comprising the sequence of
EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCHQYGSTPLTFGGGTKAEIK (SEQ ID NO:65). In some embodiments, the antigen binding domain that binds EGFR comprises the VH and VL domain sequences from cetuximab or necitumumab.

[0133] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to DLL3 (*e.g.*, human DLL3). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN

GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTG EPTYADDFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARIGDSSPSDYWGQGTLV TVSS (SEQ ID NO:68) and a VL domain comprising the sequence of EIVMTQSPATLSVSPGERATLSCKASQSVSNDVVWYQQKPGQAPRLLIYYASNRYTGIPA RFSGSGSGTEFTLTISSLQSEDFAVYYCQQDYTSPWTFGQGTKLEIK (SEQ ID NO:69). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYVYYSGTTNYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSS (SEQ ID NO:70) and a VL domain comprising the sequence of EIVLTQSPGTLSLSPGERVTLSCRASQRVNNNYLAWYQQRPGQAPRLLIYGASSRATGIP DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDRSPLTFGGGTKLEIK (SEQ ID NO:71). In some embodiments, the antigen binding domain that binds DLL3 comprises the VH and VL domain sequences from rovalpituzumab or DLL3-4.

[0134] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to mesothelin (*e.g.*, human mesothelin). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ

QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
QVQLQQSGPELEKPGASVKISCKASGYSFTGYTMNWVKQSHGKSLEWIGLITPYNGASS
YNQKFRGKATLTVDKSSSTAYMDLLSLTSEDSAVYFCARGGYDGRGFDYWGSGTPVTV
SS (SEQ ID NO:72) and a VL domain comprising the sequence of
DIELTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPG
RFSGSGSGNSYSLTISSVEAEDDATYYCQQWSKHPLTFGSGTKVEIK (SEQ ID NO:73). In some embodiments, the antigen binding domain that binds mesothelin comprises the VH and VL domain sequences from amatuximab.

[0135] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to CD33 (*e.g.*, human CD33). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS

NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of EVQLVQSGAEVKKPGSSVKVSCKASGYTITDSNIHWVRQAPGQSLEWIGYIYPYNGGTD YNQKFKNRATLTVDNPTNTAYMELSSLRSEDTAFYYCVNGNPWLAYWGQGTLVTVSS (SEQ ID NO:74) and a VL domain comprising the sequence of DIQLTQSPSTLSASVGDRVTITCRASESLDNYGIRFLTWFQQKPGKAPKLLMYAASNQGS GVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQTKEVPWSFGQGTKVEVK (SEQ ID NO:75). In some embodiments, the antigen binding domain that binds CD33 comprises the VH and VL domain sequences from gemtuzumab.

[0136] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to CCR8 (*e.g.*, human CCR8). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH

domain comprising the sequence of
EVQLVESGGRLVQPKGSLKLSCAASGFAFNTYALYWIRQAPGKGLEWVARIRSKSNNY
ATYYADSVKDRFTISRDDSQSMLYLQMNNLKTEDTAMYYCVRARFYYSDYGYAMDY
WGQGTSVTVSS (SEQ ID NO:76) and a VL domain comprising the sequence of
DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLA
SGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTFGAGTKLELK (SEQ ID
NO:77). In some embodiments, the antigen binding domain that binds CCR8 comprises the VH and VL domain sequences from 10A11.

[0137] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to CTLA4 (*e.g.*, human CTLA4). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNK
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTV

SS (SEQ ID NO:78) and a VL domain comprising the sequence of EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPD RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK (SEQ ID NO:79). In some embodiments, the antigen binding domain that binds CTLA4 comprises the VH and VL domain sequences from ipilimumab.

[0138] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to cMET (*e.g.*, human cMET). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWLHWVRQAPGKGLEWVGMIDPSNSDT RFNPNFKDRFTISADTSKNTAYLQMNSLRAEDTAVYYCATYRSYVTPLDYWGQGTLVT VSS (SEQ ID NO:80) and a VL domain comprising the sequence of DIQMTQSPSSLSASVGDRVTITCKSSQSLLYTSSQKNYLAWYQQKPGKAPKLLIYWASTR ESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYAYPWTFGQGTKVEIK (SEQ ID

NO:81). In some embodiments, the antigen binding domain that binds cMET comprises the VH and VL domain sequences from onartuzumab.

[0139] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to LIV-1 (*e.g.*, human LIV-1). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
QVQLVQSGAEVKKPGASVKVSCKASGYTIEDYYMHWVRQAPGQGLEWMGWIDPENG
DTEYAPTFQGRVTMTRDTSINTAYMELSRLRSDDTAVYYCARHDAHYGTWFAYWGQG
TLVTVSS (SEQ ID NO:82) and a VL domain comprising the sequence of
DVVMTQSPLSLPVTLGQPASISCRSSQSIIRNDGNTYLEWYQQRPGQSPRRLIYRVSNRFS
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGGGTKVEIK (SEQ ID NO:83). In some embodiments, the antigen binding domain that binds LIV-1 comprises the VH and VL domain sequences from hLIV14.

[0140] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to ROR-1 (*e.g.*, human ROR-1). In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ
QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF
GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of
QVQLQESGPGLVKPSQTLSLTCTVSGYAFTAYNIHWVRQAPGQGLEWMGSFDPYDGGS
SYNQKFKDRLTISKDTSKNQVVLTMTNMDPVDTATYYCARGWYYFDYWGHGTLVTVS
S (SEQ ID NO:84) and a VL domain comprising the sequence of
DIVMTQTPLSLPVTPGEPASISCRASKSISKYLAWYQQKPGQAPRLLIYSGSTLQSGIPPRF
SGSGYGTDFTLTINNIESEDAAYYFCQQHDESPYTFGEGTKVEIK (SEQ ID NO:85). In some embodiments, the antigen binding domain that binds ROR-1 comprises the VH and VL domain sequences from Ab1.

[0141] In some embodiments, provided herein is a multispecific (*e.g.*, bispecific) binding molecule that comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising VH and VL domains of the present disclosure that bind to human Dectin-1 and a first

Fc region, and a second antibody arm comprising an antibody heavy chain that comprises a VH domain in association with an antibody light chain that comprises a VL domain and a second Fc region connected to the VH domain, wherein the VH and VL domains of the second antibody arm form an antigen binding domain that binds to serum amyloid P (SAP), *e.g.*, human SAP. In some embodiments, the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations. In some embodiments, the scFv comprises a first linker of the present disclosure between the VH and VL domains and a second linker of the present disclosure between the VL domain and the first Fc region. In some embodiments, the first antibody arm comprises the amino acid sequence of QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:31). In some embodiments, the second antibody arm comprises a VH domain comprising the sequence of QVQLVQSGAEVKKPGSSVKVSCKASGFTFATYNMHWVRQAPGQGLEWMGYIYPGDG NANYNQQFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGDFDYDGGYYFDSWG QGTLVTVSS (SEQ ID NO:86) and a VL domain comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLIHNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQHHYGAPLTFGQGTKLEIK (SEQ ID NO:87). In some embodiments, the antigen binding domain that binds SAP comprises the VH and VL domain sequences from dezamizumab.

[0142] Multispecific antibodies have binding specificities for at least two different epitopes, usually from different antigens. Multispecific or bispecific antibodies can be prepared as full-length antibodies or antibody fragments (e.g., $F(ab')_2$ bispecific antibodies).

[0143] To enable the targeted removal of a disease-causing agent via phagocytosis, an antigen-binding domain of the present disclosure may be selected from IgGs, intrabodies, peptibodies,

nanobodies, single domain antibodies, SMTPs, and multispecific antibodies (e.g., bispecific antibodies, diabodies, triabodies, tetrabodies, tandem di-scFV, tandem tri-scFv, ADAPTIR).

[0144] Methods for making bispecific antibodies are known in the art. One well-established approach for making bispecific antibodies is the "knobs-into-holes" or "protuberance-into-cavity" approach. *See e.g.,* US Pat. No. 5,731,168. Two immunoglobulin polypeptides (*e.g.,* heavy chain polypeptides) each comprise an interface; an interface of one immunoglobulin polypeptide interacts with a corresponding or cognate interface on the other immunoglobulin polypeptide, thereby allowing the two immunoglobulin polypeptides to associate. In some embodiments, interfaces may be engineered such that a "knob" or "protuberance" located in the interface of one immunoglobulin polypeptide corresponds with a cognate "hole" or "cavity" located in the interface of the other immunoglobulin polypeptide. In some embodiments, a knob may be constructed by replacing a small amino acid side chain with a larger side chain. In some embodiments, a hole may be constructed by replacing a large amino acid side chain with a smaller side chain. Knobs or holes may exist in the original interface, or they may be introduced synthetically. Polynucleotides encoding modified immunoglobulin polypeptides with one or more corresponding knob- or hole-forming mutations may be expressed and purified using standard recombinant techniques and cell systems known in the art. See, e.g., U.S. Pat. Nos. 5,731,168; 5,807,706; 5,821,333; 7,642,228; 7,695,936; 8,216,805; 8,679,785; 8,844,834; U.S. Pub. No. 2013/0089553; Spiess et al., Nature Biotechnology 31: 753-758, 2013; and Ridgway and Carter (1996) Protein Eng. 9:617-621. Modified immunoglobulin polypeptides may be produced using prokaryotic host cells, such as *E. coli*, or eukaryotic host cells, such as mammalian cells (*e.g.*, CHO cells) or yeast cells. Corresponding knob- and hole-bearing immunoglobulin polypeptides may be expressed in host cells in co-culture and purified together as a heteromultimer, or they may be expressed in single cultures, separately purified, and assembled *in vitro*. Exemplary cognate knob and hole mutations are provided below (numbering according to EU index). EU numbering as used herein is known in the art; *see, e.g.,* IMGT resources at www.imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html and www.imgt.org/IMGTScientificChart/Numbering/Hu_IGKCnber.html. As used herein, an "antibody arm" may refer to the pairing between an antibody heavy chain and an antibody light chain, wherein the variable domains of the heavy and light chains form an antigen binding site that binds a target antigen.

Fc region 1	Y407T	Y407A	F405A	T394S	T366S L368A Y407V	T394W Y407T	T394S Y407A	T366W T394S

Fc region 2	T366Y	T366W	T394W	F405W	T366W	T366Y F405A	T366W F405W	F405W Y407A

[0145] According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences.

[0146] In some embodiments, multispecific (*e.g.*, bispecific) antibodies further comprise one or more mutations on only one of the antibody arms to improve heavy chain/light chain pairing. For example, amino acid substitutions can be used to replace a native disulfide bond in the CH1-CL interface of one antibody arm with an engineered disulfide bond. *See, e.g.,* Mazor, Y. *et al.* (2015) *MAbs* 7:377-389 and EP3452089A2. In some embodiments, the multispecific or bispecific antibody comprises two antibody light chains and two antibody heavy chains, wherein only one of the antibody heavy chains comprises amino acid substitutions F126C and C220V, and only the corresponding or cognate light chain comprises amino acid substitutions S121C and C214V, according to EU numbering.

[0147] Multispecific (*e.g.*, bispecific) antibodies also include cross-linked or "heteroconjugate" antibodies. Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. In some embodiments, a bispecific antibody comprises a first IgG antibody comprising the first antigen binding domain covalently linked to a second IgG antibody comprising the second antigen binding domain.

[0148] In some embodiments, multispecific (*e.g.*, bispecific) antibodies further comprise one or more mutations on only one of the antibody arms to reduce binding affinity for Protein A. *See, e.g.,* Ollier, R. *et al.* (2019) *MAbs* 11:1464-1478 and AU2018204314. In some embodiments, the multispecific or bispecific antibody comprises two antibody light chains and two antibody heavy chains, wherein only one of the antibody heavy chains comprises amino acid substitutions H435R and Y436F, according to EU numbering.

[0149] In some embodiments, the monospecific or multispecific (*e.g.*, bispecific) antibodies further comprise one or more mutations to reduce effector function, *e.g.*, to reduce or eliminate binding of the Fc region to an Fc receptor. In some embodiments, the antibody comprises two antibody Fc regions, wherein the antibody Fc regions comprise an amino acid substitution at one or more of positions 234, 235, and 237, according to EU numbering. In some embodiments, the antibody comprises two antibody Fc regions, wherein the antibody Fc regions comprise L234A, L235E, and G237A substitutions, according to EU numbering.

[0150] In some embodiments, the monospecific or multispecific (*e.g.*, bispecific) antibodies comprise two antibody heavy chains and two antibody light chains, wherein the VH domain of the first antibody heavy chain forms an antigen binding domain with the VL domain of the first antibody light chain, wherein the VH domain of the second antibody heavy chain forms an antigen binding domain with the VL domain of the second antibody light chain, wherein the first antibody heavy chain comprises F126C, C220V, and T366W substitutions, wherein the first antibody light chain comprises S121C and C214V substitutions, and wherein the second antibody heavy chain comprises T366S, L368A, Y407V, H435R, and Y436F substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains further comprise L234A, L235E, and G237A substitutions, according to EU numbering. In some embodiments, the first and second antibody heavy chains comprise human IgG1 Fc domains.

[0151] In some embodiments, provided herein is a polynucleotide encoding the antibody or multispecific binding molecule of any one of the above embodiments. In some embodiments, provided herein is a vector (*e.g.*, an expression vector) comprising the polynucleotide of any one of the above embodiments. In some embodiments, provided herein is a host cell (*e.g.*, an isolated host cell or cell line) comprising the polynucleotide or vector of any one of the above embodiments. In some embodiments, provided herein is a pharmaceutical composition comprising the antibody or multispecific binding molecule of any one of the above embodiments and a pharmaceutically acceptable carrier. Any of these may find use in the methods of production and/or treatment disclosed herein.

[0152] In some embodiments, provided herein is a method of producing an antibody or multispecific binding molecule, comprising culturing the host cell of any one of the above embodiments under conditions suitable for production of the antibody or multispecific binding molecule. In some embodiments, the method further comprises recovering the antibody or multispecific binding molecule. The antibodies or multispecific binding molecules may be produced using standard recombinant techniques, as described herein, and/or as exemplified *infra*.

[0153] Antibodies and antibody fragments may be produced using recombinant methods. For example, nucleic acid encoding the antibody/fragment can be isolated and inserted into a replicable vector for further cloning or for expression. DNA encoding the antibody/fragment may be readily isolated and sequenced using conventional procedures (*e.g.*, via oligonucleotide probes capable of binding specifically to genes encoding the heavy and light chains of the antibody/fragment). Many vectors are known in the art; vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one

or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Suitable host cells for cloning or expressing the DNA in the vectors herein are the prokaryote, yeast, or higher eukaryote cells. When using recombinant techniques, the antibody/fragment can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody/fragment is produced intracellularly, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Where the antibody/fragment is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter.

[0154] In some embodiments, an antibody or multispecific binding molecule of the present disclosure is part of a pharmaceutical composition, *e.g.*, including the antibody and one or more pharmaceutically acceptable carriers. Pharmaceutical compositions and formulations as described herein can be prepared by mixing the active ingredients (such as a fusion protein) having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.* Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG).

[0155] Certain aspects of the present disclosure relate to kits or articles of manufacture comprising any of the antibodies or multispecific binding molecules disclosed herein. In some embodiments, the article of manufacture comprises a container and a label or package insert on or associated with the container. In some embodiments, the kit or article of manufacture further comprises instructions for using the antibody or multispecific binding molecule according to any of the methods disclosed herein, *e.g.*, for treating a disease or disorder such as cancer.

[0156] Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition that is effective for treating the condition and may have a sterile access port (for example the

container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an antibody or multispecific binding molecule as described herein. The label or package insert indicates that the composition is used for treating the particular condition. The label or package insert will further comprise instructions for administering the antibody or multispecific binding molecule composition to the subject. Articles of manufacture and kits comprising combinatorial therapies described herein are also contemplated.

II. Methods of Production and Identification

[0157] In certain aspects, the present disclosure provides methods of producing or generating multispecific (*e.g.*, bispecific) antibodies and antibody fragments. In some embodiments, the methods comprise providing a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain that binds to a first target of interest; providing a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain that binds to a second target of interest; and contacting the first antibody or fragment with the second antibody or fragment under conditions suitable for binding between the first antibody or fragment and the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof, thereby generating a multispecific binding molecule. In some embodiments, the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof. In some embodiments, the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof. Any of the antigen binding domains, antibodies, and antibody fragments of the present disclosure (*e.g.*, as described *supra* in section I) may be produced or generated using the methods of producing or generating multispecific (*e.g.*, bispecific) antibodies and antibody fragments disclosed herein. Advantageously, this platform provides a modular format for generation of a variety of multispecific (*e.g.*, bispecific) binding molecules in which distinct antigen binding domains, antibodies, and/or antibody fragments are coupled together via a high affinity avidin: biotin interaction.

[0158] In certain aspects, the present disclosure provides methods of identifying a multispecific (*e.g.*, bispecific) binding molecule that binds a first and a second target of interest. In some embodiments, the methods comprise providing a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain that binds to a first target of interest; providing

a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain that binds to a second target of interest; contacting the first antibody or fragment with the second antibody or fragment under conditions suitable for binding between the first antibody or fragment and the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof, thereby generating a multispecific binding molecule; and measuring binding between the multispecific binding molecule and at least one of the first and the second target of interest. In some embodiments, the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof. In some embodiments, the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof. Advantageously, this platform allows for screening a variety of antigen-binding domains for binding a target of interest in a multispecific (*e.g.*, bispecific) format.

[0159] In some embodiments, the first target of interest is human Dectin-1 (*e.g.*, isoform(s) A and/or B). In some embodiments, the second target of interest is a disease-causing agent. In some embodiments, the second target of interest is human Dectin-1 (*e.g.*, isoform(s) A and/or B). In some embodiments, the first target of interest is a disease-causing agent.

[0160] Any of the antigen binding domains, antibodies, and antibody fragments of the present disclosure (*e.g.*, as described *supra* in section I) may find use in the methods of identifying multispecific (*e.g.*, bispecific) antibodies and antibody fragments disclosed herein. In some embodiments, the antigen binding domains, antibodies, and antibody fragments bind to human Dectin-1. For example, in some embodiments, the antibody or fragment binds human Dectin-1 and is coupled to mSA via a linker. In some embodiments, the antibody or fragment comprises a sequence selected from the group consisting of SEQ ID NOs:15-17.

[0161] Assays for measuring binding between the multispecific binding molecule and at least one of the first and the second target of interest are known in the art. In some embodiments, binding between the multispecific binding molecule and a purified antigen is measured, *e.g.*, as with an ELISA or SPR binding assay. In some embodiments, binding between the multispecific binding molecule and a cell expressing the antigen on its surface is measured, *e.g.*, as with a flow cytometry-based binding assay. In some embodiments, binding between the multispecific binding molecule and a bead or other solid substrate coated with the antigen is measured. In some embodiments, a functional assay is used to detect an interaction between two or more cells (each expressing a surface antigen bound by an antigen binding domain of the multispecific

binding molecule) brought together by binding the multispecific binding molecule, *e.g.,* by measuring cytokine production, cell death/phagocytosis, etc.

III. Methods of Use

[0162] In certain aspects, the present disclosure provides methods of treating a disease or disorder, comprising administering an effective amount of an antibody, antibody fragment, multispecific (*e.g.*, bispecific) binding molecule, or composition of the present disclosure to an individual in need thereof. In some embodiments, the individual is a human.

[0163] Any of the antigen binding domains, antibodies, and antibody fragments of the present disclosure (*e.g.*, as described *supra* in section I) may find use in the methods of treatment and uses disclosed herein, as well as the compositions (*e.g.*, pharmaceutical compositions) related thereto. For example, in some embodiments, the methods include using a multispecific (*e.g.*, bispecific) binding molecule of the present disclosure with a first antigen binding domain that binds to human Dectin-1, and a second antigen binding domain that binds to a disease-causing agent. In some embodiments, the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate (*e.g.*, amyloid beta, or lambda or kappa light chain amyloids), LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell. In some embodiments, the target of interest is a surface antigen of the virus. In some embodiments, the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR. Binding of the molecule that mediates targeted removal of a disease-causing agent via phagocytosis could be with and without avidity i.e., with and without inducing dimerization of the phagocytosis receptor such as Dectin-1 or the target antigen present on the agent.

[0164] In some embodiments, the disease or disorder is cancer, a bacterial infection, a fungal infection, a viral infection, a mast cell disease or disorder, systemic mastocytosis, amyloidosis, or an aging-related disease or disorder. There are variety of accumulated and not cleared aberrant host cells such as tumor, lymphoma, dead, necrotic, apoptotic, dying, infected, damaged cells that are associated with diseases. In addition, diverse cell products such as aggregated proteins (β-amyloid plaque, Tau aggregates, or antibody lambda or kappa light chain amyloids), lipoprotein particles, could cause a disease upon increased accumulation. Disease-causing cell may have glycoprotein, surface protein, or glycolipid typical of aberrant cells associated with a disease, disorder, or other undesirable condition. Besides the host generated agents, variety of foreign

pathogens such as infectious microbes (e.g., viruses, fungus and bacteria) and the microbe generated products and debris (e.g., viral particle envelopes, endotoxin) may not be well cleared in patients. In some embodiments, the virus is an influenza virus. In some embodiments, the virus is SARS-CoV-2.

[0165] The above listed abnormalities may cause illnesses such as cancer, Alzheimer disease, fibrosis, Parkinson disease, Huntington disease, HIV, Hepatitis A, B or C, sepsis etc. Many of these disorders or diseases are characterized by an accumulation of disease-causing agents in different organs in human subjects. In addition to the beneficial removal of a disease-causing agent via phagocytosis, the molecule may induce production of inflammatory mediators to alter the disease microenviroment such as in tumors, cancers and lymphomas. Without wishing to be bound to theory, it is thought that the molecule that performs targeted phagocytosis may demonstrate clear benefits for patients such as Alzheimer disease, Parkinson disease, cancer, infectious diseases (viral, bacterial, fungal, protozoan infections), inflammatory, or immune diseases (e.g., autoimmune diseases, inflammatory bowel diseases, multiple sclerosis), degenerative disease (e.g., joint and cartilage) Rheumatoid arthritis, Felty's syndrome, aggressive NK leukemia, IBM, IBD etc. In addition, targeted phagocytosis antibody treatment may have better activity of depleting cells in tissues over ADCC that relies on NK cells. The treatment may have a selective activity for removal of a particular disease-causing agent over a therapy that targets myeloid cells and improves phagocytosis in general. For example, targets of interest for treatment of cancer include, without limitation, CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, and EGFR.

[0166] The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

EXAMPLES

Example 1: Functional characterization of 2M24 anti-Dectin-1 antibody

[0167] This example describes the production of monoclonal antibodies specific for human Dectin-1. This example also describes the characterization of a novel anti-human Dectin-1 antibody.

Materials and methods

Production of anti-Dectin-1 antibodies

[0168] Four-week-old, ATX-Gx transgenic mice were immunized subcutaneously with recombinant human Dectin-1 isoform B for five weeks, with one boost of antigen per week. Antibody titers in mouse serum were assessed during pre- and post-boosts via ELISA and flow cytometry. The mice with the highest serum antibody titer were selected to supply B cells for the generation of hybridomas.

[0169] Prior to cell fusion, mice were administered with one additional boost of recombinant human Dectin-1 isoform B. Mice were sacrificed and the spleens were harvested. Spleen cells and SP2/0-Ag14 myeloma cells were mixed, in which fusion was then induced by 37 C incubation and in the presence of polyethylene glycol (PEG) or electroporation. The cells were then harvested and plated into 96 well plates with limited dilution to achieve one cell per well. The cells were subsequently treated with hypoxanthine, aminopterin and thymidine (HAT) medium and selected for over 2 weeks in culture.

[0170] To identify candidates specific towards Dectin-1, the hybridoma supernatants were screened by flow cytometry on cells overexpressing Dectin-1 and human primary monocytes. Cynomolgus monkey Dectin-1 cross-reactivity was assessed by antibody binding to cynomolgus monkey primary monocytes using flow cytometry.

Healthy donor samples

[0171] Fresh healthy donor buffy coats were obtained from Stanford Blood Center Peripheral blood mononuclear cells were isolated via ficoll paque (GE Healthcare, Chicago, IL) separation and cryopreserved in Bambanker cell freezing media (Bulldog Bio, Portsmouth, NH). Briefly, buffy coats were diluted in phosphate buffered saline (in 1:1 ratio), followed by layering of the diluted buffy coat in ficoll and centrifugation at 760 g. The PBMC layer was isolated and washed in PBS prior to downstream analysis Peripheral blood leukocytes were isolated through red blood cell lysis Cryopreserved cynomolgus monkey PBMC were obtained from Human Cells Biosciences.

Primary cells and cell culture

[0172] Human monocytes were isolated from healthy donor PBMCs according to the manufacturer's instructions of the pan monocyte isolation kit (Miltenyi Biotec, Inc., Auburn, CA) For macrophage and dendritic cells differentiation, monocytes were cultured in RPMI with 10 Human Serum (Millipore Sigma) in the presence of 50 ng/ml MCSF(Peprotech, Rocky Hill, NJ) for 6 days to fully differentiate into macrophages or in the presence of 50 ng/ml GMCSF and 50 ng/ml IL-4 (Peprotech, Rocky Hill, NJ) for 6 days to fully differentiate into dendritic cells. The medium with cytokines was refreshed every 3 days.

[0173] HEK Blue hDectin-1-a cells and HEK Blue hDectin-1-b cells (Invivogen, San Diego, CA) were maintained in DMEM/10% FBS supplemented with mormocin and puromycin according to manufacturer's instructions. Freestyle 293F cells were transiently transfected according to the manufacturer's suggestion (Thermo Fisher, Waltham, MA) Briefly, viable cell density and percent viability was determined Cells were diluted to a final density of 11×10^6 viable cells/mL with Freestyle 293 Expression Medium. Freestyle Max Reagent was diluted with OptiPro SFM Medium, mixed and incubated at room temperature for 5 minutes. The diluted Freestyle Max Reagent was added to plasmid DNA diluted with OptiPro SFM Medium and mixed. The Freestyle Max Reagent/plasmid DNA complexes were incubated at room temperature for 10-20 minutes. The complexes were slowly transferred to the cells, swirling the culture flask gently during the addition, and the cells were then incubated in a 37 °C incubator with 80% relative humidity and 8% CO2 on an orbital shaker.

Binding of Dectin-1 antibodies to Dectin-1 expressing cells

[0174] Dectin-1 expressing cells (HEK Blue hDectin-1-a, HEK Blue hDectin-1-b, HEK293F hDectin-1 a FL, human monocytes or cyno monocytes) were plated at $1x10^5$-$2x10^5$ cells per well in non-tissue culture treated, 96 well V bottom plates. Additionally, human monocytes were incubated in human FcgR blocking antibody (Biolegend, San Diego, CA) for 10 minutes at room temperature to reduce binding of the antibodies to the Fc receptor. The cells were subsequently stained with the eFluor 506 viability dye (ThermoFisher, Waltham, MA) in a 1:1000 dilution for 30 minutes on ice, followed by a wash step in FACS buffer (PBS with 2% fetal bovine serum). Primary Dectin-1 antibodies or isotypes were used at a titration of 300, 100, 33.3, 11.1, 3.7, 1.23, 0.41, and 0.14 nM and incubated on ice for 30 minutes, followed by another wash step in FACS buffer.

[0175] For detection of mouse primary antibodies, the cells were incubated with a fluorescently labeled AF647 anti-mouse Fc-specific secondary antibody (Jackson Immuno). For detection of human IgG4 primary antibody, the cells were incubated for 30 minutes on ice with an Alexa

Fluor 647 anti-human Fc-specific secondary antibody (Jackson Immuno) (detection in HEK cells) or a FITC anti-human IgG4 antibody (Sigma) (detection in primary monocytes). Data acquisition was performed using a CytoFlex flow cytometer (Beckman Coulter, Atlanta, GA) and analyzed using Graphpad Prism 8.4.

Dectin-1 antibody blocking of laminarin

[0176] HEK Blue hDectin-1a cells were plated at $1x10^5$ cells per well in non-tissue culture treated, 96 well V bottom plates. Primary anti-Dectin-1 antibodies were used at a titration of 300, 100, 33.3, 11.1, 3.7, 1.23, 0.41, 0.14, 0.05, 0.015 and 0.005 nM and incubated on ice for 30 minutes in the presence of 8 μ g/ml biotin laminarin. Following a wash step in FACS buffer, binding of biotin laminarin on the HEK cells was detected using streptavidin-AF647 for 30 minutes on ice. For analysis, 4000 cell events were acquired in a CytoFlex flow cytometer (Beckman Coulter, Atlanta, GA) and analyzed using Graphpad Prism 8.4.

Labelling of polysterene beads with pHrodo and conjugation to antibodies

[0177] Polystyrene beads of different sizes coated with goat anti-mouse IgG (or biotin) (Spherotech, Lake Forest, IL) were washed with PBS/Tween20 0.05% twice. pHrodo Red, succinimidyl ester (pHrodo Red, SE) (ThermoFisher, Waltham, MA) was added to the beads at 10 μ M and allowed to incubate for 60 minutes at room temperature with shaking. The beads were then washed with PBS/BSA 0.1% to remove excess pHrodo Red.

[0178] After pHrodo labeling, the antibody was conjugated to the beads according to the manufacturer's recommendations. Briefly, based on the binding capacity of the beads to antibody, an 5x excess of antibody was added to the beads and allowed to incubate at room temperature for 60 minutes with shaking. The beads were then washed with PBS/BSA 0.1% to remove unbound antibody. To assess the quality of the beads, pHrodo red activation was assessed in low pH buffer by flow cytometry. Antibody bound on the beads was assessed using a fluorescently labeled AF647 anti-mouse Fc specific or a FITC anti-human IgG4 antibody secondary antibody.

Antibody-dependent targeted phagocytosis of Phrodo labeled beads

[0179] For phagocytosis experiments, 50,000 HEK cells overexpressing Dectin-1 or primary cells (macrophages or dendritic cells) were seeded in a 96-well plate in RPMI with 10 ultra-low IgG FBS. pHrodo-labelled beads conjugated to anti-Dectin-1 antibodies or isotypes were added at a desired ratio ranging from 1:1 to 1:3 cells beads, and the plates were briefly spun down.

[0180] In some experiments cell tracker Calcein AM (Thermo Fisher, Waltham, MA) was added to label the cells. Phagocytosis was monitored in an IncuCyte S3 live imaging system (Germany) by taking images at desired time points and analyzed using the IncuCyte S3 software. Phagocytosis was quantified as the overlap of bright red fluorescence (engulfed beads) with Calcein AM positive cells or integrated red intensity of bright red fluorescence.

SEAP reporter assay in HEK cells overexpressing Dectin-1 with anti Dectin-1 antibodies

[0181] Anti-Dectin-1 monoclonal antibodies 2M24 (VH and VL domains comprising SEQ ID NO:7 and 8, respectively) or 15E2 and control isotypes were immobilized by coating onto the surfaces of wells of untreated 96-well, U bottomed polypropylene microtiter plates. For coating, 10, 2, 1, 0.5 and 0.1 μg of the anti-Dectin-1 antibody diluted in 50 μl sterile PBS was added to each well. Plates were left overnight in a class II laminar flow cabinet with the lids removed to allow the solutions to evaporate. Coated plates were washed twice with 200 μl sterile PBS to remove salt crystals and unbound antibody. HEK Blue hDectin-1-a cells were then cultured on the plates in RPM1 with 10% ultra-low IgG FBS (VWR)for 22 hours and alkaline phosphatase levels were assessed in the supernatant at OD 630 nm using QUANTI Blue Solution (Invivogen, San Diego, CA) per manufacturer's instructions.

[0182] To determine HEK cells SEAP secretion induced by anti-Dectin-1 antibody conjugated beads, streptavidin-2M24 (hIgG4) was conjugated to biotin polystyrene beads of 3, 10 and 16 μm in size (Spherotech, Lake Forest, IL) by incubating the beads with the antibody for 30 minutes in room temperature and washing twice with PBS to remove the unbound antibody. Anti-Dectin-1 antibody-conjugated beads were mixed with $1x10^5$ HEK Blue hDectin-1-a cells at a ratio of 1:3 cells: bead in RPM1 with 10% ultra-low IgG FBS for 22 hours, followed by evaluation of alkaline phosphatase secretion at OD 630 nm in the supernatant as described above.

Cytokine secretion

[0183] Anti-Dectin-1 monoclonal antibodies 2M24 or 15E2 clones and control isotypes were immobilized by coating 10 ug onto the surfaces of wells of untreated 96-well, U bottomed polypropylene microtiter plates as described above. Freshly isolated monocytes or peripheral blood mononuclear cells were then cultured on the plates with the immobilized antibodies in RPM1 with 10% ultra-low IgG FBS at 200,000 cell/per well for 24 hours. In other wells the cells were treated with 10 μ g/ml of Dectin-1 antibodies in solution instead of immobilized antibodies. TNFa, IL-6 and IFNg in the supernatant were assessed using the U-PLEX Assay Platform (Meso Scale Discovery) and their levels were expressed as fold change of Dectin-1 antibody-induced

cytokine secretion versus the isotype control. As a positive control, cells were stimulated with zymosan at 25 μ g/ml.

Results

[0184] To generate Dectin-1 antibodies, four-week-old, ATX-Gx Alloy transgenic mice were immunized subcutaneously with recombinant Dectin-1 isoform B protein, with one boost of antigen per week. The antibodies generated from this immunization have a human variable domain and a mouse constant domain.

[0185] From the 56 candidate anti-Dectin-1 antibody clones generated in this study, the 2M24 clone was the only one that showed binding to both Dectin-1 isoforms A and B in HEK cells as well as to monocytes. As shown in **FIG. 1A**, the 2M24 anti-Dectin-1 antibody clone demonstrated high affinity to Dectin-1 expressing human monocytes. In contrast, other clones bound only to Dectin-1 isoform A (e.g., 2M08, 2M12, 2M38) or showed no binding at all (2M49). Moreover, the affinity to Dectin-1 of2M24 was superior to the affinity presented by other clones and the commercial Dectin-1 antibodies (15E2, 259931, GE2). **FIG. 1C** shows a comparison of the binding to human monocytes and HEK cells overexpressing Dectin-1 between 2M24 clone and other Dectin-1 clones identified from the Alloy transgenic mice immunization, as well as commercial Dectin-1 clones.

[0186] The 2M24 antibody was also assessed for its cross-reactivity to cynomolgus Dectin-1. The binding was assessed by flow cytometry analysis of cynomolgus monkey monocytes derived from PBMCs. As shown in **FIG. 1B**, anti-human Dectin-1 clone 2M24 antibody demonstrated cross-reactivity and high affinity to cynomolgus monkey Dectin-1 expressed on monocytes. The 2M24 anti-Dectin-1 antibody was superior to commercial antibodies tested in terms of affinity, exhibiting an EC50 of 0.3 nM. The agonistic 15E2 and the 255931 commercial antibodies exhibited EC50 of 14 nM and16 nM, respectively, in cynomolgus monkey monocytes. **FIG. 1C** shows a comparison of binding to cynomolgus monkey monocytes between 2M24 clone and the commercial clones 15E2 and 259931.

[0187] To assess the functionality of the 2M24 Dectin-1 antibody in promoting phagocytosis, polystyrene beads were coated with the 2M24 antibody and mixed with HEK-Blue hDectin-1a cells or primary human monocytes. The 2M24 antibody efficiently induced the phagocytosis of the beads. As shown in **FIGs. 2A-2B**, the 2M24 anti-Dectin-1 antibody coupled to polystyrene beads promoted phagocytosis in both HEK-Blue hDectin-1a cells and human primary monocytes.

[0188] From the mIgG1 2M24 clone, a fully human 2M24 antibody of the IgG4 isotype was developed. This antibody has human constant and variable regions. The functionality of the

hIgG4 2M24 was then assessed for binding to two Dectin-1 expressing cell types, HEK-Blue hDectin-1a cells and human monocytes. As shown in **FIGs. 3A-3B**, the fully human 2M24 showed high affinity binding to Dectin-1 in transfected HEK cells (EC50 = 1.6 nM) and human monocytes (EC50 = 0.7 nM).

[0189] Next, the hIgG4 2M24 antibody was tested for its ability to promote phagocytosis of beads in Dectin-1 expressing cells. As shown in **FIG. 4**, the hIgG4 2M24 antibody exhibited efficient phagocytic ability in HEK cells overexpressing Dectin-1, human monocytes, and human macrophages. Thus, the fully human IgG4 2M24 antibody can promote phagocytosis in Dectin-1 expressing cells.

[0190] The fully human 2M24 (hIgG4) anti-Dectin-1 antibody was also tested for its ability to promote signaling through Dectin-1. Activation of Dectin-1 signaling by the antibodies can be assessed with a secreted alkaline phosphatase assay using HEK-Blue hDectin-1a cells. The HEK-Blue hDectin-1a cells have been engineered to express Dectin-1 isoform A and genes involved in the Dectin-1/NF-κB/SEAP signaling pathway and thus express a secreted alkaline phosphatase (SEAP) in response to stimulation by Dectin-1 ligands. As shown in **FIGs. 5A-5B**, the 2M24 (hIgG4) anti-Dectin-1 antibody induced alkaline phosphatase secretion in HEK-Blue hDectin-1a cells both in immobilized form and conjugated to beads. These observations support the idea that the 2M24 (hIgG4) antibody promotes SEAP secretion by engaging Dectin-1 on the surface of the cells, indicating clustering of the receptor and an agonistic activity by this antibody. Moreover, efficient clustering signaling of Dectin-1 can be promoted by beads conjugated to 2M24 (hIgG4). Signaling was better induced with bigger beads, reflecting better clustering of the receptor. This supports that clustering of Dectin-1 promoted by a bispecific antibody comprising the anti-Dectin-1 antibody, which targets a phagocyte, and an antibody targeting another cell, such as a cancer cell, could promote clustering and signaling by Dectin-1 on the phagocyte.

[0191] Natural ligands of Dectin-1 cluster the receptor and signal downstream of Dectin-1/Syk/NFkB to induce inflammatory gene expression. To assess if engagement of Dectin-1 antibody in solution can trigger cytokine secretion, monocytes or macrophages were treated with 10 ug/ml of a commercial anti-Dectin-1 antibody. As shown in **FIGs. 6A-6B**, the 15E2 commercial anti-Dectin-1 antibody did not induce cytokine secretion in primary human macrophages and monocytes, indicating that there was insufficient clustering of the Dectin-1 receptor. This data supports that free Dectin-1 antibody in solution does not induce immunostimulation, due to lack of sufficient Dectin-1 clustering.

[0192] To assess if cytokine secretion could be induced by the 2M24 (hIgG4) anti-Dectin-1 antibody, the antibody was immobilized on beads and cultured with monocytes or PBMCs. As

shown in **FIGs. 7A-7B**, the 2M24 anti-Dectin-1 antibody induced cytokine secretion in primary human monocytes and PBMCs. The 2M24 antibody not only promoted cytokine secretion, but also exhibited superior immunostimulation as compared to that promoted by the 15E2 anti-Dectin-1 agonistic antibody. Of the cytokines measured in this experiment, TNFa and IL6 are secreted by monocytes that express Dectin-1. In contrast, IFNg is mainly secreted by T-cells that exist in PBMCs. Because T-cells do not express Dectin-1, they are not activated directly by the anti-Dectin-1 antibodies, but rather from cytokines secreted by the monocytes in the PBMCs that are stimulated by the Dectin-1 antibodies. The differential effect of Dectin-1 antibodies on IFNg was therefore more prominent in PBMCs than in pure monocytes.

[0193] Finally, the activation of Dectin-1 by natural ligands in the presence of anti-Dectin-1 antibody was tested. HEK-Blue hDectin-1a cells were incubated in a 1/3 serial dose titration of 2M24 (hIgG4) Dectin-1 antibody or the 15E2, 259931, GE2 anti-Dectin-1 commercial antibodies starting at 300 nM in the presence of 8 ug/ml of biotinylated laminarin. As shown in **FIG. 8**, binding of the 2M24 (hIgG4) antibody to Dectin-1 did not block the binding of laminarin, a natural ligand of Dectin-1. Thus, engaging Dectin-1 with the 2M24 anti-Dectin-1 antibody does not block clearance of pathogens and is unlikely to increase susceptibility to potential fungal infections.

[0194] In conclusion, the 2M24 anti-Dectin-1 antibody can induce phagocytosis by Dectin-1 expressing cells and can induce activation of Dectin-1 signaling without competing with the natural ligands for Dectin-1. The properties of the 2M24 and 15E2 antibodies are summarized in **FIG. 9**.

Example 2: Bispecific anti-Dectin-1 antibodies

[0195] This example describes the generation and characterization of bispecific antibodies comprising a Dectin-1-binding arm and a second arm that binds specific tumor antigens.

Materials and Methods

Generation of bispecifics

[0196] Antibodies were differentially labeled with MTA or FOL reagent following manufacturer's guidelines (AAT Bioquest). Labeled antibodies were mixed and incubated to allow for covalent assembly via MTA and FOL interaction. The following antibodies were used for bioin: streptavidin-induced bispecific antibodies:

Anti-Dectin-1 15E2 antibody heavy chain: mSA fusion

QWQLQQSGAELARPGASWKMSCKASGYTFTTYTMHWWKQRPGQGLEWIGYINPSSGY
TNYNQKFKDKATLTADKSSSTASMQLSSLTSEDSAWYYCARERAVLVPYAMDYWGQG
TSVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVGGGSGGGSGGGSEFA
SAEAGITGTWYNQHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLE
WRVEWNNSTENCHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFTKVK
PSAASGSAAAGASHHHHHH (SEQ ID NO:18)

Anti-Dectin-1 15E2 antibody light chain
QIVLTQSPAVMSASPGEKWTITCTASSSLSYMHWFQQKPGTSPKLWLYSTSILASGVPTR
FSGSGSGTSYSLTISRMEAEDAATYYCQQRSSSPFTFGSGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS
KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:19)

Avi-tagged anti-CD20 Fab heavy chain (CH1 domain based on hIgG4 sequence)
QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD
TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG
TTVTVSAASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVAAAGASHHHHHHG
SGLNDIFEAQKIEWHE (SEQ ID NO:20)

Anti-CD20 Fab light chain
QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF
SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS
KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:21)

Avi-tagged anti-HER2 Fab heavy chain (CH1 domain based on hIgG4 sequence)
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR
YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTL
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVAAAGASHHHHHHGSG
LNDIFEAQKIEWHE (SEQ ID NO:22)

Anti-HER2 Fab light chain
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPS
RFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:23)

Cell coupling assay

[0197] Dectin-1-expressing cells were labelled with calcein green, and target cells were labelled with calcein reds. The cells were incubated in the presence of a bispecific or an isotype control antibody, then analyzed by flow cytometry. Coupling of the cells was indicated by a double positive signal (green+red+). Coupling efficiency was quantified as the percentage of total target cells that forms doublets with Dectin-1-expressing cells.

[0198] Five million effector (Dectin-1 expressing cells) or target cells (cells expressing the target of interest, *e.g.*, CD20 positive Raji cells or HER2 positive SKBR3 cells) were differentially labeled with either calcein green (0.5nM) or calcein red/pHrodo-red (0.5 nM). Cells were thoroughly washed with PBS and kept on ice. Effector and target cells were then co-cultured at a 3:1 ratio (effector: target) in the presence of 2M24 bispecific antibody or isotype control and incubated for 30 minutes at 37°C. Following incubation, samples were gently resuspended and analyzed by flow cytometry. PMT voltages were adjusted accordingly, and cells were gated based on FITC and/or PE fluorescence corresponding to calcein green or red fluorescence. Coupling efficiency is reported as the number of PE-positive cells (target cells) in the doublet population, divided by the total number of PE-positive target cells in the reaction.

SEAP reporter assay in HEK cells overexpressing Dectin-1 with anti Dectin-1 antibodies

[0199] To determine HEK cell SEAP secretion induced by Raji cells (expressing CD20), Raji cells were coated with a 2M24/anti-hCD20 or a hIgG4 /anti-CD20 bispecific for 30 minutes on ice, followed by washing twice with PBS to remove the unbound bispecific. The bispecific-coated Raji cells were mixed with $1x10^5$ HEK Blue hDectin-1-a cells at a ratio of 1:2 (HEK cells Raji cells) in RPM1 with 10% ultra-low IgG FBS. After 22 hours, alkaline phosphatase secretion in the supernatant was evaluated at OD 630 nm as described in Example 2.

Results

[0200] Dectin-1 agonist bispecific antibodies can exploit various modes of activity (e.g., immune activation, phagocytosis, neoantigen presentation and adaptive immunity activation) for

the targeted depletion of cancer cells (**FIGs. 11A-11B**). As a proof-of-concept to engage a Dectin-1 antibody (15E2 or 2M24) and a target antibody, a click-chemistry approach was used to develop bispecifics comprising an anti-Dectin-1-targeting arm and a second arm targeting a protein of interest. This approach enabled the generation of bispecifics for various assays. A schematic of this approach is shown in **FIGs. 10A-10B**. As binding of Dectin-1 by Dectin-1-specific antibodies can induce phagocytosis of targets (see Example 1 and Example 2), the bispecific antibodies were evaluated for their ability to promote phagocytosis of specific target cells. First, the bispecifics were evaluated for their ability to eliminate CD70-expressing cancer cells by phagocytosis. CD70 is a type II transmembrane glycoprotein that belongs to the tumor necrosis factor (TNF) superfamily. CD70 is expressed at low levels in normal tissues, but is highly overexpressed in various diseases, including acute myeloid leukemia (AML), renal cell carcinoma, rheumatoid arthritis and lupus.

[0201] Using click chemistry, a bispecific molecule comprising a Dectin-1-targeting arm (anti-Dectin-1; clone 2M24) and a CD70-targeting arm (anti-hCD70; clone 113-16) was generated. The purity of the bispecific (2M24/anti-hCD70) antibody was assessed by SDS-PAGE analysis (**FIG. 12A**), while binding was assessed by flow cytometry analysis (**FIG. 12B**). As shown in **FIG. 12B**, binding studies on cells revealed that 2M24/anti-hCD70 bound to the HEK293 cell line expressing Dectin-1 with an EC50 of 1.8 nM and bound to CD70-positive renal carcinoma cell lines with an EC50 of 12.34 nM (A498 cells) or 11.62 nM (786-0 cells). The bispecific was then evaluated for its ability to induce cell coupling. As shown in **FIG. 13**, the 2M24/anti-hCD70 bispecific induced coupling of Dectin-1-expressing HEK293 cells and CD70-expressing renal carcinoma cells, resulting in cell doublets of HEK293 cells (labeled with calcein green) and A498 cells (labeled with calcein red).

[0202] Next, targeting of CD20-expressing cells with a bispecific was evaluated. CD20 is a transmembrane protein present on virtually all B cells from the stage at which they become committed to B-cell development until it is downregulated when they differentiate into antibody-secreting plasma cells and is considered a pan-B-cell antigenic marker. As shown in **FIGs. 14A-14B**, a 2M24/anti-hCD20 bispecific induced coupling of Dectin-1-expressing cells (both Dectin-1-expressing HEK293 cells and human M0 macrophages) with CD20-expressing B cells (Raji cell line). This cell-to-cell coupling mediated by the bispecific could induce synapse formation between effector and target cell that may alter cytokine signaling, activate phagocytosis and ultimately target antigen presentation.

[0203] To test for induction of signaling resulting from stimulation with bispecific antibodies that bind Dectin-1, a secreted alkaline phosphatase assay was performed. As shown in **FIG. 15**,

Raji cells coated with an anti-Dectin-1/anti-CD20 bispecific induced alkaline phosphatase secretion in HEK-Blue hDectin-1a cells. Thus, using a bispecific antibody to connect a target cell with a cell expressing Dectin-1 (such as phagocyte) can promote signaling by the Dectin-1 expressing cell. In the case of phagocytes, signaling may result in the production of cytokines and immunostimulation.

[0204] Previously, it was demonstrated that Dectin-1 expression in HEK 293 cells is necessary and sufficient to induce phagocytosis of various size beads coated with anti-Dectin-1 targeting antibody (see Example 1 and Example 2). To demonstrate phagocytosis of live target cells, a bispecific comprising an Dectin-1-targeting arm and a CD20-targeting arm was developed. In a co-culture assay of HEK 293 cells and CD20-expressing Raji cells, phagocytosis in cells treated with anti-Dectin-1/anti-hCD20 bispecific was observed, in contrast to isotype control bispecifics (**FIG. 16**). Furthermore, pre-incubation of cells with Latrunculin A, an inhibitor of phagocytosis that blocks actin polymerization, blocked phagocytosis of cells treated with anti-Dectin-1/anti-hCD20 bispecific. These findings indicate that Dectin-1 expression is sufficient to induce phagocytosis, and that co-targeting Dectin-1 and a target of interest with an Dectin-1-agonistic bispecific is sufficient to induce phagocytosis of a target cell.

[0205] A proof-of-concept experiment was performed for co-targeting Dectin-1-expressing cells and HER2-positive breast cancer cells using an anti-Dectin-1/anti-HER2 bispecific antibody. Approximately 20% to 25% of invasive breast cancers exhibit overexpression of the human epidermal growth factor receptor HER2 tyrosine kinase receptor. As shown in **FIG. 17**, anti-Dectin-1 (15E2)/anti-HER2 bispecific induced coupling of Dectin-1- and HER2-expressing cells. This interaction is thought to promote synapse formation between effector and target cells, as Dectin-1 clustering induces cytokine secretion by effector cells, triggers phagocytosis of target cells, and leads to neo-antigen presentation and activation of adaptive immune cells (B and T cells).

[0206] Finally, an anti-Dectin-1 (2M24)/anti-hCD94 bispecific was also evaluated. Large granular lymphocyte (LGL) leukemia is a rare chronic lymphoproliferative disease of T cell and natural killer (NK) cell lineage. CD94/NKG2 is a family of C-type lectin receptors which are expressed predominantly on the surface of NK cells and a subset of CD8+ T-lymphocytes. As shown in **FIG. 18**, an anti-Dectin-1 (2M24)/anti-hCD94 bispecific induced coupling of Dectin-1-expressing cells and CD94-expressing cells. Thus, bispecific antibodies that bind Dectin-1 can mediate coupling of Dectin-1-expressing cells with a variety of target cells.

Example 3: Generation of bispecific anti-Dectin-1 antibodies using streptavidin-biotin.

[0207] This example describes the biochemical and functional characterization of bispecific antibodies that bind Dectin-1 generated using streptavidin-biotin conjugation.

Materials and Methods

Generation of bispecifics

[0208] mSA was genetically fused to either Fab 2M24 or full length 2M24. Chimeric fusions were incubated with biotinylated target antibodies to generate a bispecific comprising a Dectin-1-binding arm and a second arm binding a target receptor or protein of interest.

Full-length 2M24 sequence fused to mSA:

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSEFASAEAGITGTWYN
QHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLEWRVEWNNSTEN
CHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFTKVKPSAASGS (SEQ ID NO:15)

Fab 2M24 sequence fused to mSA:

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVGGGSGGGSGGGSEFASAEA
GITGTWYNQHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLEWRV
EWNNSTENCHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFTKVKPSA
ASGSAAAGASHHHHHH (SEQ ID NO:17)

Antibody-dependent targeted phagocytosis of Phrodo-labeled beads

[0209] Antibody-dependent targeted phagocytosis of Phrodo-labeled beads was performed as described in Example 2. To monitor phagocytosis by flow cytometry, HEK cells overexpressing Dectin-1 were incubated with biotin beads conjugated to Fab 2M24-mSA for 30 minutes on ice

or at 37 °C for 30 minutes, followed by washing with PBS twice. Phagocytosis was assessed by detecting activated Phrodo red within the HEK cell/beads duplet population by flow cytometry in the PE channel using a CytoFlex flow cytometer (Beckman Coulter, Atlanta, GA).

Results

[0210] To enable the efficient generation of bispecific antibodies, a novel strategy was developed which utilizes the high affinity interaction of streptavidin and biotin. A monomeric streptavidin (mSA) construct was fused to the Fc-domain of 2M24, or CH1 domain of Fab 2M24. The recombinant fusion proteins were incubated with various biotinylated antibodies of interest to assemble the bispecifics. A schematic of this strategy is shown in **FIGs. 19A-19B**.

[0211] This fusion technology enables the high-throughput generation and screening of bispecific antibodies. To test this approach, a Fab 2M24-mSA fusion protein was generated and purified. As shown in **FIGs. 20A-20C**, the Fab 2M24-mSA fusion showed high affinity binding (EC50 = 1.45 nM) to Dectin-1 expressing cells. This Fab 2M24-mSA fusion protein can be combined with various biotinylated antibodies against targets of interests. Moreover, the Fab 2M24-mSA fusion also induced binding and phagocytosis of beads by Dectin-1-expressing HEK 293 cells (**FIGs. 21A-21B**), indicating that the Fab version of the 2M24 antibody can efficiently promote phagocytosis in cells expressing Dectin-1.

[0212] Using the anti-Dectin-1-streptavidin fusion, bispecifics against various targets (e.g., CD20, CD19, CD70, amyloid B (1-42)) were developed. As shown in **FIGs. 22A-22D**, these bispecifics showed high homogeneity based on HPLC analysis. These data demonstrate robust feasibility of this technology for bispecific antibody generation.

[0213] Next, the anti-Dectin-1 bispecifics generated using the Fab 2M24-mSA fusion protein were evaluated for their ability to induce cell coupling. As shown in **FIG. 23**, the Fab 2M24-mSA/biotin anti-hCD20 bispecific induced coupling of Dectin-1-expressing HEK293 cells and CD20-expressing B cells (Raji cell line). This interaction can promote Dectin-1 clustering, which induces cytokine secretion by effector cells, triggers phagocytosis of target cells, and leads to neo-antigen presentation and activation of adaptive immune cells (B and T-cells).

Example 4: Targeted phagocytosis of amyloid deposits using anti-Dectin-1 bispecific antibodies

[0214] This example describes the use of bispecific antibodies that bind Dectin-1 in the targeted delivery of pathogen antigens to phagocytic cells.

[0215] Dectin-1-induced targeted phagocytosis can be used to mediate amyloid clearance by antigen presenting (e.g., monocytes, macrophages, dendritic cells, and neutrophils), and maximize depletion of circulating amyloid precursors (free light chains) and deposited amyloid fibrils. The targeted phagocytosis relies on the bispecific antibody targeting of Dectin-1 (by 2M24) and AL amyloids (by an amyloid-reactive antibody or serum amyloid protein P antibody).

[0216] To test this approach, recruitment or presence of antigen presenting cells to sites of amyloid deposits is first demonstrated. Immune cell populations in freshly isolated, amyloid-laden tissues from AL amyloidosis patients are phenotyped. Frequency of antigen presenting cells (*e.g.*, macrophages, monocytes, neutrophils, and dendritic cells) is determined. Dectin-1 expression on APCs in AL amyloidosis patient tissues is assessed.

[0217] Then, bispecific antibodies comprising a Dectin-1 binding arm (*e.g.*, clone 2M24) and amyloid-binding arm (based on external antibodies) are developed. For proof-of-concept studies, phagocytosis of AL amyloid fibrils by circulating monocytes, monocyte-derived macrophages (*in vitro* differentiated) or patient-derived macrophages (*in situ*) is demonstrated with Dectin-1 bispecific antibodies prepared with external antibodies (**FIG. 24**). An antibody discovery campaign to identify high affinity binders to amyloid fibrils or amyloid precursors is initiated, from which the resulting antibodies are used to further develop Dectin-1 bispecific antibodies to target amyloid deposits.

Example 5: Targeted phagocytosis of mast cells using anti-Dectin-1 bispecific antibodies

[0218] This example describes the use of bispecific antibodies that bind Dectin-1 in the targeted delivery of pathogen antigens to phagocytic cells.

Materials and Methods

Bead phagocytosis assay

[0219] Large (~ 16.5 μm) polystyrene anti-mouse Fc IgG beads were labeled with a pH-sensitive fluorescent dye (pHrodo red) and conjugated with an anti-Dectin-1 antibody or isotype control. For the phagocytosis assay, the beads were incubated with cultured dendritic cells at a ratio of 1:3 (cells: beads). Bead phagocytosis was monitored by IncuCyte live cell imaging. Phagocytosis was quantified using the IncuCyte analysis software and expressed as total integrated intensity (total sum fluorescent intensity) of red objects (pHrodo fluorescense) in the image.

[0220] Mastocytosis is characterized by a pathological accumulation of mast cells in one or more organs. Given the tissue-resident nature of mast cells, and difficulty in accessing these cells therapeutically, tissue-resident macrophages can be engaged and enlisted to deplete and reduce pathological levels of mast cells. As described in Example 1, engagement of Dectin-1 can promote phagocytosis of particles with similar size to cells, including mast cells. Thus, for the targeted depletion of mast cells, the Dectin-1 induced targeted phagocytosis platform can be applied.

[0221] First, bispecific antibodies with a macrophage-targeting arm (via Dectin-1 binding) and a mast cell-targeting arm (via mast cell surface antigen) are developed, as depicted in **FIG. 25A**. Potential mast cell surface antigens/receptors that can be used as lead candidates for bispecific development are summarized in **FIG. 25B**. These bispecific antibodies are then evaluated for their ability to bind and target mast cells for phagocytosis by Dectin-1 expressing cells and deplete patient mast cells *in situ*. Phagocytosis of in vitro-differentiated mast cells or mast cell lines by monocyte-derived macrophages (in vitro differentiated) or patient-derived macrophages (in situ) is demonstrated using Dectin-1 bispecific antibodies.

[0222] The presence or recruitment of antigen presenting cells (*e.g.*, macrophages, monocytes, neutrophils, and dendritic cells) is demonstrated in patient tissues/organs with high number of mast cells. Immune cell populations are phenotyped in fresh tissues isolated from mastocytosis patients. Dectin-1 expression is assessed on APCs. Binding of external antibodies is assessed on donor mast cells.

[0223] Given the large size of mast cells, we assessed if Dectin-1 can promote phagocytosis of large entities by conjugating anti-Dectin-1 antibody to large beads (~16.5um), which are similar in size to large cells. Since macrophages are large phagocytic cells and can ingest large targets, the phagocytosis assay for large beads was performed using macrophages differentiated from monocytes in the presence of MCSF for 6 days. As shown in **FIG. 26**, anti-Dectin-1 antibody promoted the directed phagocytosis of large beads in cultured human macrophages. Anti-Dectin-1-conjugated beads were more readily engulfed by the macrophages compared to isotype control-conjugated beads. These data support that targeting Dectin-1 enables targeting of large cells, such as mast cells (size: 16-20μm), for phagocytosis.

Example 6: Targeted depletion of microbes using anti-Dectin-1 bispecific antibodies

[0224] This example describes the use of bispecific antibodies that bind Dectin-1 in the targeted phagocytosis of microbes.

Materials and Methods

Binding to H3N2 flu virus by ELISA

[0225] To assess the binding of the anti-Dectin-1/a-hemagglutinin bispecific antibody to the H3N2 flu virus, H3N2 flu particles at 2.5, 5, and 10ug/mL were coated overnight on high binding 96-well plates. The plates were washed twice with PBS, blocked with 3% BSA in PBS/Tween-20 0.05% for 1 hour at RT, followed by more washes with PBS/Tween-20 0.05%. Primary antibodies, including anti-Dectin-1 (15E2), anti-hemagglutinin (12CA5), anti-Dectin-1/anti-hemagglutinin bispecific, and isotype controls were incubated at 20nM for 1 hour at RT. The plates were then washed with PBS/Tween-20 0.05% twice, and a secondary anti-mouse Fcg: HRP at 1:5000 was incubated for 1 hour at RT. Finally, the plates were washed, incubated with TMB substrate for 30 minutes, and the reaction was stopped with 2N H_2SO_4. The plates were read at 450nm on a plate reader.

[0226] Innate immune cells play a vital role in recognition and elimination of microbial pathogens. To aid phagocytes in attacking bacteria, viruses, or fungal pathogens, a bispecific comprising a Dectin-1-targeting arm which binds antigen presenting cells (macrophages, monocytes, dendritic cells, and neutrophils) and a second arm targeting an antigen expressed on the surface of pathogens can be used for Dectin-1-induced targeted depletion **(FIG. 27).** The targeted phagocytosis of pathogens enables effector cells to efficiently recognize a target pathogen and secrete cytokines and proteases that can directly kill the bound pathogen Furthermore, the bispecific antibody can mediate Dectin-1 clustering, induced targeted-phagocytosis of the bound target. Finally, following degradation of the target, target antigens are presented and modulates the adaptive immune response which further enables the host organism to fight off the pathogen.

[0227] As a proof-of-principle, high affinity antibodies against pathogen-specific surface antigens of interest are identified and used to generate bispecific antibodies comprising a Dectin-1-binding arm (anti-Dectin-1 antibody 2M24) and a pathogen-targeting arm. The anti-Dectin-1/anti-pathogen bispecific antibodies are tested for target binding, cytokine secretion by phagocytes following target engagement, target phagocytosis and degradation of the pathogen, and target antigen presentation. Moreover, high affinity antibodies are developed to validate the pathogen targets and are used to subsequently develop Dectin-1 bispecific antibodies from lead candidates.

[0228] To test for the targeted delivery of pathogen to phagocytic cells antigens, a bispecific antibody with a Dectin-1-binding arm and a second arm that binds Hematogglutinin from influenza H3N2 virus was generated. The anti-Dectin-1/anti-Hemagglutinin bispecific antibody

was then tested for binding using both ELISA and flow cytometry. As shown in **FIGs. 28A-28B**, the anti-Dectin-1/anti-Hemagglutinin bispecific antibody bound efficiently to both the H3N2 flu virus and to HEK cells expressing Dectin-1. This antibody format could be used to target the flu virus or an antigen of the flu virus to antigen presenting cells (*e.g.*, dendritic cells, macrophages).

Example 7: Targeted delivery of antigens for vaccine development

[0229] This example describes the targeted delivery of viral antigens to phagocytic cells.

Materials and Methods

Bead phagocytosis assay

[0230] Small (~ 3.4 μm) polystyrene anti-mouse Fc IgG beads were labeled with a pH-sensitive fluorescent dye (pHrodo red) and conjugated with an anti-Dectin-1 antibody or isotype control. For the phagocytosis assay, the beads were incubated with cultured dendritic cells at a ratio of 1:3 (cells: beads). Bead phagocytosis was monitored by IncuCyte live cell imaging. Phagocytosis was quantified using the IncuCyte analysis software and expressed as total integrated intensity (total sum fluorescent intensity) of red objects (pHrodo fluorescense) in the image.

Labelling of polysterene beads with pHrodo and conjugation to antibodies

[0231] Labelling of polysterene beads with pHrodo and conjugation to antibodies was performed as described earlier.

[0232] To coat polystyrene beads with the SARS-Cov-2 spike protein S1, goat anti Rabbit IgG (Fc) beads (Spherotech) were labeled with pHrodo Red and conjugated to a rabbit anti-Flag antibody (Cell Signaling) as described above. Flag-tagged Spike protein (Genscript) was then coupled to pHrodo/anti-Flag beads, and unbound Spike protein was washed off with PBS.

Antibody-dependent targeted phagocytosis of Phrodo labeled beads

[0233] For phagocytosis of SARS-CoV-2 spike protein coated beads, the beads were pre-incubated with anti-Dectin-1/anti-SARS-CoV-2 spike protein bispecific (anti-SARS-CoV-2 spike protein antibody was purchase from Genscript) for 60 minutes in RT and unbound antibody was washed off. The beads were then mixed with HEK cells.

Results

[0234] Dendritic cells are specialized antigen-presenting cells. Targeting an antigen expressed on a disease-causing agent (cancer cell, pathogen, or protein-aggregate) or the agent itself to

dendritic cells through Dectin-1 can potentially elicit a protective immune response directed against the antigen and the disease-causing agent from which it was derived. This response will involve T cell activation and expansion, cytokine secretion and B cell activation. Thus, a Dectin-1 antibody-targeted vaccine could be designed to deliver antigens to dendritic cells and promote the recognition and elimination the disease-causing agent (e.g., cancer cells or pathogen). Target antigen could be fused to an anti-Dectin-1 antibody for delivery to APCs (**FIG. 29A**), or anti-Dectin-1 bispecific antibody could be used to target delivery of a disease-causing agent to APCs (**FIG. 29B**).

[0235] To determine if phagocytosis in human dendritic cells can be promoted by antibody engagement of Dectin-1, purified monocytes (CD14+) from human PBMC were differentiated to Dendritic cells in the presence of IL4/GMCSF. After 6 days the dendritic cells were incubated with pHrodo-labeled polystyrene beads conjugated with the 15E2 anti-Dectin-1 antibody or an isotype control. As shown in **FIG. 30**, anti-Dectin-1 antibodies promoted directed phagocytosis of beads in cultured monocyte-derived dendritic cells. Significantly more phagocytosis of anti-Dectin-1-conjugated beads than of isotype-conjugated beads was observed, as evidenced by the bright red phrodo particles within the cells. Dendritic cells are specialized antigen-presenting cells. Targeting an antigen on a disease-causing agent (*e.g.*, a cancer cell, pathogen, or protein aggregate), or the agent itself, to dendritic cells through Dectin-1 can potentially elicit a protective immune response directed against the antigen and the disease-causing agent from which it was derived. This response can involve T cell activation and expansion, cytokine secretion, and B cell activation. Therefore, a Dectin-1 antibody-targeted vaccine can be designed to deliver antigens to dendritic cells and promote the recognition and elimination of a disease-causing agent (*e.g.*, a cancer cell or pathogen).

[0236] Targeting of a different virus, SARS-CoV-2, using Dectin-1 agonist bispecific antibodies was also evaluated. A bispecific antibody was generated using click chemistry to target Dectin-1 and the spike S1 protein of SARS-CoV-2. The spike protein was coated onto beads, and the beads were then engulfed in the presence of the anti-Dectin-1/anti-SARC-CoV-2 spike S1 bispecific (**FIG. 31A**). The anti-Dectin-1/anti-SARS-CoV-2 spike S1 bispecific induced coupling between Dectin-1 expressing HEK 293 cells and the spike coated beads (**FIG. 31B**), as well as promoted phagocytosis of the spike-coated beads by the Dectin-1-expressing cells (**FIG. 31C**). Based on these results, the anti-Dectin-1/anti-SARS-CoV-2 spike S1 bispecific could mediate targeted delivery of SARS-CoV-2 Spike protein to macrophages.

Conclusions

[0237] Bispecific antibody comprising a Dectin-1-binding arm and a second arm that binds an antigen from a pathogen, such as influenza virus or SARS-CoV-2 as described in this example, can promote engulfment of the target pathogen, and presentation of the antigens followed by activation and expansion of T cells and antibody production by B cells. The adaptive immune response can promote elimination of the virus and virus-infected cells. Dectin-1 antibody-targeted vaccine approach has the potential to work against other pathogens of bacterial or viral origin.

[0238] Various anti-Dectin-1 (*e.g.*, 2M24)/antigen-specific bispecific antibodies are developed and demonstrated to efficiently bind to APCs. Internalization of the targeted antigen from APCs is assessed. Methods to assess antigen presentation of the targeted antigen on the surface of dendritic cells are developed. Activation of CD4+ and CD8+ T cells (T cell expansion and cytokine secretion) is assessed from dendritic cells that have received antigen through Dectin-1. B cell activation and antibody production against the antigen are assessed. Mice are vaccinated, and adaptive immune response is assessed in vivo, along with protection against the disease caused by the pathogen/malignant cells.

Example 8: Bispecific design for development of a human bispecific antibody targeting Dectin-1 and a disease target or antigen

[0239] To enable the assembly and efficient production of highly purified and active bispecifics, design principles were adopted based on previously reported strategies including "knobs-into-holes" (Ridgway, 1996; patent US8679785B2), DuetMab (Mazor, 2015; patent EP3452089A2), single-step Protein A and G avidity purification methods (Ollier, 2019; AU2018204314B2), and mutations to eliminate FcR binding (patent WO 2016/081746 A2). Assembly of complete bispecific involves expression of 4 individual subunits, *e.g.*, cloned into expression vectors such as pFUSE. A diagram of an exemplary anti-Dectin-1 bispecific antibody is shown in **FIG. 32A**.

[0240] As shown in Table 1, bispecific antibodies using this design were constructed for proof-of-concept studies. These bispecific antibodies have one arm that targets hDectin-1 and a second arm that targets hCD20, hHER2, hCD70, or a protein on RSV. The bispecific antibodies described in Table 1 were generated by expressing all 4 chains and purifying to 95% purity and homogeneity. All bispecifics were found to bind their respective targets.

Table 1. Bispecific antibodies targeting human Dectin-1 and antigen expressed on cancer cells/disease targets.

Name	Target 1	Target 2
2M24/CD20 hIgG1 (fucosylated or afucosylated)	hDectin-1 (variable domain from clone 2M24)	hCD20 (variable domain based on Rituximab antibody)
2M24/HER2 hIgG1 (fucosylated or afucosylated)	hDectin-1 (variable domain from clone 2M24)	hHER2 (variable domain based on Trastuzumab antibody)
2M24/CD70 hIgG1 (fucosylated or afucosylated)	hDectin-1 (variable domain from clone 2M24)	hCD70 (variable domain based on Cusatuzumab antibody)
2M24/RSV hIgG1 (fucosylated or afucosylated)	hDectin-1 (variable domain from clone 2M24)	This bispecific is used as an isotype control antibody for POC studies. The second arm binds a protein on respiratory syncytial virus (RSV).

[0241] Variable domains for the antibody arm opposite anti-Dectin-1 in Table 1 were as follows.

CD20 VH:

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24)

CD20 VL:

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25)

HER2 VH:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTL VTVSS (SEQ ID NO:34)

HER2 VL:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (SEQ ID NO:35)

CD70 VH:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSVYYMNWVRQAPGKGLEWVSDINNEGGTT YYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCARDAGYSNHVPIFDSWGQGT LVTVSS (SEQ ID NO:38)

CD70 VL:
QAVVTQEPSLTVSPGGTVTLTCGLKSGSVTSDNFPTWYQQTPGQAPRLLIYNTNTRHSG
VPDRFSGSILGNKAALTITGAQADDEAEYFCALFISNPSVEFGGGTQLTVL (SEQ ID NO:39)
RSV VH:
QVTLRESGPALVKPTQTLTLTCTFSGFSLSTSGMSVGWIRQPPGKALEWLADIWWDDKK
DYNPSLKSRLTISKDTSANQVVLKVTNMDPADTATYYCARSMITNWYFDVWGAGTTVT
VSS (SEQ ID NO:36)
RSV VL:
DIQMTQSPSTLSASVGDRVTITCKCQLSVGYMHWYQQKPGKAPKLLIYDTSKLASGVPS
RFSGSGSGTAFTLTISSLQPDDFATYYCFQGSGYPFTFGGGTKLEIK (SEQ ID NO:37).

[0242] These hDectin-1 bispecific antibodies engage 3 targets: Dectin-1 on myeloid cells, an antigen on a target cell or disease-causing agent, and Fc receptors on myeloid and NK cells, eliciting robust immune stimulation and phagocytosis (**FIG. 32B**). In particular, bispecific antibodies with a non-fucoyslated, active hIgG1 Fc domain allow the bispecific antibody to recruit myeloid cells (*e.g.*, monocytes, macrophages, and dendritic cells) and natural killer (NK) cells to eliminate disease-causing target cells, such as tumor cells expressing specific antigens. In the context of cancer, and without wishing to be bound to theory, dual engagement of Dectin-1 and Fcγ receptors on myeloid and NK cells is thought to elicit a strong immune response that ultimately eliminates cancer cells via the following actions: (1) bispecific antibody-induced cross-linking of Dectin-1 and Fcγ receptors leads to ITAM-dependent activation of downstream inflammatory pathways and release of immuno-modulatory cytokines and cytotoxic proteins (proteases, perforin) which modulates the tumor microenvironment and may directly kill targeted cells; (2) bispecific antibody-induced clustering of Dectin-1 and Fcγ receptors triggers phagocytosis and elimination of targeted cancer cells by monocytes, macrophages and dendritic cells; and (3) phagocytosed antigens are presented by macrophages and DCs, a process that triggers a T cell immune response aimed at eliminating cancer cells.

[0243] The 2M24/CD20 and 2M24/RSV bispecific antibodies described in Table 1 were tested for binding to cells expressing human Dectin-1 or CD20. 2M24/RSV was used in all assays as an isotype control for the target binding arm. The bispecific variants tested here contained mutations in the hIgG1 Fc domain (hIgG1 inert) that eliminate Fc binding to Fc receptors (L234A, L235E, and G237A, according to EU numbering). Binding of 2M24/CD20 or 2M24/RSV bispecific to HEK293 cells stably expressing human Dectin-1 was assessed by flow cytometry (**FIG. 33A**). 2M24/CD20 and 2M24/RSV hIgG1 inert bispecific antibodies were able to bind cells expressing

human Dectin-1 with similar affinities (cell-based binding EC50 values of 1.4 and 1.7 nM, respectively). Thus, 2M24/CD20 or 2M24/RSV bispecific antibodies displayed high affinity binding to Dectin-1-expressing HEK293 cells.

[0244] Binding of Rituximab, 2M24/CD20, or 2M24/RSV hIgG1 active or inert bispecific antibodies was also assessed using the CD20-expressing B cell lymphoma Raji cell line (**FIG. 33B**). 2M24/CD20 bispecific (active or inert hIgG1 isotypes) antibodies were able to bind to CD20-expressing Raji cells, but with at least 10-fold reduced affinity compared to Rituximab. Without wishing to be bound to theory, it is thought that the difference in CD20 binding affinity between 2M24/CD20 bispecific and Rituximab is likely mediated by the loss of avidity (monovalent versus bivalent binding) in the bispecific antibody.

[0245] Next, the ability of 2M24/CD20 bispecific antibody to induce coupling of cells expressing hDectin-1 and cells expressing hCD20 was assayed. Dectin-1-expressing HEK293 cells (effector) and CD20-expressing Raji cells (target) were differentially labeled with calcein green (effector) or calcein red (target) dyes. Labeled cells were co-cultured and treated with hIgG1 inert 2M24/CD20 or 2M24/RSV (control) bispecific antibody to induce effector: target coupling. Successful coupling of effector: target cells was indicated by the double-positive staining (Calcein green+, calcein red+, square box; **FIG. 34A**). Coupling efficiency (quantified as the percentage of total target cells that binds or couples to effector cells) was assayed using dose titration of bispecific antibody in co-cultures of effector: target cells (**FIG. 34B**).

[0246] These results indicate that 2M24/CD20 bispecific antibody can couple Dectin-1-expressing 'effector' cells and CD20-expressing 'target' cells with a potent EC50 of 0.17 nM. Despite the low affinity binding of 2M24/CD20 bispecific to CD20 on Raji cells (**FIG. 33B**), the 2M24/CD20 was highly efficient at coupling. These findings suggest that 2M24/CD20 binding affinity is enhanced by the high expression of Dectin-1 or CD20 on both effector and target cells (avidity), thereby promoting efficient coupling of the two cells. Based on these findings, it is thought that 2M24/CD20 bispecific antibody could effectively engage Dectin-1-expressing monocytes, macrophages or dendritic cells with target disease cells, such as B cell lymphoma, which express high levels of CD20. Effector: target engagement is the first step in the MOA of 2M24 bispecific antibodies.

[0247] Human IgG1 active isotype binds Fcγ receptors on NK cells or monocytes. Therefore, it was assessed whether the hIgG1 active isotype of 2M24/CD20 can trigger monocyte killing by NK cells (via antibody dependent-cellular cytotoxicity, ADCC) or other monocytes (Fratricide or antibody-dependent cellular phagocytosis, ADCP). In this scenario, the active hIgG1 domain of 2M24/CD20 engages the Fcγ receptors on NK cells or monocytes, and Dectin-1 receptor on

monocytes, thereby inducing Fcγ-mediated activation and depletion of target. PBMCs from two healthy donors – donor 76 (**FIG. 35A**) and donor 77 (**FIG. 35B**) were treated with increasing concentrations of 2M24/CD20 bispecifics (hIgG1 active or inert isotypes) and rituximab for 24 h, and subsequently analyzed by flow cytometry to quantify the levels of live, CD14+ monocytes remaining (as a % of isotype controls). No decrease in the number of monocytes was found in either donor, indicating that 2M24/CD20 active IgG1 did not induce monocyte depletion. Without wishing to be bound to theory, it is thought that 2M24/CD20 hIgG1 (active isotype) should not affect the levels of monocytes and thus poses minimal risk of infection.

[0248] Based on the proposed MOA of 2M24/CD20 bispecific antibody (described in **FIG. 32B**), B cell depletion by 2M24/CD20 hIgG1 (active isotype) bispecific antibody or Rituximab was assessed in order to compare B cell depletion. PBMCs from two healthy donors – donors 83 (**FIG. 36A**) and 84 (**FIG. 36B**) – were treated with increasing concentrations of the indicated antibodies for 24 hours, and subsequently analyzed by flow cytometry to quantify the levels of remaining live, CD19+ B cells (reported as a % of B cells in isotype control-treated PBMCs). Thus, in two healthy donors, high concentrations of 2M24/CD20 bispecific antibody induced superior B cell depletion (~80% reduction) compared to Rituximab (~40% reduction), despite the bivalent binding nature of Rituximab and ~10-fold difference in binding affinity (as shown in **FIG. 33B**). The unique mechanism of action of 2M24/CD20 active IgG1, which involves binding to Dectin-1 on myeloid cells, Fcγ receptors on NK cells and monocytes, and CD20 on target B cells (**FIG. 32B**), leads to an overall superior depletion of B cells compared to Rituximab. These data support the concept that Dectin-1 induced immune stimulation via 2M24/CD20 bispecific enhances depletion of the target cells.

[0249] Ability of 2M24/CD20 hIgG1 (active isotype) bispecific antibody or Rituximab (hIgG1) to downregulate CD19 expression on B cells in a process known as shaving or trogocytosis was assessed. Expression of CD19+ on B cells from two healthy donors – donor 83 (**FIG. 37A**) and donor 84 (**FIG. 37B**) – was quantified by flow cytometry following a 24-hour incubation with increasing concentration of 2M24/CD20 hIgG1 (active isotype) bispecific antibody, Rituximab, or isotype controls. The mean fluorescent intensity (MFI) for CD19 staining using anti-CD19 (BV605 conjugated) was used to evaluate the effect of 2M24/CD20 bispecific and Rituximab on CD19 expression on B cells. In PBMCs from donor 83, the EC50 with respect to CD19 expression was 0.014nM for rituximab and 0.080nM for 2M24/CD20 hIgG1 bispecific (**FIG. 37A**). In PBMCs from donor 84, the EC50 with respect to CD19 expression was 0.013nM for rituximab and 0.090nM for 2M24/CD20 hIgG1 bispecific (**FIG. 37B**). Both 2M24/CD20 active IgG1 bispecific Ab and Rituximab led to downregulation of CD19 expression on B cells.

Interestingly, Rituximab demonstrated at least five-fold more potent shaving compared to 2M24/CD20 bispecific Ab. Downregulation of target CD20 on B cells was previously reported as a mechanism by which malignant B cells escape Rituximab-mediated depletion (Beum, P.V. *et al.* (2006) *J. Immunol.* 176:2600-2609). These findings therefore suggest that 2M24/CD20 active IgG1 bispecific may be superior in depleting B-cells as compared to Rituximab due to reduced shaving potential.

[0250] Immune stimulation triggered by 2M24/CD20 active IgG1 bispecific antibody led to secretion of a unique repertoire of cytokines compared to Rituximab (**FIG. 38**). ELISA-based (mesoscale discovery) quantification of cytokines was undertaken in supernatants isolated from healthy donor PBMCs treated with 2M24/CD20 active hIgG1 bispecific, Rituximab, or isotype controls. PBMCs were stimulated with antibodies overnight, and supernatants were subsequently analyzed by MSD. Cytokines tested were IFNγ, IL-12p70, IL-6, TNFα, IL-1β, IL-4, IL-13, IL-10, and IL-8. The results indicated that 2M24/CD20 active IgG1 triggered higher level and distinct cytokine activation in PBMCs compared to Rituximab. Furthermore, engagement of Dectin-1 and Fc receptor alone by the 2M24/RSV bispecific does not induce cytokine release, excluding the possibility of systemic cytokine activation. These findings highlight a unique MOA that distinguishes 2M24/CD20 active IgG1 bispecific antibody from Rituximab. Without wishing to be bound to theory, these findings further indicate that 2M24/CD20 could trigger release of Th1 and Th2-type of responses and promote immune stimulation of tumor microenvironment.

[0251] 2M24/CD20 hIgG1 (active isotype) bispecific antibody was also found to induce superior B-cell depletion and lower CD19 shaving compared to Rituximab in co-cultures of human macrophages and GFP-expressing Raji B cells. Co-cultures of human macrophages and Raji-GFP cells (3:1 ratio) were analyzed by flow cytometry in the presence of 2M24/CD20 hIgG1 (active isotype) bispecific, 2M24/RSV control, fucosylated Rituximab or isotype hIgG1 control (**FIG. 39A**). Co-cultures were incubated at 37°C for 24 hours and then stained with a PE a-CD206 Ab to label macrophages and a BV-605 a-CD19 antibody to label Raji cells. The number of the remaining live/Raji-GFP+ cells was assessed in the end of the experiment. The primary antibodies were used in a serial dose titration. CD19 was assessed on Raji-GFP cells after 24 hours (**FIG. 39B**), with B-cell receptor shown as the reduction in the CD19 MFI in the presence of a-Dectin-1/a-hCD20 bispecific or Rituximab. The EC50 with respect to CD19 expression was 0.020nM for rituximab and 0.95nM for 2M24/CD20 hIgG1 bispecific. These results demonstrate enhanced B-cell depletion (Fcγ receptor mediated) by the 2M24/CD20 bispecific antibody compared to Rituximab. Rituximab reduced the B-cell receptor CD19 surface levels more potently than the a-Dectin-1/a-hCD20 bispecific antibody. Similarly, B-cell receptor

shaving has been observed for CD20 by Rituximab, and the reduction of the CD20 limits the effectiveness of Rituximab to deplete B-cell. Without wishing to be bound to theory, it is thought that these data indicate that the superiority of the 2M24/CD20 hIgG1 (active isotype) bispecific to deplete B-cells is due to the lower B-cell receptor shaving compared to Rituximab. This highlights a differential mechanism of cell depletion by 2M24/CD20 hIgG1 (active isotype) bispecific.

[0252] B-cell depletion was also analyzed in single cell suspensions from kidney cancer tissue biopsies. Single cell suspensions from two Kidney cancer tissue biopsies were analyzed by flow cytometry in the presence of 2M24/CD20 hIgG1 (active or inert) bispecific antibody, 2M24/RSV hIgG1 controls, fucosylated Rituximab, and respective isotype controls. Kidney cancer tissue biopsies were dissociated to single cell suspensions and treated with primary antibodies (2 μg/ml) for 24 hours at 37°C. Immune cell populations were analyzed by flow cytometry (**FIGS. 40A & 40B**). The number of the remaining live B cells was assessed by an anti-CD19 antibody and expressed as percentage of the CD45+ immune cell population (**FIG. 40C**). 2M24/CD20 active IgG1 bispecific antibody induced superior tissue B cell depletion as compared to Rituximab in single cell suspension of kidney cancer biopsies. The 2M24/CD20 hIgG1 (active isotype) bispecific antibody reduced B cells in the two kidney cancer donor biopsies by 44% and 46% (respectively), whereas Rituximab induced a B cell reduction of 33% and 18%, respectively (**FIG. 40C**). The data support the functionality of the 2M24/CD20 hIgG1 (active isotype) bispecific to deplete cells in cancer tissues via Dectin-1 induced immune stimulation and Fcγ receptor engagement. Without wishing to be bound to theory, it is thought that, since Dectin-1 is predominantly expressed on tumor associated macrophages (TAMs) in the above-described biopsies, 2M24/CD20 hIgG1 (active isotype) bispecific antibody may engage TAMs to enhance the target cell depletion.

[0253] Cytokine secretion by cultured macrophages and single cell suspension of kidney cancer biopsies stimulated with immobilized anti-Dectin-1 antibody (clone 2M24) or 2M24/CD20 bispecific antibody was tested. The anti-Dectin-1 antibody (clone 2M24), isotype control or the 2M24/CD20 bispecific antibody were immobilized overnight in U-bottomed polypropylene microtiter plates at 10 ug per well, followed by culture of human monocyte-derived macrophages (**FIGS. 41A & 41B**) or single cell suspension from kidney cancer biopsy (**FIG. 41C**). The cells were cultured for 24 hours and evaluation of TNFα secretion in the supernatant was assessed by ELISA. As a positive control, cells were stimulated with zymosan. Anti-Dectin 1 antibody (clone 2M24) was found to induce Dectin 1-clustering and TNFα secretion from human macrophages. These data provide evidence that the parental anti-Dectin-1 antibody (clone

2M24) can promote immune-stimulation in primary macrophage cultures as well as in single cell homogenate of cancer biopsies. Since Dectin-1 is expressed in myeloid cells, tumor associated macrophages in the cancer biopsies are expected to produce cytokines in response to the anti-Dectin-1 antibody stimulation. This promotes the transition of the tumor associated macrophages from anti-inflammatory to pro-inflammatory with strong anti-tumoral effects. Moreover, monovalent binding of the 2M24/CD20 bispecific antibody to Dectin-1 was sufficient to promote Dectin-1 clustering and immune-stimulation on macrophages.

[0254] Immune stimulation by immobilized anti-Dectin-1 antibody in single cell suspensions from kidney cancer biopsies were also analyzed (**FIG. 42**). Single-cell suspensions from kidney cancer biopsies were treated with immobilized anti-Dectin-1 antibody (clone 2M24) or isotype control hIgG4 antibody for 24 h. Supernatants were analyzed by ELISA for the release of various cytokines, including IFNγ, IL-6, TNFα, IL-23, IL-12p70, IL-10, and IL-13. These results show that activation of Dectin-1 on myeloid cells (in this example, Dectin-1 is expressed predominantly by tumor-associated macrophages, TAMs), elicited the release of specific repertoire of cytokines that are either directly downstream of Dectin-1 signaling pathway, or indirectly through activation of other immune cells. Without wishing to be bound to theory, it is thought that Dectin-1 engagement by 2M24 bispecific antibody promotes immune stimulation that could modulate the tumor microenvironment to support the elimination of target-expressing cancer cells.

Example 9: Characterization of a bispecific antibody targeting Dectin-1 and CD20

[0255] This Example describes the further characterization of a bispecific antibody targeting human Dectin-1 and human CD20. The anti-Dectin-1 arm included the variable domains of 2M24, and the anti-CD20 arm included the variable domains of Rituximab (*see* SEQ ID Nos:24 and 25 for VH and VL domains, respectively).

Materials and Methods

CD16 expression on NK cells

[0256] Human PBMCs from a healthy donor were treated with a serial dilution of 2M24/CD20 hIgG1 KIF, Rituximab KIF, and isotype control RSV hIgG1 KIF antibodies. After 24 hours of treatment, PBMCs were stained with antibodies against lineage-specific markers for flow cytometry analysis. CD16 expression on CD56+ NK cells was quantified and compared to expression levels in the isotype control treated group.

CD19 expression on B cells

[0257] Human PBMCs from a healthy donor were treated with 0.1 nM of 2M24/CD20 hIgG1 KIF, Rituximab KIF, and isotype control RSV hIgG1 KIF antibodies. After 24 hours of treatment, PBMCs were stained with antibodies against lineage-specific markers for flow cytometry analysis. CD19 expression (MFI) on B cells was quantified.

B cell depletion in PBMCs

[0258] Human PBMCs from a healthy donor were treated with a serial dilution of the indicated antibodies. After 24 hours of treatment, PBMCs were stained with antibodies against lineage-specific markers for flow cytometry analysis. B cells were quantified relative to an untreated control group (indicated by the dotted line in **FIG. 45**).

B cell depletion in kidney cancer biopsies

[0259] Single-cell suspension was generated from kidney cancer biopsy and the cells were treated with 2M24/CD20 hIgG1, 2M24/RSV hIgG1, Rituximab hIgG1, and isotype control RSV hIgG1 antibodies. After 24 hours of treatment, the cells were stained with antibodies against lineage-specific markers for flow cytometry analysis. B cells were quantified as the percentage of CD19+ cells within the CD45+ immune cell population.

Results

[0260] First, the effect of the 2M24/CD20 bispecific on CD16 expression was examined in human NK cells. CD16 is required for ADCC activity by NK cells, therefore the loss of CD16 expression can decrease the cytotoxic potential of NK cells. Rituximab induced potent and robust shedding of CD16 on NK cells compared to 2M24/CD20 hIgG1 KIF (**FIG. 43**). In contrast, CD16 levels on NK cells were better maintained after 2M24/CD20 bispecific antibody treatment compared to rituximab treatment. Without wishing to be bound to theory, it is thought that 2M24/CD20 bispecific has the potential to better preserve NK cell cytotoxic potential.

[0261] Next, the effect of the 2M24/CD20 bispecific on CD19 expression was examined in human B cells. Preserving target antigen expression is critical for therapeutic activity of monoclonal antibodies. B cell antigens such as CD20, CD19, and BCMA are validated immuno-oncology targets. CD19 is known to be downregulated via shaving/shedding following binding of anti-CD19 antibodies. Using CD20-targeting antibodies, a bystander effect was observed where CD19 expression was reduced upon treatment with Rituximab, but not with the 2M24/CD20 hIgG1 KIF bispecific (**FIG. 44**). CD19 levels on B cells were better maintained by 2M24/CD20

bispecific antibody compared to rituximab. Without wishing to be bound to theory, it is thought that, therapeutically, 2M24/CD20 bispecific may exhibit prolonged activity due to minimal impact on target antigen expression.

[0262] To compare rituximab with the anti-CD20 antibody obinutuzumab, 2M24 bispecific antibodies against CD20 were generated using the variable domain sequences from either Rituximab or Obinutuzumab. Obinutuzumab variable domain sequences were as follows. VH: QVQLVQSGAEVKKPGSSVKVSCKASGYAFSYSWINWVRQAPGQGLEWMGRIFPGDGD TDYNGKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARNVFDGYWLVYWGQGTL VTVSS (SEQ ID NO:46); VL: DIVMTQTPLSLPVTPGEPASISCRSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLVS GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPYTFGGGTKVEIK (SEQ ID NO:47).

[0263] In an ADCC/ADCP assay, 2M24/CD20 (derived from Rituximab sequence) demonstrated almost complete depletion of B cells, superior to that of 2M24/CD20 (derived from obinutuzumab) or parental bivalent antibodies and isotype control (**FIG. 45**). These data support utilization of the rituximab sequence for 2M24/CD20 bispecific development

Example 10: Characterization of a bispecific antibody targeting Dectin-1 and CD20 in an exploratory study in non-human primates

[0264] This Example describes the results of an exploratory study on the safety and efficacy of the bispecific antibody targeting human Dectin-1 and human CD20 described in Example 9 in cynomolgus monkeys.

Materials and methods

[0265] Three groups of Cynomolgus monkeys (1 male and 1 female per group) were treated with a single dose (5 mg/kg) of test articles: A) 2M24/CD20 hIgG1 KIF, B) 2M24/CD20 hIgG1 inert, and C) Rituximab hIgG1 KIF. Blood was collected at the indicated time points. Abbreviations for test articles (2M24/CD20 KIF, 2M24/CD20 inert, RTX KIF).

[0266] B cell levels were assessed by flow cytometry. Depletion was quantified by the number of CD19+ B cells remaining in samples post-dose compared to the levels before test-articles were administered. Bone marrow and lymph node aspirates were collected at the indicated time points, and B cell levels were assessed by flow cytometry. Depletion was quantified by the number of CD19+ B cells remaining in samples post-dose (Day 7) compared to the levels before test-articles were administered (Day -7).

[0267] For PBMC assay, PBMCs from a healthy Cyno were treated with a serial dilution of 2M24/CD20 hIgG1 KIF, Rituximab KIF, and isotype control RSV hIgG1 KIF antibodies. After 24 hours of treatment, PBMCs were stained with antibodies against lineage-specific markers for flow cytometry analysis. B cell depletion was quantified relative to the isotype control group.

Results

[0268] This exploratory study was designed to examine the safety and efficacy of 2M24/CD20 bispecific antibody in non-human primates. The study design is shown in **FIG. 46**. Cynomolgus monkeys were divided into three treatment groups comprising 2 animals (1 male, 1 female) per group. Each group was administered a specific test article at a single dose of 5 mg/kg. The test articles included: 1) 2M24/CD20 hIgG1 KIF, 2) 2M24/CD20 hIgG1 inert, and 3) Rituximab hIgG1 KIF. Animals were monitored daily, and samples such as whole blood, bone marrow, lymph node, and colorectal tissues were collected as indicated. The study was planned for 8 weeks.

[0269] As shown in **FIG. 47** (upper), 2M24/CD20 hIgG1 KIF bispecific antibody depleted B cells *in vivo* in Cynomolgus monkeys. Nearly complete and sustained B cell depletion (~98%) was observed in both animals treated with a single dose (5 mg/kg) of 2M24/CD20 hIgG1 KIF. In the Rituximab group (**FIG. 48**), one animal showed complete depletion, whereas the second showed robust yet incomplete depletion (~87%). Partial B cell depletion was observed for one animal in the 2M24/CD20 hIgG1 inert group (**FIG. 47** lower), whereas the second animal showed no depletion at Day 7. 2M24/CD20 hIgG1 KIF bispecific antibody was well-tolerated in cynomolgus monkeys.

[0270] 2M24/CD20 hIgG1 KIF bispecific also depleted bone marrow (**FIG. 49A**) and lymph node (**FIG. 49B**) B cells *in vivo* in Cynomolgus monkey. A single dose (5 mg/kg) of 2M24/CD20 hIgG1 KIF induced robust B cell depletion in the bone marrow (~87-88%) and partial depletion in the lymph node (60-78%) in both animals. In the Rituximab group, B cell depletion was also observed in both tissues. Partial B cell depletion was observed in the 2M24/CD20 hIgG1 inert group, except for animal CB764A with minimal B cell depletion in the lymph node.

[0271] 2M24/CD20 hIgG1 KIF bispecific antibody also induced robust depletion of Cyno B cells *ex vivo* (**FIG. 50**). 2M24/CD20 hIgG1 KIF induced robust depletion of B cells compared to Rituximab hIgG1 KIF. The maximum depletion achieved by Rituximab was ~30% of B cells, whereas 2M24/CD20 hIgG1 KIF bispecific demonstrated maximum depletion at ~50%.

Example 11: Purification and functional characterization of the 2M24/CD20 bispecific antibody in scFv format

[0272] This Example describes the production, purification, and characterization of a 2M24/CD20 bispecific antibody in which the Dectin-1 targeting arm (based on 2M24 variable domains) was an scFv fused to a human IgG1 Fc domain with knob-forming mutations, and the CD20 targeting arm was based on rituximab hIgG1 with hole-forming mutations. A diagram of the molecule is shown in **FIG. 51**. Knob-forming mutation on Dectin-1 targeting arm was T366W; hole-forming mutations on CD20 targeting arm were T366S, L368A, and Y407V. Without wishing to be bound to theory, it is thought that this format provides a universal platform for generating anti-Dectin-1 bispecific antibodies with simpler manufacturing requirements (*e.g.*, as compared to bispecific antibodies having an anti-Dectin-1 arm with multiple polypeptide chains).

[0273] 2M24 scFv/CD20 hIgG1 was expressed in Hek293 cells by transfecting 3 plasmids (2M24 scFv hIgG1 plasmid, CD20 heavy chain, and CD20 light chain). Supernatant was harvested after four days of expression and purified via Protein A. Aggregates were removed with size exclusion chromatography. As shown in **FIG. 52A**, the 2M24 scFv/CD20 hIgG1 bispecific antibody purified as a homogenous molecule on SEC.

[0274] Next, co-cultures of CD20-expressing Raji cells and the Dectin-1-expressing HEK reporter assay were treated with increasing concentration of 2M24 scFv/CD20 hIgG1 bispecific. Reporter activation was assessed by measuring SEAP levels (based on absorbance at 630 nm) in media. The bispecific molecule promoted targeted immune stimulation, as assessed by this NFkB reporter assay (**FIG. 52B**).

[0275] To examine B cell depletion, human PBMCs from a healthy donor were treated with a serial dilution of the indicated antibodies. After 24 hours of treatment, PBMCs were stained with antibodies against lineage-specific markers for flow cytometry analysis. B cells were quantified relative to an untreated control group (indicated by the dotted line in **FIG. 52C**). The results demonstrated that the 2M24 scFv/CD20 hIgG1 bispecific antibody, similar to the 2M24/CD20 hIgG1 KIF molecule, was able to deplete human B cells (**FIG. 52C**).

Example 12: Development and characterization of an anti-Dectin-1/anti-Trop-2 bispecific antibody

[0276] Trop-2 is a 323 aa type I membrane protein involved in calcium signal transduction, embryonic and fetal development, tight junction formation, and integrin-dependent signaling. Mutations in Trop-2 are associated with gelatinous drop-like corneal dystrophy, characterized by

corneal amyloidosis and blindness. Trop-2 is overexpressed in various epithelial cancers, promoting cell proliferation, invasion and neovascularization. High expression correlates with poor prognosis and survival in many cancers (notably in TNBC breast and NSCLC lung cancer). Sacituzumab govitecan (Trodelvy ®), a Trop-2–directed ADC, is the only therapeutic that is approved for the treatment of patients with metastatic TNBC. FDA-accelerated approval in 2020.

[0277] Therefore, Trop-2 is an oncology target that is clinically validated. However, there is an unmet need: Trodelvy® achieved a 33% response rate in a heavily pretreated population of patients with metastatic TNBC. Adverse reactions such as neutropenia, diarrhea, and vomiting are associated with Trodelvy toxin (SN-38) conjugate.

[0278] In contrast, an anti-Dectin-1-targeted approach has the potential to restrict anti-tumor activity to the disease microenvironment. Immune modulation and phagocytosis activities of 2M24 are tightly regulated by the presence of cancer cells. While Trodelvy® has a single mode of action (toxin conjugate delivery to induce target cell killing), the anti-Dectin-1-targeted approach utilizes multiple modes of action (targeted immune stimulation, phagocytosis, and antigen presentation) to eliminate cancer cells and promote lasting immunity.

[0279] This Example describes the development and characterization of an anti-Dectin-1 (2M24)/anti-Trop-2 bispecific antibody. Variable domains used for anti-Trop-2 were as follows.

VH:

QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTG

EPTYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCARGGFGSSYWYFDVWGQGS

LVTVSS (SEQ ID NO:42); VL:

DIQLTQSPSSLSASVGDRVSITCKASQDVSIAVAWYQQKPGKAPKLLIYSASYRYTGVPD

RFSGSGSGTDFTLTISSLQPEDFAVYYCQQHYITPLTFGAGTKVEIK (SEQ ID NO:43).

[0280] 2M24/Trop-2 bispecific antibody was purified by size exclusion chromatography, and purified antibody was analyzed by SDS-PAGE under non-reducing (NR) or reducing (R) conditions (**FIG. 53A**). 2M24/Trop2 bispecific antibody purified as a monodispersed molecule. 2M24/Trop2 bispecific antibody was found to bind with high affinity to Dectin-1-expressing HEK cells (**FIG. 53B**) and moderate affinity to Trop-2-expressing A431 cancer cell line (**FIG. 53C**).

[0281] To evaluate the level of Trop-2 expression on different cancer cells, cancer cell lines (A431 and SKBR3) were stained with anti-human PE Trop-2 or isotype control antibodies to evaluate Trop-2 expression. Receptor copy number was assessed by comparing the fluorescence intensity of fluorochrome-labeled microspheres with known amounts of the fluorophore to the fluorescence intensity of the labeled cells by flow cytometry. Trop-2 was found to be highly

expressed on the cancer cell lines A431 and SKBR3, with receptor copy numbers of 8.4 million and 1.1 million, respectively (**FIG. 54**). These results demonstrate that Trop-2 polypeptide is highly expressed on cancer cells. High expression on cancer cells makes Trop-2 an attractive antigen for the targeted-killing of cancer cells by a 2M24/Trop-2 bispecific antibody.

[0282] Next, binding of the 2M24/Trop-2 bispecific antibody to Trop-2-expressing cell lines was examined. Cancer cell lines (HeLa, SiHa, BxPC-3, and Capan-2) were incubated with serial dilutions of the 2M24/Trop-2 hIgG1bispecific antibody or an isotype control antibody as a single concentration (300 nM). The secondary antibody (AF647 goat Anti-Human) was used for detection by flow cytometry. Binding EC50 was determined using four-parameter logistic (4PL) non-linear regression. The results demonstrated that 2M24/Trop-2 bispecific antibody binds with variable sub-micromolar affinity to different Trop-2-expressing cell lines (**FIGS. 55A-55D**).

[0283] 2M24/Trop-2 bispecific antibody was assayed for ability to deplete Trop-2 expressing cell lines. Macrophages were generated by monocytes cultured with MCSF for 6 days. After differentiation, macrophages were co-cultured with Trop-2-expressing cancer cell lines, SKBR3 or A431, for 24 hours in the presence of 10 ug/ml 2M24/Trop-2 hIgG1 or 2M24/RSV hIgG1. To detect macrophages, PE-CD206 antibody was used. The cancer cells were detected either by pre-staining with Calcein AM (**FIG. 56A**, SKBR3 cells) or using an APC-EPCAM antibody (**FIG. 56B**, A431 cells). Phagocytosis was assessed by flow cytometry as double positive PE-CD206+Calcein+ cells in the single cell gate for SKBR3 cells (**FIG. 56A**) or remaining EPCAM+ cells for A431 cells (**FIG. 56B**). The results demonstrated that 2M24/Trop-2 bispecific antibody induced robust depletion of both cancer cell lines that express Trop-2. 2M24/Trop-2 bispecific antibody induced phagocytosis of Trop-2 expressing cell lines by macrophages. The cancer cell reduction was 56% for SKBR3 (**FIG. 56A**) and 87% for A431 cancer cells (**FIG. 56B**). The data provide strong evidence that the 2M24/Trop-2 bispecific antibody can direct the macrophages to eliminate cancer cells that express Trop-2.

[0284] Trop-2 expression in non-immune cells and Dectin-1 expression in tumor associated macrophages was assessed in a single-cell suspension of lung cancer biopsy tissue. Trop-2 was evaluated in CD45- cancer cells using a PE Trop-2 antibody. Expression of EPCAM was also confirmed in the same population. Expression of Dectin-1 was confirmed in tumor associated macrophages gated as CD45+CD11b+CD163+ cells after excluding B-cell, T-cells and NK-cells (**FIGS. 57A & 57B**). Dectin-1 is expressed in tumor associated macrophages and Trop-2 is expressed in cancer cells of lung cancer biopsy.

[0285] To examine whether 2M24/Trop-2 bispecific antibody was able to induce depletion of Trop-2-expressing cancer cells from lung cancer biopsy tissue, a single-cell suspension was

generated from lung cancer biopsy, and the cells were treated with 2M24/Trop-2 hIgG1 or 2M24/RSV hIgG1 antibodies. After 24 hours of treatment, the cancer cells were quantified by staining with FITC CD45 and APC EPCAM antibodies for flow cytometry analysis. Cancer cell reduction was expressed as the percentage of CD45-EPCAM+ cells within the live cell population. The results demonstrated that 2M24/Trop-2 bispecific depleted Trop-2-expressing cancer cells in the lung cancer biopsy (**FIG. 58**). 2M24/Trop-2 bispecific antibody induced a 50% reduction of cancer cells expressing Trop-2 in the lung cancer biopsy. The data indicate that the 2M24/Trop-2 bispecific antibody can induce the phagocytosis and elimination of cancer cells by the tumor associated macrophages within the lung cancer tissue.

[0286] To assess Dectin-1 signaling as stimulated by 2M24/Trop-2 bispecific antibody, NFκB reporter HEK cells expressing Dectin-1 were incubated with A431 cancer cells in the presence of serial titration of the 2M24/Trop-2 bispecific or 2M24/RSV antibodies. 2M24/Trop-2 bispecific engaged the two cell lines, promoting Dectin-1 receptor clustering and downstream activation of NFkB. Upon activation, SEAP is released into the media and used as a readout for Dectin-1activation. Media levels of SEAP were quantified using a spectrophotometer. 2M24/Trop-2 bispecific antibody induced robust stimulation of Dectin-1 and downstream NFκB activity (**FIG. 59**). These data indicate that the 2M24/Trop-2 bispecific promotes Dectin-1 signaling in effector cells in the presence of Trop-2 expressing cells. Therefore, the 2M24/Trop-2 bispecific antibody has the potential to drive Dectin-1 mediated immune stimulation by monocytes and macrophages that express high levels of Dectin-1.

[0287] Next, effects of 2M24/Trop-2 bispecific antibody on antigen presentation and T cell activation were examined. In this assay, as shown in **FIG. 59B**, monocyte-derived macrophages were co-cultured with SKBR3 breast cancer cells in the presence of 2M24/Trop-2 bispecific antibody. Macrophages are NY ESO-negative, while SKBR3 cells are NY ESO-positive. Bispecific antibody promoted phagocytosis and degradation of SKBR3 cells, and subsequent loading of the ESO peptide on MHC Class I or II on the surface of macrophages. Antigen-specific (ESO-reactive) T cells were then added to the co-culture assay where the TCR recognizes the ESO/MHC complex. This interaction triggered T cell activation, resulting in the release of cytokines (e.g., IFNγ) and expression of early activation markers such as CD69. This assay enables direct assessment of 2M24/Trop-2 bispecific-dependent phagocytosis and presentation of target cell antigens. The results are shown in **FIGS. 59C-59E**. Macrophages and SKBR3 breast cancer cells were co-incubated in the presence of 2M24/Trop-2 hIgG1 or control 2M24/RSV hIgG1 bispecific antibody. Phagocytosis or depletion of SKBR3 cells was assessed by flow cytometry by staining for EPCAM expression on SKBR3 cells (**FIG. 59C**). T cell

activation is measured by the release of IFN gamma and expression of CD69. IFN gamma levels in the supernatants were quantified (**FIG. 59D**), and expression of CD69, an early activation marker, on T cells was assessed by flow cytometry (**FIG. 59E**). These data demonstrated that 2M24/Trop-2 bispecific antibody promotes antigen-presentation and T cell activation. The bispecific antibody 2M24/Trop-2 hIgG1 induced T cell activation by promoting phagocytosis of target cell or antigen by macrophages, and subsequent presentation of neoantigen (ESO-peptide) on MHC Class I on the surface of macrophages. These findings demonstrate that bispecific antibodies targeting Dectin-1 on antigen presenting cells (APCs) are sufficient to activate T cells.

Example 13: Development and characterization of an anti-Dectin-1/anti-Nectin-4 bispecific antibody

[0288] Nectin-4, or PVRL4, belongs to the nectin subfamily of immunoglobulin-like adhesion molecules that participate in Ca(2+)-independent cell-cell adhesion. It consists of three conserved immunoglobulin-like domains (V, C, C) in its extracellular region. Nectin-4 is mainly expressed during fetal development (embryo and placenta) and expression decreases with age.

[0289] Nectin-4 overexpression has been reported in many types of cancer. Its re-expression during tumor development makes it a tumor-associated antigen with the possibility of developing a targeted therapy. Silencing Nectin-4 inhibits tumor growth, cell proliferation and migration (Deng et al (2019) *Cancer Cell Int.* 19:106; Nishiwada et al (2015) *J. Exp. Clin. Cancer Res.* 34:30). Nectin-4 interacts with ErbB2 and its trastuzumab-resistant splice variants, enhancing their activation and DNA synthesis. (Kedashiro et al (2019) *Sci. Rep.* 9:18997). Nectin-4 is cleaved by ADAM-17, and circulating Nectin-4 is detected in breast cancer (Fabre-Lafay et al. (2005) *J. Biol. Chem.* 280:19543-19550; Fabre-Lafay et al. (2007) *BMC Cancer* 7:73).

[0290] Enfortumab vedotin (ASG-22ME) is a first-in-class antibody-drug conjugate (ADC) directed against Nectin-4. Enfortumab vedotin monoclonal antibody binds to Nectin-4 expressing cells followed by the internalization and release of the anti-tumor agent monomethyl auristatin E (MMAE) into the cell, which result in cell cycle arrest and apoptosis. Enfortumab vedotin (Padcev) was approved for treatment of urothelial cancer in patients who have previously received PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy, based on NCT03219333 trial in Dec 2019.

[0291] In summary, Nectin-4 is a clinically validated target with an approved ADC. Nectin-4 is minimally expressed in normal tissues, but highly expressed in bladder, breast, cervical, pancreatic, lung, and esophageal cancers, among others. Nectin-4-positive solid tumor types have elevated levels of tumor-associated macrophages (TAMs). Dectin-1 expression on TAMs

has been confirmed by single cell RNA sequencing and flow cytometry. As such, and without wishing to be bound to theory, it is thought that targeting Nectin-4 with a Dectin-1 bispecific antibody has the potential to treat Nectin-4-positive cancers by mechanisms including: (1) dual engagement of Nectin-4 on tumor cells and Dectin-1 on TAMs; (2) induction of phagocytosis and depletion of Nectin-4-expressing tumor cells by macrophages; (3) re-programming the immune-suppressive environment by inducing cytokine release through Dectin-1 clustering on TAMs; and/or (4) presenting tumor neoantigens, activating adaptive immune cells like T and B cells, and promoting durable anti-tumor immunity through engagement of professional antigen-presenting cells in the tumor microenvironment.

[0292] The bispecific 2M24/Nectin-4 antibody is shown in **FIG. 60A**, which uses the 2M24 anti-Dectin-1 variable domains and the Ha22 anti-Nectin-4 variable domains (VH: EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNWVRQAPGKGLEWVSYISSSSSTIY YADSVKGRFTISRDNAKNSLSLQMNSLRDEDTAVYYCARAYYYGMDVWGQGTTVTVS S (SEQ ID NO:40); VL: DIQMTQSPSSVSASVGDRVTITCRASQGISGWLAWYQQKPGKAPKFLIYAASTLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGGGTKVEIK (SEQ ID NO:41)). DuetMab mutations on the heavy chain included F126C and C220V; mutations on the light chain included S121C and C214V. It was produced by transfecting 4 plasmids (2M24 heavy chain, 2M24 light chain, Nectin-4 heavy chain, and Nectin-4 light chain) into HEK293 cells. Supernatant was harvested after four days of expression and purified via Protein A (**FIG. 60B**).

[0293] Nectin-4 expression was assessed in cancer cell lines SKBR3 and A431 (**FIG. 61A**), and in single-cell suspension of prostate or ovarian cancer biopsies (**FIG. 61B**). Nectin-4 was detected using an anti-Nectin-4 mIgG2b antibody and an Alexa Fluor-647-conjugated secondary antibody. An isotype mIgG2b antibody was used as a negative control for background staining. Nectin-4 expression was observed in cancer cell lines as well as cancer cells in the tumor biopsy tissues.

[0294] Binding of 2M24/Nectin-4 bispecific antibody to cells that express Dectin-1 or Nectin-4 was analyzed. Cell lines expressing Dectin-1 (HEK cells) or Nectin-4 (A431 cells) were incubated with serial dilutions of the 2M24/Nectin-4 hIgG1bispecific antibody or RSV hIgG1 (isotype control) to assess target binding. The secondary antibody (AF647 goat Anti-human IgG) was used for detection by flow cytometry. Binding EC50 values were determined using four parameter logistic (4PL) non-linear regression. The results demonstrated that 2M24/Nectin-4 bispecific antibody bound with high affinity to Dectin-1 and low affinity to Nectin-4 (**FIG. 62**).

[0295] Activity of the 2M24/Nectin-4 bispecific antibody was measured using an NFkB reporter assay. Schematic representation of assay setup is shown in **FIG. 63** (upper). NFkB reporter HEK cells expressing Dectin-1 were incubated with A431 cancer cells in the presence of serial titration of the 2M24/Nectin-4 bispecific or bivalent anti-Nectin-4 antibody. 2M24/Nectin-4 bispecific engages the two cell lines, promoting Dectin-1 receptor clustering and downstream activation of NFkB. Upon activation, SEAP was released into the media and used as a readout for Dectin-1activation. Media levels of SEAP were quantified using a spectrophotometer (**FIG. 63**, lower). The results demonstrated robust stimulation of Dectin-1 and downstream NFkB activity by the 2M24/Nectin-4 bispecific antibody.

[0296] 2M24/Nectin-4 bispecific antibody was analyzed for depletion of Nectin-4-expressing cancer cells. Macrophages were generated by monocytes cultured with MCSF for 6 days. After differentiation, macrophages were co-cultured with the Nectin-4-expressing cancer cell line A431 for 24 hours in the presence of 2M24/Nectin-4 bispecific, anti-Nectin-4 bivalent parental antibody, or RSV hIgG1 (isotype control). To detect macrophages (**FIG. 64A**), a PE-CD206 antibody was used. The cancer cells were detected using an APC-EPCAM antibody. Phagocytosis or depletion was assessed by quantifying the remaining EPCAM-positive cells. Data were reported as relative to the RSV control (**FIG. 64B**). 2M24/Nectin-4 bispecific antibody was able to deplete Nectin-4-expressing cancer cell lines via targeted phagocytosis by macrophages. Thus, this bispecific molecule has the potential for targeted depletion of Nectin-4-positive cancers.

Example 14: Development and characterization of an anti-Dectin-1 bispecific antibody targeting light chain amyloids

[0297] Light chain amyloidosis (AL) is caused by the expansion of an indolent B cell clone that produces an immunoglobulin light chain λ in 75–80% of cases and κ light chains in the remaining cases (Dispenzieri, A. and G. Merlini (2016). *Cancer Treat Res* 169: 273-318). High concentrations of misfolded light chain proteins are secreted into circulation and deposit in various organs. Amyloid deposition leads to irreversible organ failure and death if remains untreated. Greater than 4000 new AL cases are diagnosed annually in the U.S. 10-15% of multiple myeloma patients develop AL.

[0298] There is an unmet need for AL treatments. Myeloid cells such as tissue resident macrophages are involved in tissue amyloid clearance (Wall et al. (2012) *PLoS ONE* 7:e52686). Patients with hereditary transthyretin amyloidosis (ATTR) have impaired phagocytosis activity by myeloid cells (Suenaga et al. (2016) *PLoS ONE* 11:e0163944). Targeted phagocytosis of light

chain amyloids via the Dectin-1 receptor on myeloid cells, like macrophages, monocytes and dendritic cells, is an attractive approach for amyloid clearance from tissues. The targeted myeloid engager bispecific strategy could enable Dectin-1 dependent, Fc-independent phagocytosis. Without wishing to be bound to theory, it is hypothesized that this approach may potentially overcome the limitations of current monoclonal antibody strategies that rely primarily on Fc-mediated signaling for amyloid clearance.

[0299] A bispecific antibody targeting Dectin-1 and light chain amyloids was constructed using the 2M24 anti-Dectin-1 and 11-1F4 anti-amyloid variable domains. 11-1F4 variable domains were as follows. VH: QVQLKESGPGLVAPSQSLSITCTVSGFSLSSYGVSWVRQPPGKGLEWLGVIWGDGSTNY KPNLMSRLSISKDISKSQVLFKLNSLQTDDTATYYCVTLDYWGQGTSVTVSS (SEQ ID NO:44); VL: DVVMTQTPLSLPVSLGDQASISCRSSQSLVHRNGNTYLHWYLQKPGQSPKLLIYKVSNR FSGVPDRFSGSGSGTDFTLKISRVEAEDLGLYFCFQTTYVPNTFGGGTKLEIK (SEQ ID NO:45).

[0300] The bispecific molecule was purified, and binding activity assayed. The parental bivalent antibody 11-1F4 hIgG1 (**FIG. 65A**, upper) and bispecific antibody 2M24/11-1F4 hIgG1 (**FIG. 65A**, lower) were purified in PBS by size exclusion chromatography. Purified antibodies were then evaluated for binding to recombinant light chain amyloids from different patients (AL30, AL47, AL48, and AL55) by Octet (**FIG. 65B** for 11-1F4 hIgG1 and **FIG. 65C** for 2M24/11-1F4 hIgG1). These results demonstrate that 2M24/11-1F4 bispecific antibody bound to light chain amyloids *in vitro*.

[0301] The ability of 2M24/11-1F4 bispecific antibody to induce phagocytosis of light chain amyloids was also examined. Monocytes were freshly isolated from healthy donor PBMCs and co-cultured with pHrodo-labeled light chain amyloids in the presence of either 2M24/11-1F4 hIgG1 inert bispecific antibody or the parental bivalent 11-1F4 hIgG1 antibody. Phagocytosis of light chain amyloids was monitored by the change in pHrodo fluorescence in the low-pH environment of phagosomes. Change in pHrodo activity over 24 hours was monitored in real-time using an Incucyte. The results demonstrated that 2M24/11-1F4 bispecific antibody induced robust phagocytosis of light chain amyloid fibrils compared to the control 11-1F4 hIgG1 antibody (**FIG. 66**). In this study, an Fc inactive or effectorless 2M24/11-1F4 demonstrated robust amyloid clearance activity, indicating that Dectin-1 binding was sufficient to promote phagocytosis. The 11-1F4 hIgG1 antibody contains an active Fc domain, however minimal

clearance activity was observed. These findings suggest that targeting the phagocytic receptor Dectin-1 is an attractive approach treating light chain amyloidosis.

Example 15: Development and characterization of an anti-Dectin-1 bispecific antibody targeting amyloid beta in Alzheimer's disease (AD)

[0302] AD is the most common cause of dementia worldwide. It accounts for about 80% of all diagnosed cases (Weller and Budson, (2018) *F1000Res* 7). In the United States, AD claims more lives than prostate and breast cancer combined (Patterson, C. (2018). World Alzheimer Report 2018. The State of the Art of Dementia Research: New Frontiers. London, UK: Alzheimer's Disease International. Available at www.alz.co.uk/research/world-report-2018). AD is categorized into two forms: sporadic and familial. Ninety-nine percent of AD cases are sporadic, i.e., the exact cause of onset is unknown (Wang, J., Gu, B. J., Masters, C. L., and Wang, Y.-J. (2017). *Nat. Rev. Neurol.* 13, 612–623). Sporadic AD (SAD) or late-onset AD (LOAD) is most likely driven by genetic and environmental factors (Bondi, M. W., Edmonds, E. C., and Salmon, D. P. (2017). *J. Int. Neuropsychol. Soc.* 23, 818–831). The major genetic factor for SAD is the apolipoprotein E (APOE) gene. Other targets identified by GWAS studies include triggering receptor expressed in myeloid cells 2 (TREM2), complement C3b/C4b receptor 1 (CR1), CR1 (complement C3b/C4b receptor 1), CD33, and ABCA7 (Hansen, D. V., et al. (2018). *J Cell Biol* 217(2): 459-472). Many of these genes are expressed on microglial cells, suggesting a critical role of these cells AD etiology (Hansen, D. V., et al. (2018). *J Cell Biol* 217(2): 459-472). TREM2 is a microglial cell surface receptor central to phagocytosis, chemotaxis, survival, and proliferation of microglia (Carmona, S., Zahs, K., Wu, E., Dakin, K., Bras, J., and Guerreiro, R. (2018). *Lancet Neurol.* 17, 721–730). The TREM2 loss-of-function mutation R47H results in a two- to four-fold increase in the risk of AD like the risk associated with inheriting one copy of the e4 variant of APOE (Gratuze, M., Leyns, C. E. G., and Holtzman, D. M. (2018). *Mol. Neurodegener.* 13:66).

[0303] Most risk genes for Alzheimer's are highly expressed by microglia, suggesting that microglial dysfunction is associated with AD development and progression (Hansen, 2018). For instance, loss-of-function variants of the microglial phagocytic receptor TREM2 impairs clearance of amyloid β deposits and is linked to enhanced risk of dementia. The Dectin-1 phagocytic receptor is expressed on microglial cells and is not known to be a risk gene for AD. Therefore, without wishing to be bound to theory, it is thought that targeting Dectin-1 on microglial cells could induce targeted phagocytosis and clearance of amyloid beta in AD patients. Targeting Dectin-1 may bypass loss-of-function variants of microglial genes such as TREM2.

Unlike current monoclonal antibody approaches such as aducanumab that rely on Fc receptors on microglial cells to execute phagocytosis (Sevigny, J., et al. (2016). *Nature* 537(7618): 50-56), this approach targets a conserved microbial pathway to induce phagocytosis and immune stimulation.

[0304] Bispecific antibodies were generated with one arm targeting Dectin-1 and the other arm targeting amyloid beta (based on the variable domain sequences of aducanumab or lecanemab). Aducanumab variable domain sequences are as follows. VH:
QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAVIWFDGTK
KYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGARRGPYYMDVW
GKGTTVTVSS (SEQ ID NO:48); VL:
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO:49).
Lecanemab variable domain sequences are as follows. VH:
EVQLVESGGGLVQPGGSLRLSCSASGFTFSSFGMHWVRQAPGKGLEWVAYISSGSSTIY
YGDTVKGRFTISRDNAKNSLFLQMSSLRAEDTAVYYCAREGGYYYGRSYYTMDYWGQ
GTTVTVSS (SEQ ID NO:50); VL:
DVVMTQSPLSLPVTPGAPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRFS
GVPDRFSGSGSGTDFTLRISRVEAEDVGIYYCFQGSHVPPTFGPGTKLEIK (SEQ ID
NO:51).

[0305] Although the present disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the present disclosure. The disclosures of all patent and scientific literature cited herein are expressly incorporated in the entirety by reference.

CLAIMS

What is claimed is:

1. An antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

2. An antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

3. The antibody of claim 2, wherein the VH domain comprises a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and wherein the VL domain comprises a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

4. The antibody of any one of claims 1-3, wherein the VH domain comprises a sequence with at least 90% identity to the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises a sequence with at least 90%

identity to the sequence
DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS
RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

5. The antibody of claim 4, wherein the VH domain comprises the sequence
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD
TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV
SS (SEQ ID NO:7); and/or wherein the VL domain comprises the sequence
DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS
RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

6. The antibody of any one of claims 1-3, wherein the antibody or fragment is a human, humanized, or chimeric antibody or fragment.

7. An antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment binds to human Dectin-1 expressed on the surface of a cell with an EC50 of less than 2nM.

8. An antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment is capable of binding human or cynomolgus Dectin-1.

9. An antibody or antigen-binding fragment thereof that binds to human Dectin-1, wherein the antibody or fragment does not compete with a native ligand of human Dectin-1.

10. The antibody of any one of claims 7-9, wherein the antibody or fragment is a human or humanized antibody or fragment.

11. The antibody of any one of claims 7-10, wherein the antibody or fragment competes for binding to human Dectin-1 with a reference antibody that comprises:

(a) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6);

(b) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6); or

(c) a heavy chain variable (VH) domain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGDTNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTVSS (SEQ ID NO:7) and a light chain variable (VL) domain comprising the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

12. The antibody of any one of claims 7-11, wherein the antibody or fragment binds the same epitope of human Dectin-1 as a reference antibody that comprises:

(a) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6);

(b) a heavy chain variable (VH) domain comprising a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and a light chain variable (VL) domain comprising a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6); or

(c) a heavy chain variable (VH) domain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGDTNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTVSS (SEQ ID NO:7) and a light chain variable (VL) domain comprising the sequence

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

13. The antibody of any one of claims 1-12, wherein the antibody or fragment binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, and/or granulocyte.

14. The antibody of any one of claims 1-13, wherein the antigen-binding antibody fragment is a Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibody, nanobody, or scFv fragment.

15. The antibody of any one of claims 1-13, wherein the antibody further comprises an Fc region.

16. The antibody of any one of claims 1-15, wherein the antibody or fragment is a multispecific antibody or fragment.

17. The antibody of claim 16, wherein the antibody or fragment is a bispecific antibody, fragment, or diabody comprising a first antigen binding domain comprising the VH and VL domains that bind to human Dectin-1 and a second antigen binding domain comprising second VH and VL domains that bind to a target of interest.

18. The antibody of claim 17, wherein the bispecific antibody comprises a first IgG antibody comprising the first antigen binding domain covalently linked to a second IgG antibody comprising the second antigen binding domain.

19. The antibody of claim 17, wherein the bispecific antibody comprises a first antibody arm comprising a first antibody heavy chain that comprises the VH domain of the first antigen binding domain and a first Fc region, and a second antibody arm comprising a second antibody heavy chain that comprises the VH domain of the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations.

20. The antibody of claim 19, wherein the first Fc region comprises a T366W substitution, and wherein the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering.

21. The antibody of claim 17, wherein the bispecific antibody comprises a first antibody arm comprising a first antibody heavy chain that comprises the VH domain of the first antigen binding domain and a first Fc region, and a second antibody arm comprising a second antibody

heavy chain that comprises the VH domain of the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more hole-forming mutations, and the second Fc region comprises one or more cognate knob-forming mutations.

22. The antibody of claim 21, wherein the first Fc region comprises T366S, L368A, and Y407V substitutions, and wherein the second Fc region comprises a T366W substitution, according to EU numbering.

23. The antibody of claim 17, wherein the bispecific antibody comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising the VH and VL domains that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises the VH domain of the second antigen binding domain in association with an antibody light chain that comprises the VL domain of the second antigen binding domain and a second Fc region connected to the VH domain of the second antigen binding domain.

24. The antibody of claim 23, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or wherein the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations.

25. The antibody of claim 23 or claim 24, wherein the first antibody arm comprises a first linker between the VH and VL domains, and a second linker between the VL domain and the first Fc region.

26. The antibody of claim 25, wherein the first linker comprises one or more repeats of the sequence GGGGS (SEQ ID NO:26).

27. The antibody of claim 26, wherein the first linker comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:27) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:28).

28. The antibody of any one of claims 25-27, wherein the second linker comprises the sequence EPKRSDKTHTCPPC (SEQ ID NO:29) or SATHTCPPC (SEQ ID NO:30).

29. The antibody of claim 17, wherein the bispecific antibody comprises a first IgG antibody comprising the first antigen binding domain coupled to biotin or an avidin-binding derivative thereof, and a second IgG antibody comprising the second antigen binding domain coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, wherein the biotin or

avidin-binding derivative thereof is bound to the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof.

30. The antibody of claim 17, wherein the bispecific antibody comprises a first IgG antibody comprising the first antigen binding domain coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and a second IgG antibody comprising the second antigen binding domain coupled to biotin or an avidin-binding derivative thereof, wherein the biotin or avidin-binding derivative thereof is bound to the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof.

31. The antibody of any one of claims claim 17-30, wherein the target of interest is a disease-causing agent.

32. The antibody of claim 31, wherein the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate, LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

33. The antibody of claim 32, wherein the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

34. The antibody of claim 32, wherein the target of interest is a surface antigen of the virus.

35. The antibody of claim 31 or claim 32, wherein the target of interest is an antigen expressed on the surface of a cancer cell.

36. The antibody of claim 35, wherein the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR.

37. The antibody of claim 32, wherein the target of interest is amyloid beta, lambda light chain amyloid, or kappa light chain amyloid.

38. The antibody of any one of claims 15-37, wherein the antibody comprises two antibody heavy chains, and wherein each of the antibody heavy chains comprises an amino acid substitution at one or more of positions 234, 235, and 237, according to EU numbering.

39. The antibody of claim 38, wherein each of the antibody heavy chains comprises L234A, L235E, and G237A substitutions, according to EU numbering.

40. The antibody of any one of claims 17-39, wherein the antibody comprises two antibody heavy chains, and wherein only one of the antibody heavy chains comprises H435R and Y436F substitutions, according to EU numbering.

41. The antibody of any one of claims 17-40, wherein the antibody comprises two arms, wherein only one of the two antibody arms comprises a heavy chain comprising F126C and C220V substitutions and a light chain comprising S121C and C214V substitutions, according to EU numbering.

42. The antibody of claim 17, wherein the bispecific antibody comprises two antibody heavy chains and two antibody light chains, wherein the VH domain of the first antibody heavy chain forms an antigen binding domain with the VL domain of the first antibody light chain, wherein the VH domain of the second antibody heavy chain forms an antigen binding domain with the VL domain of the second antibody light chain, wherein the first antibody heavy chain comprises F126C, C220V, and T366W substitutions, wherein the first antibody light chain comprises S121C and C214V substitutions, and wherein the second antibody heavy chain comprises T366S, L368A, Y407V, H435R, and Y436F substitutions, according to EU numbering.

43. The antibody of claim 42, wherein the first and second antibody heavy chains further comprise L234A, L235E, and G237A substitutions, according to EU numbering.

44. The antibody of any one of claims 17-43, wherein the bispecific antibody comprises a first and a second antibody heavy chain, wherein the first and second antibody heavy chains comprise human IgG1 Fc domains.

45. The antibody of any one of claims 17-44, wherein the bispecific antibody comprises a first and a second antibody heavy chain, wherein at least one or two of the first and second antibody heavy chains is/are non-fucosylated.

46. A multispecific binding molecule, comprising:

(a) a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to human Dectin-1; and

(b) a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a target of interest.

47. The multispecific binding molecule of claim 46, wherein the target of interest is a disease-causing agent.

48. The multispecific binding molecule of claim 47, wherein the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate, LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

49. The multispecific binding molecule of claim 48, wherein the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

50. The multispecific binding molecule of claim 48, wherein the target of interest is a surface antigen of the virus.

51. The multispecific binding molecule of claim 47 or claim 48, wherein the target of interest is an antigen expressed on the surface of a cancer cell.

52. The multispecific binding molecule of claim 51, wherein the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR.

53. The multispecific binding molecule of claim 48, wherein the target of interest is amyloid beta, lambda light chain amyloid, or kappa light chain amyloid.

54. The multispecific binding molecule of any one of claims 46-53, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

55. The multispecific binding molecule of any one of claims 46-53, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence

QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD

TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

56. The multispecific binding molecule of any one of claims 46-53, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence DYYI (SEQ ID NO:88), a CDR-H2 comprising the sequence WINPNSGDTNYAQKFQG (SEQ ID NO:89), and a CDR-H3 comprising the sequence NSGSYSFGY (SEQ ID NO:90), and wherein the VL domain comprises a CDR-L1 comprising the sequence RASQGISSWLA (SEQ ID NO:91), a CDR-L2 comprising the sequence GASSLQS (SEQ ID NO:92), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

57. The multispecific binding molecule of any one of claims 54-56, wherein the VH domain comprises a sequence with at least 90% identity to the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises a sequence with at least 90% identity to the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

58. The multispecific binding molecule of claim 57, wherein the VH domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

59. The multispecific binding molecule of any one of claims 46-58, wherein the first antigen-binding domain:

(a) binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, or granulocyte;

(b) binds to human Dectin-1 expressed on the surface of a cell with an EC50 of less than 2nM;

(c) is capable of binding human or cynomolgus Dectin-1; and/or

(d) does not compete with a native ligand of human Dectin-1.

60. The multispecific binding molecule of any one of claims 46-59, wherein the second antigen-binding domain binds to CD20 and comprises a VH domain comprising the sequence of SEQ ID NO:24 and a VL domain comprising the sequence of SEQ ID NO:25.

61. The multispecific binding molecule of any one of claims 46-59, wherein the second antigen-binding domain binds to Trop-2 and comprises a VH domain comprising the sequence of SEQ ID NO:42 and a VL domain comprising the sequence of SEQ ID NO:43.

62. The multispecific binding molecule of any one of claims 46-59, wherein the second antigen-binding domain binds to light chain amyloid and comprises a VH domain comprising the sequence of SEQ ID NO:44 and a VL domain comprising the sequence of SEQ ID NO:45.

63. The multispecific binding molecule of any one of claims 46-59, wherein one or both of the first and second antibodies or fragments are human or humanized antibodies or fragments.

64. The multispecific binding molecule of any one of claims 46-63, wherein one or both of the first and second antibodies or fragments are Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibodies, nanobodies, or scFv fragments.

65. The multispecific binding molecule of any one of claims 46-63, wherein one or both of the first and second antibodies or fragments further comprise an Fc domain.

66. The multispecific binding molecule of any one of claims 46-63, wherein the first antibody or fragment is a Fab fragment, and wherein the second antibody comprises an antibody heavy chain and an antibody light chain.

67. The multispecific binding molecule of any one of claims 46-63, wherein the first and the second antibodies both comprise an antibody heavy chain and an antibody light chain.

68. The multispecific binding molecule of any one of claims 46-67, wherein the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or wherein the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; and wherein the first antibody or fragment is bound to the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof.

69. The multispecific binding molecule of claim 68, wherein the first antibody or fragment is a Fab fragment coupled to monomeric streptavidin (mSA), and wherein the second antibody is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain.

70. The multispecific binding molecule of claim 68, wherein the first antibody or fragment is a full-length antibody coupled to monomeric streptavidin (mSA), and wherein the second antibody is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain.

71. The multispecific binding molecule of any one of claims 46-63, wherein the multispecific binding molecule comprises a first IgG antibody comprising the first antigen binding domain covalently linked to a second IgG antibody comprising the second antigen binding domain.

72. The multispecific binding molecule of any one of claims 46-63, wherein the multispecific binding molecule comprises a first antibody arm comprising a single chain variable fragment (scFv) comprising the VH and VL domains that bind to human Dectin-1 and a first Fc region, and a second antibody arm comprising an antibody heavy chain that comprises the VH domain of the second antigen binding domain in association with an antibody light chain that comprises the VL domain of the second antigen binding domain and a second Fc region connected to the VH domain of the second antigen binding domain.

73. The multispecific binding molecule of claim 72, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations, or wherein the second Fc region comprises one or more knob-forming mutations, and the first Fc region comprises one or more cognate hole-forming mutations.

74. The multispecific binding molecule of claim 72 or claim 73, wherein the first antibody arm comprises a first linker between the VH and VL domains, and a second linker between the VL domain and the first Fc region.

75. The multispecific binding molecule of claim 74, wherein the first linker comprises one or more repeats of the sequence GGGGS (SEQ ID NO:26).

76. The multispecific binding molecule of claim 75, wherein the first linker comprises the sequence GGGGSGGGGSGGGGS (SEQ ID NO:27) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:28).

77. The multispecific binding molecule of any one of claims 74-76, wherein the second linker comprises the sequence EPKRSDKTHTCPPC (SEQ ID NO:29) or SATHTCPPC (SEQ ID NO:30).

78. The multispecific binding molecule of any one of claims 46-63, wherein the multispecific binding molecule comprises a first antibody arm comprising a first antibody heavy chain that comprises the VH domain of the first antigen binding domain and a first Fc region and a first antibody light chain comprising the VL domain of the first antigen binding domain, and a second antibody arm comprising a second antibody heavy chain that comprises the VH domain of the second antigen binding domain and a second Fc region and a second antibody light chain comprising the VL domain of the second antigen binding domain, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations.

79. The multispecific binding molecule of claim 73 or claim 78, wherein the first Fc region comprises a T366W substitution, and wherein the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering.

80. The multispecific binding molecule of any one of claims 46-63, wherein the multispecific binding molecule comprises a first antibody arm comprising a first antibody heavy chain that comprises the VH domain of the first antigen binding domain and a first Fc region, and a second antibody arm comprising a second antibody heavy chain that comprises the VH domain of the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more hole-forming mutations, and the second Fc region comprises one or more cognate knob-forming mutations.

81. The multispecific binding molecule of claim 73 or claim 80, wherein the first Fc region comprises T366S, L368A, and Y407V substitutions, and wherein the second Fc region comprises a T366W substitution, according to EU numbering.

82. The multispecific binding molecule of any one of claims 72-81, wherein the first and/or the second Fc region comprises an amino acid substitution at one or more of positions 234, 235, and 237, according to EU numbering.

83. The multispecific binding molecule of claim 82, wherein each of the first and second Fc regions comprises L234A, L235E, and G237A substitutions, according to EU numbering.

84. The multispecific binding molecule of any one of claims 78-83, wherein only one of the Fc regions comprises H435R and Y436F substitutions, according to EU numbering.

85. The multispecific binding molecule of any one of claims 78-84, wherein only one of the antibody arms comprises a heavy chain comprising F126C and C220V substitutions and a light chain comprising S121C and C214V substitutions, according to EU numbering.

86. The multispecific binding molecule of claim 46, wherein the multispecific binding molecule comprises a first antibody heavy chain and a first antibody light chain and a second antibody heavy chain and a second antibody light chain, wherein the VH domain of the first antibody heavy chain forms a first antigen binding domain with the VL domain of the first antibody light chain, wherein the VH domain of the second antibody heavy chain forms a second antigen binding domain with the VL domain of the second antibody light chain, wherein the first antibody heavy chain comprises F126C, C220V, and T366W substitutions, wherein the first antibody light chain comprises S121C and C214V substitutions, and wherein the second antibody heavy chain comprises T366S, L368A, Y407V, H435R, and Y436F substitutions, according to EU numbering.

87. The multispecific binding molecule of claim 86, wherein the first and second antibody heavy chains further comprise L234A, L235E, and G237A substitutions, according to EU numbering.

88. The multispecific binding molecule of any one of claims 78-87, wherein the first and second antibody heavy chains comprise human IgG1 Fc domains.

89. The multispecific binding molecule of any one of claims 78-88, wherein at least one or two of the first and second antibody heavy chains is/are non-fucosylated.

90. A multispecific binding molecule, comprising:

(a) a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to a first target of interest; and

(b) a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a second target of interest;

wherein:

(i) the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or

(ii) the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; and

wherein the first antibody or fragment is bound to the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof.

91. The multispecific binding molecule of claim 90, wherein the first target of interest is human Dectin-1.

92. The multispecific binding molecule of claim 91, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

93. The multispecific binding molecule of claim 91, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD

TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

94. The multispecific binding molecule of claim 92 or claim 93, wherein the VH domain comprises a sequence with at least 90% identity to the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises a sequence with at least 90% identity to the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

95. The multispecific binding molecule of claim 94, wherein the VH domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

96. The multispecific binding molecule of any one of claims 91-95, wherein the first antigen-binding domain binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, or granulocyte.

97. The multispecific binding molecule of any one of claims 46-96, wherein one or both of the first and second antibodies or fragments are humanized antibodies or fragments.

98. The multispecific binding molecule of any one of claims 46-97, wherein one or both of the first and second antibodies or fragments are Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibodies, nanobodies, or scFv fragments.

99. The multispecific binding molecule of any one of claims 46-97, wherein one or both of the first and second antibodies or fragments further comprise an Fc domain.

100. The multispecific binding molecule of any one of claims 46-97, wherein the first antibody or fragment is a Fab fragment, and wherein the second antibody or fragment comprises an antibody heavy chain and an antibody light chain.

101. The multispecific binding molecule of any one of claims 46-97, wherein the first and the second antibodies or fragments are both full-length antibodies.

102. The multispecific binding molecule of any one of claims 46-97, wherein the first antibody or fragment is a Fab fragment coupled to monomeric streptavidin (mSA), and wherein the second antibody is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain.

103. The multispecific binding molecule of any one of claims 46-97, wherein the first antibody or fragment is a full-length antibody coupled to monomeric streptavidin (mSA), and wherein the second antibody or fragment is a biotinylated full-length antibody.

104. The multispecific binding molecule of any one of claims 46-103, wherein the first target of interest is human Dectin-1, and wherein the second target of interest is a disease-causing agent.

105. The multispecific binding molecule of claim 104, wherein the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate, LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

106. The multispecific binding molecule of claim 105, wherein the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

107. The multispecific binding molecule of claim 105, wherein the target of interest is a surface antigen of the virus.

108. The multispecific binding molecule of claim 104 or claim 105, wherein the target of interest is an antigen expressed on the surface of a cancer cell.

109. The multispecific binding molecule of claim 108, wherein the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR.

110. The multispecific binding molecule of claim 109, wherein the second antigen binding domain binds to CD20; wherein the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and wherein the VH domain of the second antigen-binding domain comprises the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24) and/or wherein the VL domain of the second antigen-binding domain comprises the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25).

111. The multispecific binding molecule of claim 109, wherein the second antigen binding domain binds to Trop-2; wherein the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and wherein the VH domain of the second antigen-binding domain comprises the sequence of SEQ ID NO:42 and/or wherein the VL domain of the second antigen-binding domain comprises the sequence of SEQ ID NO:43.

112. The multispecific binding molecule of claim 109, wherein the second antigen binding domain binds to light chain amyloid; wherein the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and wherein the VH domain of the second antigen-binding domain comprises the sequence of SEQ ID NO:44 and/or wherein the VL domain of the second antigen-binding domain comprises the sequence of SEQ ID NO:45.

113. The multispecific binding molecule of claim 105, wherein the target of interest is amyloid beta, lambda light chain amyloid, or kappa light chain amyloid.

114. A multispecific binding molecule comprising a first arm comprising a first antigen-binding domain and a second arm comprising a second antigen-binding domain; wherein the first antigen-binding domain binds to human Dectin-1 and the second antigen-binding domain binds to a target of interest; and wherein the first arm comprises a polypeptide chain comprising the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQ QKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTF

GPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPG (SEQ ID NO:31).

115. A multispecific binding molecule, comprising:

(a) a first polypeptide chain comprising the sequence
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINP
NSGDTNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYW
GQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCR
ASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQP
EDFATYYCQQAYSFPFTFGPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP
PSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:31);

(b) a second polypeptide chain comprising the sequence
QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYP
GNGDTSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDW
YFNVWGAGTTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCAVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH
EALHNRFTQKSLSLSPG (SEQ ID NO:32); and

(c) a third polypeptide chain comprising the sequence
QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASG
VPVRFSGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID
NO:33).

116. A polynucleotide encoding the antibody or multispecific binding molecule of any one of claims 1-115.

117. A vector comprising the polynucleotide of claim 116.

118. An isolated host cell comprising the polynucleotide of claim 116 or the vector of claim 117.

119. The isolated host cell of claim 118, wherein the host cell is a yeast, insect, plant, or prokaryotic cell.

120. The isolated host cell of claim 118, wherein the host cell is a mammalian cell.

121. The isolated host cell of claim 120, wherein the mammalian cell is a Chinese hamster ovary (CHO) cell.

122. The isolated host cell of claim 120 or claim 121, wherein the host cell comprises an alpha1,6-fucosyltransferase (Fut8) or alpha-1,3-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltranferase (MGAT1) knockout.

123. The isolated host cell of claim 120 or claim 121, wherein the host cell overexpresses β1,4-N-acetylglucosaminyltransferase III (GnT-III).

124. The isolated host cell of claim 123, wherein the host cell further overexpresses Golgi μ-mannosidase II (ManII).

125. A method of producing an antibody or multispecific binding molecule, comprising culturing the host cell of any one of claims 118-124 under conditions suitable for production of the antibody or multispecific binding molecule.

126. The method of claim 125, further comprising recovering the antibody or multispecific binding molecule.

127. The method of claim 125 or claim 126, wherein, prior to production of the antibody or multispecific binding molecule, the host cell is treated with kifunensine.

128. An antibody or antigen-binding fragment thereof that binds to human Dectin-1 produced by the method of any one of claims 125-127.

129. A pharmaceutical composition comprising the antibody or multispecific binding molecule of any one of claims 1-115 and 128 and a pharmaceutically acceptable carrier.

130. A method of generating a multispecific binding molecule, comprising:

(a) providing a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to a first target of interest;

(b) providing a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a second target of interest;

wherein:

(i) the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or

(ii) the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; and

(c) contacting the first antibody or fragment with the second antibody or fragment under conditions suitable for binding between the first antibody or fragment and the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof, thereby generating a multispecific binding molecule.

131. A method of identifying a multispecific binding molecule that binds a first and a second target of interest, comprising:

(a) providing a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to a first target of interest;

(b) providing a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to a second target of interest;

wherein:

(i) the first antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the second antibody or fragment is coupled to biotin or an avidin-binding derivative thereof; or

(ii) the second antibody or fragment is coupled to avidin, streptavidin, neutravidin, or a biotin-binding derivative thereof, and the first antibody or fragment is coupled to biotin or an avidin-binding derivative thereof;

(c) contacting the first antibody or fragment with the second antibody or fragment under conditions suitable for binding between the first antibody or fragment and the second antibody or fragment via an interaction between the avidin, streptavidin, neutravidin, or biotin-binding derivative thereof and the biotin or avidin-binding derivative thereof, thereby generating a multispecific binding molecule; and

(d) measuring binding between the multispecific binding molecule and at least one of the first and the second target of interest.

132. The method of claim 130 or claim 131, wherein the first target of interest is human Dectin-1.

133. The method of claim 132, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

134. The method of claim 132, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD

TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

135. The method of claim 133 or claim 134, wherein the VH domain comprises a sequence with at least 90% identity to the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises a sequence with at least 90% identity to the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

136. The method of claim 135, wherein the VH domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

137. The method of any one of claims 132-136, wherein the first antigen-binding domain binds to human Dectin-1 expressed on the surface of a macrophage, monocyte, dendritic cell, or granulocyte.

138. The method of any one of claims 130-137, wherein one or both of the first and second antibodies or fragments are humanized antibodies or fragments.

139. The method of any one of claims 130-138, wherein one or both of the first and second antibodies or fragments are Fab, Fab', F(ab')2, Fv, Fab'-SH, F(ab')2, single chain antibodies, nanobodies, or scFv fragments.

140. The method of any one of claims 130-138, wherein one or both of the first and second antibodies or fragments further comprise an Fc domain.

141. The method of any one of claims 130-138, wherein the first antibody or fragment is a Fab fragment, and wherein the second antibody comprises an antibody heavy chain and an antibody light chain.

142. The method of any one of claims 130-138, wherein the first and the second antibodies both comprise an antibody heavy chain and an antibody light chain.

143. The method of any one of claims 130-138, wherein the first antibody or fragment is a Fab fragment coupled to monomeric streptavidin (mSA), and wherein the second antibody or fragment is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain.

144. The method of any one of claims 130-138, wherein the first antibody or fragment is a full-length antibody coupled to monomeric streptavidin (mSA), and wherein the second antibody is a biotinylated antibody that comprises an antibody heavy chain and an antibody light chain.

145. The method of any one of claims 130-144, wherein the second target of interest is a disease-causing agent.

146. The method of claim 145, wherein the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate, LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

147. The method of claim 146, wherein the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

148. The method of claim 146, wherein the target of interest is a surface antigen of the virus.

149. The method of claim 145 or claim 146, wherein the target of interest is an antigen expressed on the surface of a cancer cell.

150. The method of claim 149, wherein the target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR.

151. The method of claim 146, wherein the target of interest is amyloid beta, lambda light chain amyloid, or kappa light chain amyloid.

152. A method of treating a disease or disorder, comprising administering an effective amount of the antibody of any one of claims 1-44, the multispecific binding molecule of any one of claims 46-88 and 104-115, or the composition of claim 129 to an individual in need thereof.

153. The method of claim 152, wherein the first target of interest is human Dectin-1, and wherein the second target of interest is a disease-causing agent.

154. The method of claim 153, wherein the disease-causing agent is a bacterial cell, fungal cell, virus, senescent cell, tumor cell, protein aggregate, LDL particle, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

155. The method of claim 154, wherein the target of interest is an antigen expressed on the surface of the bacterial cell, fungal cell, senescent cell, tumor cell, mast cell, eosinophil, ILC2 cell, or inflammatory immune cell.

156. The method of claim 154, wherein the target of interest is a surface antigen of the virus.

157. The method of any one of claims 151-156, wherein the disease or disorder is cancer, a bacterial infection, a fungal infection, a viral infection, a mast cell disease or disorder, systemic mastocytosis, amyloidosis, or an aging-related disease or disorder.

158. The method of any one of claims 151-157, wherein the target of interest is an antigen expressed on the surface of a cancer cell.

159. The method of claim 158, wherein the second target of interest is CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR.

160. A method of treating cancer, comprising administering an effective amount of a composition comprising a multispecific binding molecule to an individual in need thereof, wherein the multispecific binding molecule comprises:

(a) a first antibody or antigen-binding fragment thereof comprising a first antigen-binding domain, wherein the first antigen-binding domain binds to human Dectin-1; and

(b) a second antibody or antigen-binding fragment thereof comprising a second antigen-binding domain, wherein the second antigen binding domain binds to CD70, HER2, DLL3, NECTIN-4, TROP-2, Mesothelin, LIV-1, C-MET, FOLR1, CD20, CCR8, CD33, or EGFR.

161. The method of claim 160, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1 comprising the sequence GYTFTDYY (SEQ ID NO:1), a CDR-H2 comprising the sequence INPNSGDT (SEQ ID NO:2), and a CDR-H3 comprising the sequence ARNSGSYSFGY (SEQ ID NO:3), and wherein the VL domain comprises a CDR-L1 comprising the sequence QGISSW (SEQ ID NO:4), a CDR-L2 comprising the sequence GAS (SEQ ID NO:5), and a CDR-L3 comprising the sequence QQAYSFPFT (SEQ ID NO:6).

162. The method of claim 160, wherein the first antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain, wherein the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3 from the VH domain sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7), and wherein the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3 from the VL domain sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

163. The method of claim 161 or claim 162, wherein the VH domain comprises a sequence with at least 90% identity to the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain comprises a sequence with at least 90% identity to the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

164. The method of claim 163, wherein the VH domain of the first antigen-binding domain comprises the sequence QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINPNSGD TNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYWGQGTLVTV SS (SEQ ID NO:7); and/or wherein the VL domain of the first antigen-binding domain comprises the sequence DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPS RFSGSGSGTDFTLTVSSLQPEDFATYYCQQAYSFPFTFGPGTKVDIE (SEQ ID NO:8).

165. The method of any one of claims 160-164, wherein the second antigen binding domain binds to CD20; wherein the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and wherein the VH domain of the second antigen-binding domain comprises the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGD TSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAG TTVTVSA (SEQ ID NO:24) and/or wherein the VL domain of the second antigen-binding domain comprises the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRF SGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:25).

166. The method of any one of claims 160-164, wherein the second antigen binding domain binds to Trop-2; wherein the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and wherein the VH domain of the second antigen-binding domain comprises the sequence of SEQ ID NO:42 and/or wherein the VL domain of the second antigen-binding domain comprises the sequence of SEQ ID NO:43.

167. The method of any one of claims 160-164, wherein the second antigen binding domain binds to light chain amyloid; wherein the second antigen-binding domain comprises a heavy chain variable (VH) domain and a light chain variable (VL) domain; and wherein the VH domain of the second antigen-binding domain comprises the sequence of SEQ ID NO:44 and/or wherein the VL domain of the second antigen-binding domain comprises the sequence of (SEQ ID NO:45.

168. The method of any one of claims 160-167, wherein:

(a) the multispecific antibody comprises a first antibody arm comprising the first antigen binding domain and a first Fc region and a second antibody arm comprising the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more knob-forming mutations, and the second Fc region comprises one or more cognate hole-forming mutations; or

(b) the multispecific antibody comprises a first antibody arm comprising the first antigen binding domain and a first Fc region and a second antibody arm comprising the second antigen binding domain and a second Fc region, wherein the first Fc region comprises one or more hole-

forming mutations, and the second Fc region comprises one or more cognate knob-forming mutations.

169. The method of claim 168, wherein:

(a) wherein the first Fc region comprises a T366W substitution, and wherein the second Fc region comprises T366S, L368A, and Y407V substitutions, according to EU numbering; or

(b) the first Fc region comprises T366S, L368A, and Y407V substitutions, and wherein the second Fc region comprises a T366W substitution, according to EU numbering.

170. The method of any one of claims 160-169, wherein the antibody comprises two antibody heavy chains, and wherein only one of the antibody heavy chains comprises H435R and Y436F substitutions, according to EU numbering.

171. The method of any one of claims 160-170, wherein only one of the antibody arms comprises a heavy chain comprising F126C and C220V substitutions and a light chain comprising S121C and C214V substitutions, according to EU numbering.

172. The method of any one of claims 160-171, wherein the first and second antibody heavy chains comprise human IgG1 Fc domains.

173. The method of any one of claims 160-164, wherein the second antigen binding domain binds to CD20; and wherein the multispecific binding molecule comprises three polypeptide chains:

(a) a first polypeptide chain comprising the sequence
QVQLVQSGAEVKKPGASVKVSCKSSGYTFTDYYIHWVRQAPGQGLEWMGWINP
NSGDTNYAQKFQGRITMTRDTSISTAYLELSRLRSDDTAVFYCARNSGSYSFGYW
GQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCR
ASQGISSWLAWYQQKPGKAPKLLIFGASSLQSGVPSRFSGSGSGTDFTLTVSSLQP
EDFATYYCQQAYSFPFTFGPGTKVDIEEPKRSDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP
PSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:31);

(b) a second polypeptide chain comprising the sequence QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYP GNGDTSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDW YFNVWGAGTTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLSCAVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMH EALHNRFTQKSLSLSPG (SEQ ID NO:32); and

(c) a third polypeptide chain comprising the sequence QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASG VPVRFSGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:33).

174. The method of any one of claims 160-173, wherein at least one or two of the first and second antibody heavy chains is/are non-fucosylated.

175. The method of any one of claims 151-174, wherein the individual is a human.

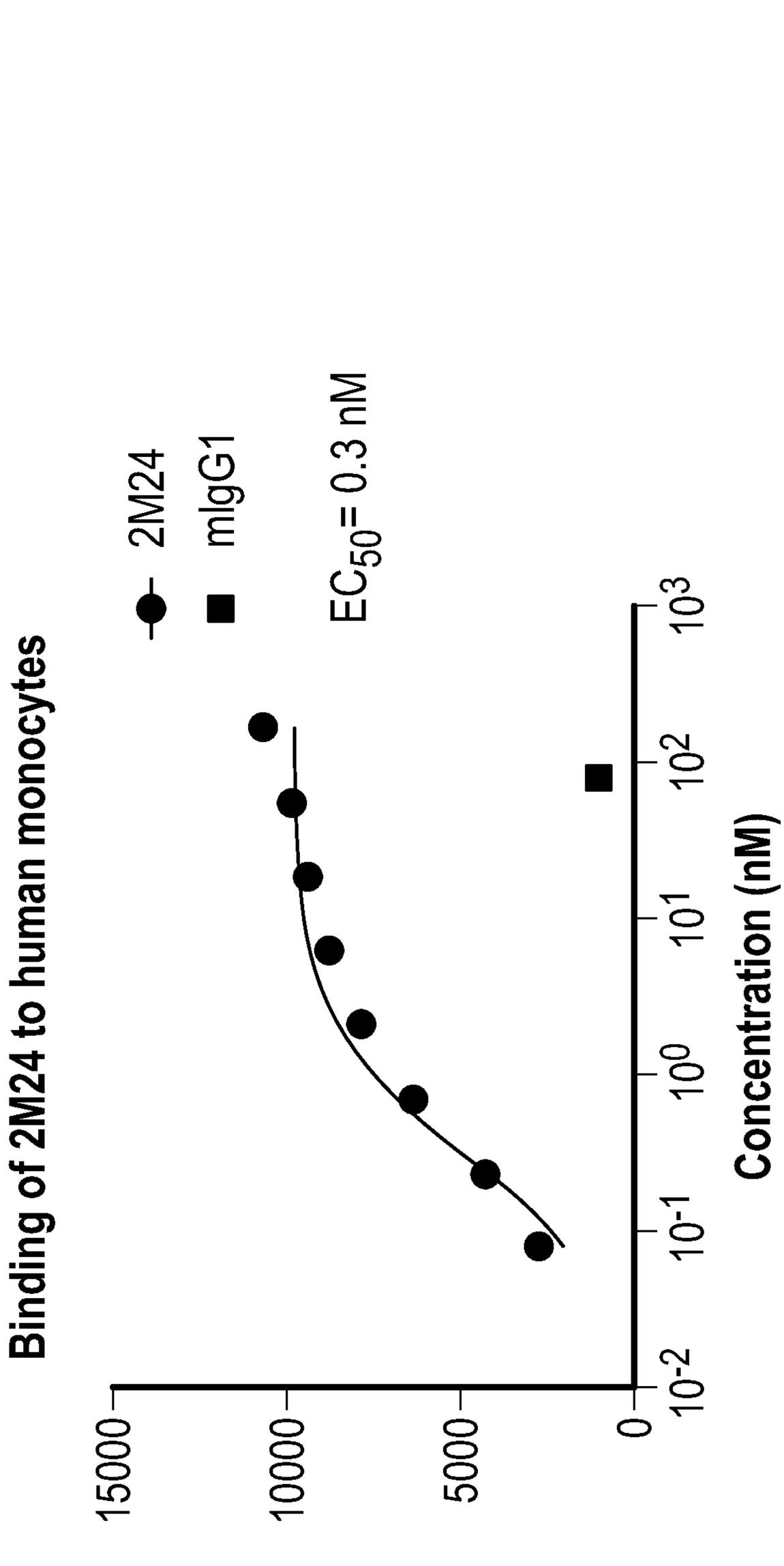

Binding of 2M24 to human monocytes
MFI
15000
10000
5000
0
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Concentration (nM)
2M24
mIgG1
EC_{50}= 0.3 nM

FIG. 1A

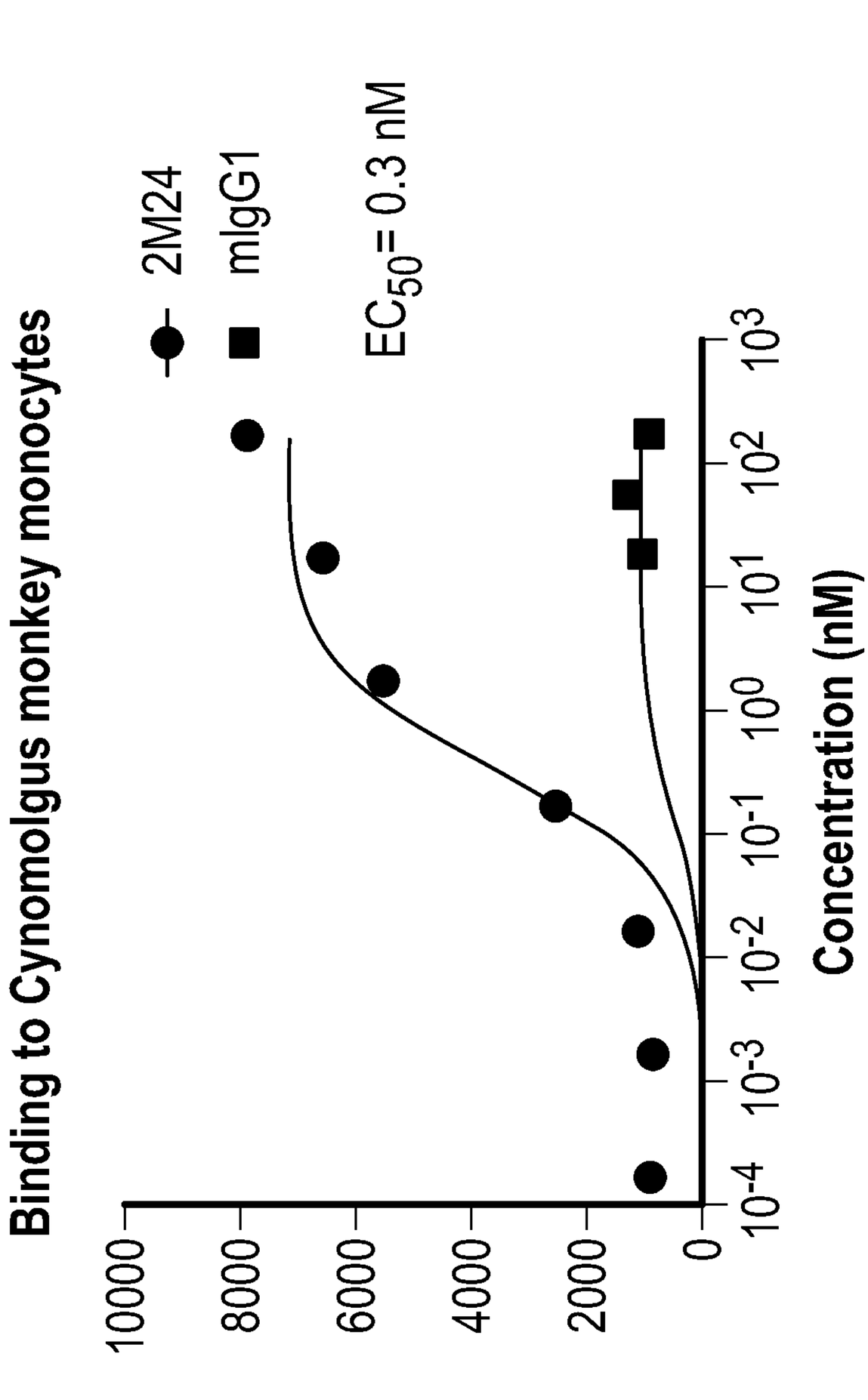

Binding to Cynomolgus monkey monocytes
2M24
mIgG1
EC_{50}= 0.3 nM
MFI
10000
8000
6000
4000
2000
0
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Concentration (nM)

FIG. 1B

Dectin-1 ab Clone	HEK-Blue hDectin-1a cells EC50 (nM)	HEK-Blue hDectin-1b cells EC50 (nM)	HEK293F hDectin-1a FL EC50 (nM))	Human monocytes EC50 (nM)	Cynomolgus monkey monocytes EC50 (nM)
2M24	0.4	1	1.1	0.3	0.3
2M08	2.6	>190	1.9	>190	N/A
2M12	16.9	>142	2.8	>142	N/A
2M38	4.5	>96	6.1	>96	N/A
2M49	>169	>169	>169	>169	N/A
15E2	1.2	9.3	1.4	0.6	14
259931	0.8	0.9	1.2	0.3	16.5
GE2	1.9	12	2.4	1.4	N/A

FIG. 1C

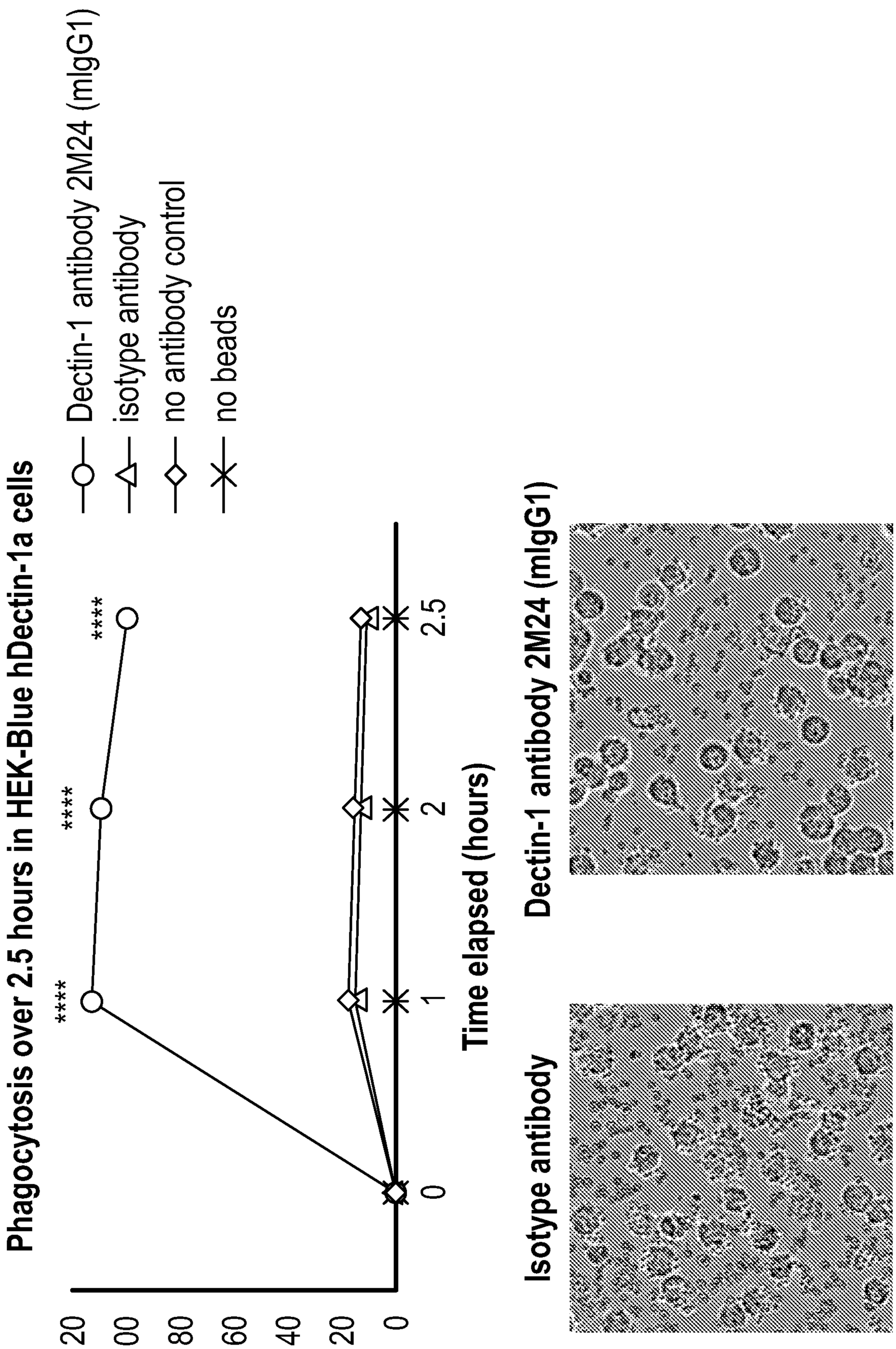

Phagocytosis over 2.5 hours in HEK-Blue hDectin-1a cells
Overlap (pHrod/calcein)/ green (calcein) object count
120
100
80
60
40
20
0
****
****
****
Time elapsed (hours)
0
1
2
2.5
Dectin-1 antibody
isotype antibody
no antibody control
no beads
Dectin-1 antibody 2M24 (mIgG1)
Isotype antibody (mIgG1)

FIG. 2A

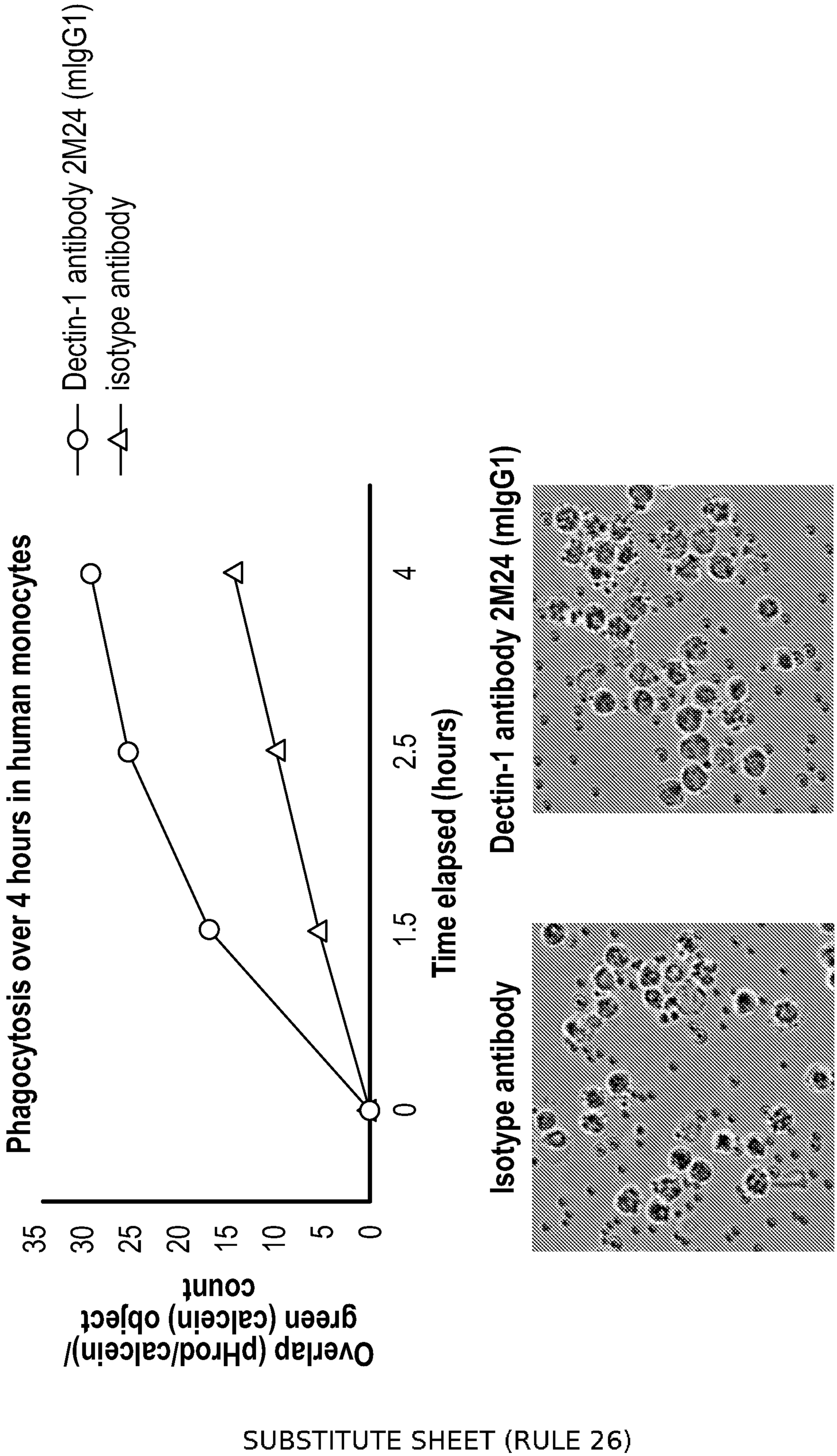

Phagocytosis over 4 hours in human monocytes
Overlap (pHrod/calcein)/ green (calcein) object count
35
30
25
20
15
10
5
0
0
1.5
2.5
4
Time elapsed (hours)
Dectin-1 antibody
isotype antibody
Dectin-1 antibody 2M24 (mIgG1)
Isotype antibody 2M24 (mIgG1)

FIG. 2B

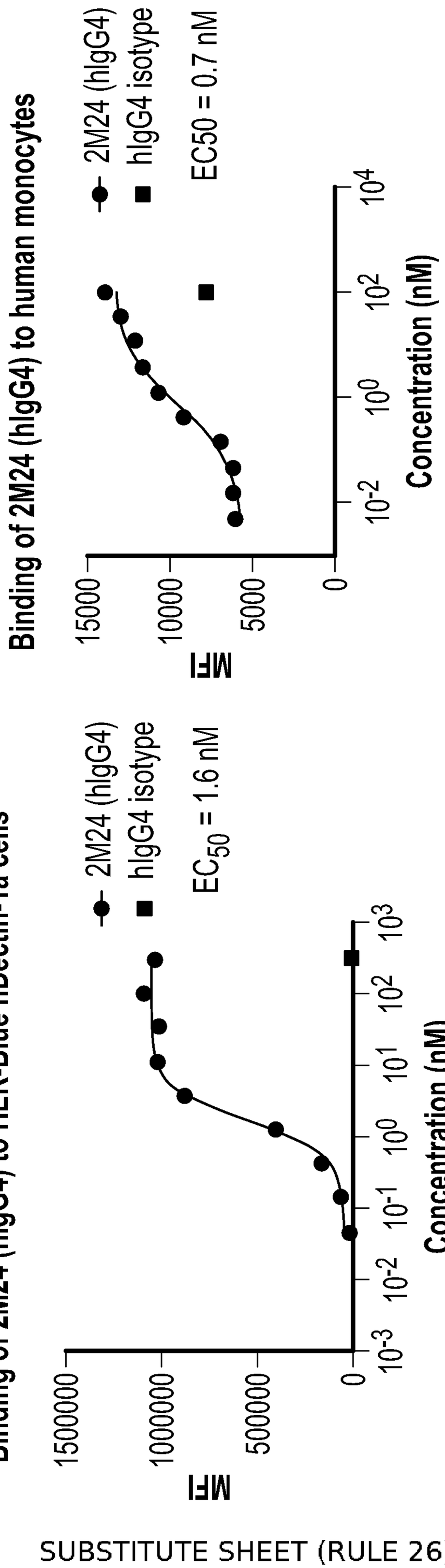

Binding of 2M24 (hIgG4) to human monocytes
2M24 (hIgG4)
hIgG4 isotype
EC50 = 0.7 nM
MFI
15000
10000
5000
0
10^{-2}
10^{0}
10^{2}
10^{4}
Concentration (nM)

FIG.3B

Binding of 2M24 (hIgG4) to HEK-Blue hDectin-1a cells
2M24 (hIgG4)
hIgG4 isotype
EC_{50} = 1.6 nM
MFI
1500000
1000000
500000
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
Concentration (nM)

FIG.3A

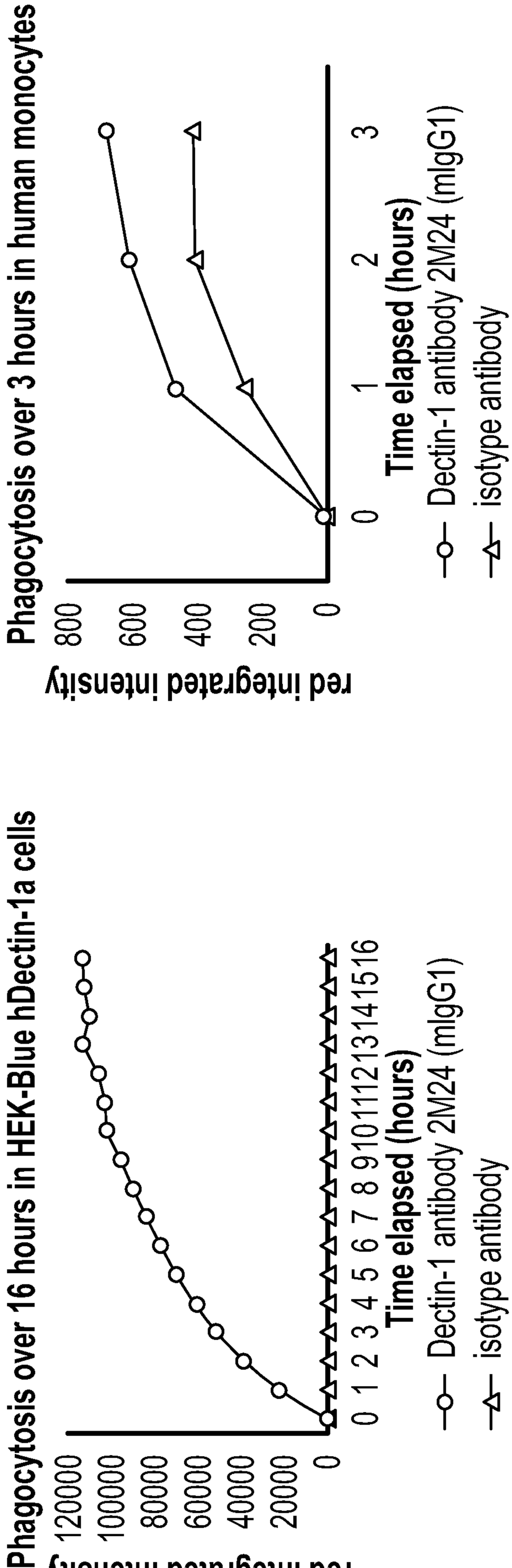

Phagocytosis over 3 hours in human monocytes
red integrated intensity
800
600
400
200
0
0
1
2
3
Time elapsed (hours)
Dectin-1 antibody 2M24 (mIgG1)
isotype antibody
Phagocytosis over 3 hours in human macrophages
red integrated intensity
50000
40000
30000
20000
10000
0
0
0.5
1
2
3
Time elapsed (hours)
Dectin-1 antibody 2M24 (mIgG1)
isotype antibody
Phagocytosis over 3 hours in HEK-Blue hDectin-1a cells
red integrated intensity
120000
100000
80000
60000
40000
20000
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time elapsed (hours)
Dectin-1 antibody 2M24 (mIgG1)
isotype antibody

FIG. 4

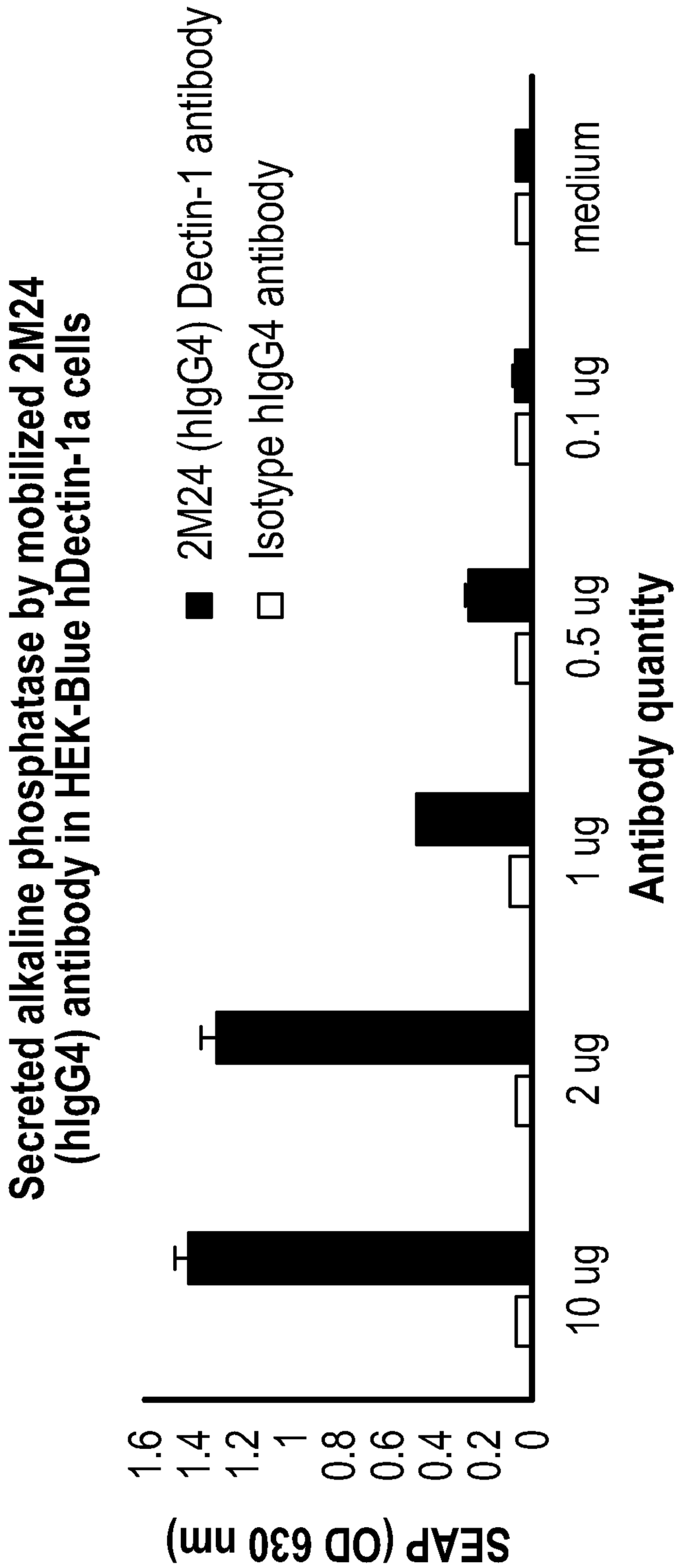

Secreted alkaline phosphatase by mobilized 2M24 (hIgG4) antibody in HEK-Blue hDectin-1a cells
2M24 (hIgG4) Dectin-1 antibody
Isotype hIgG4 antibody
SEAP (OD 630 nm)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
10 ug
2 ug
1 ug
0.5 ug
0.1 ug
medium
Antibody quantity

FIG. 5A

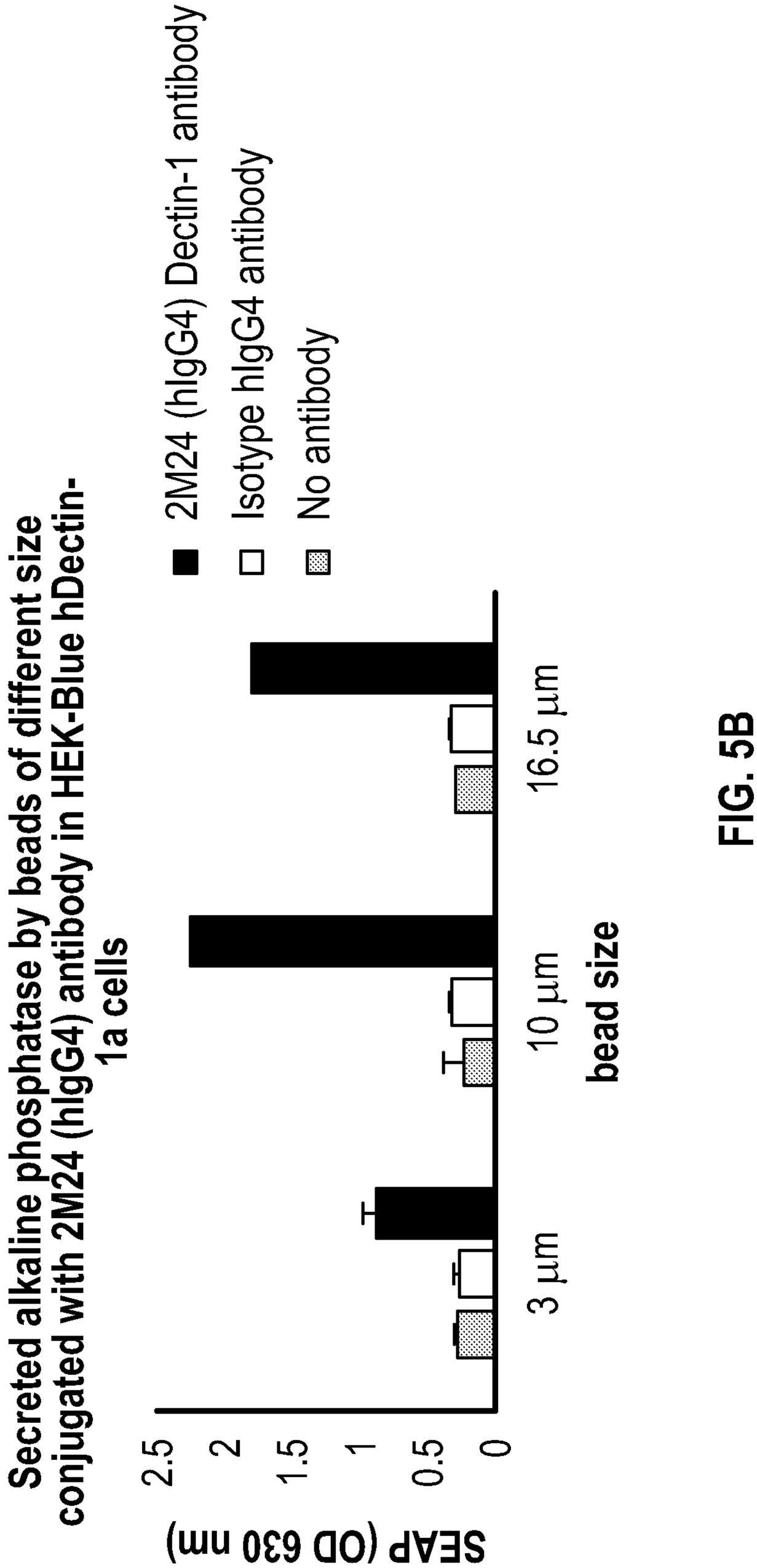

Secreted alkaline phosphatase by beads of different size conjugated with 2M24 (hIgG4) antibody in HEK-Blue hDectin-1a cells
2M24 (hIgG4) Dectin-1 antibody
Isotype hIgG4 antibody
No antibody
SEAP (OD 630 nm)
2.5
2
1.5
1
0.5
0
3 µm
10 µm
16.5 µm
bead size

FIG. 5B

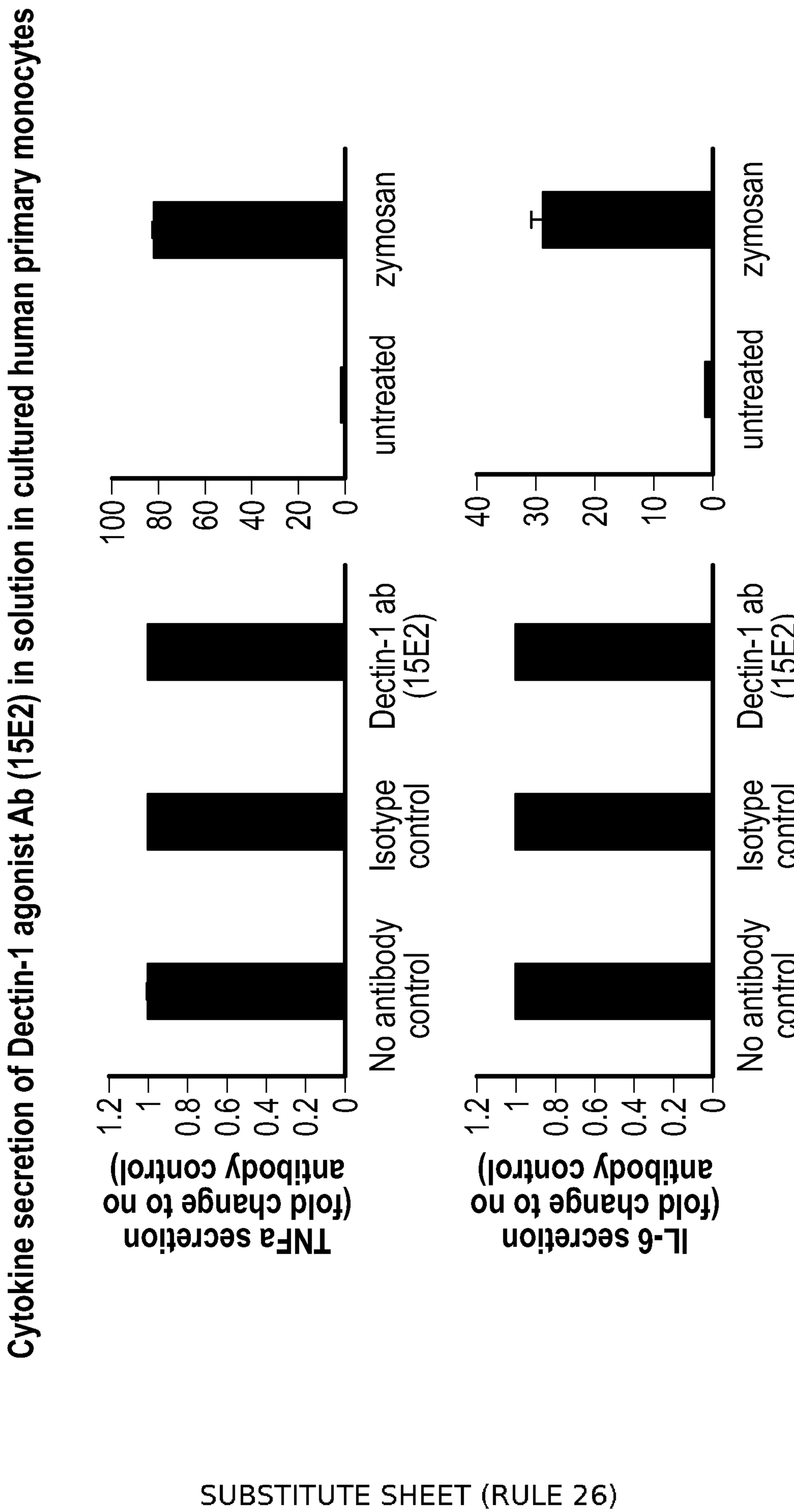

Cytokine secretion in cultured human primary monocytes
Cytokine secretion of Dectin-1 agonist Ab (15E2) in solution
TNFa secretion (fold change to no antibody control)
IL-6 secretion (fold change to no antibody control)
1.2
1
0.8
0.6
0.4
0.2
0
100
80
60
40
20
0
40
30
20
10
0
untreated
zymosan
No antibody control
Isotype control
Dectin-1 ab (15E2)

FIG. 6A

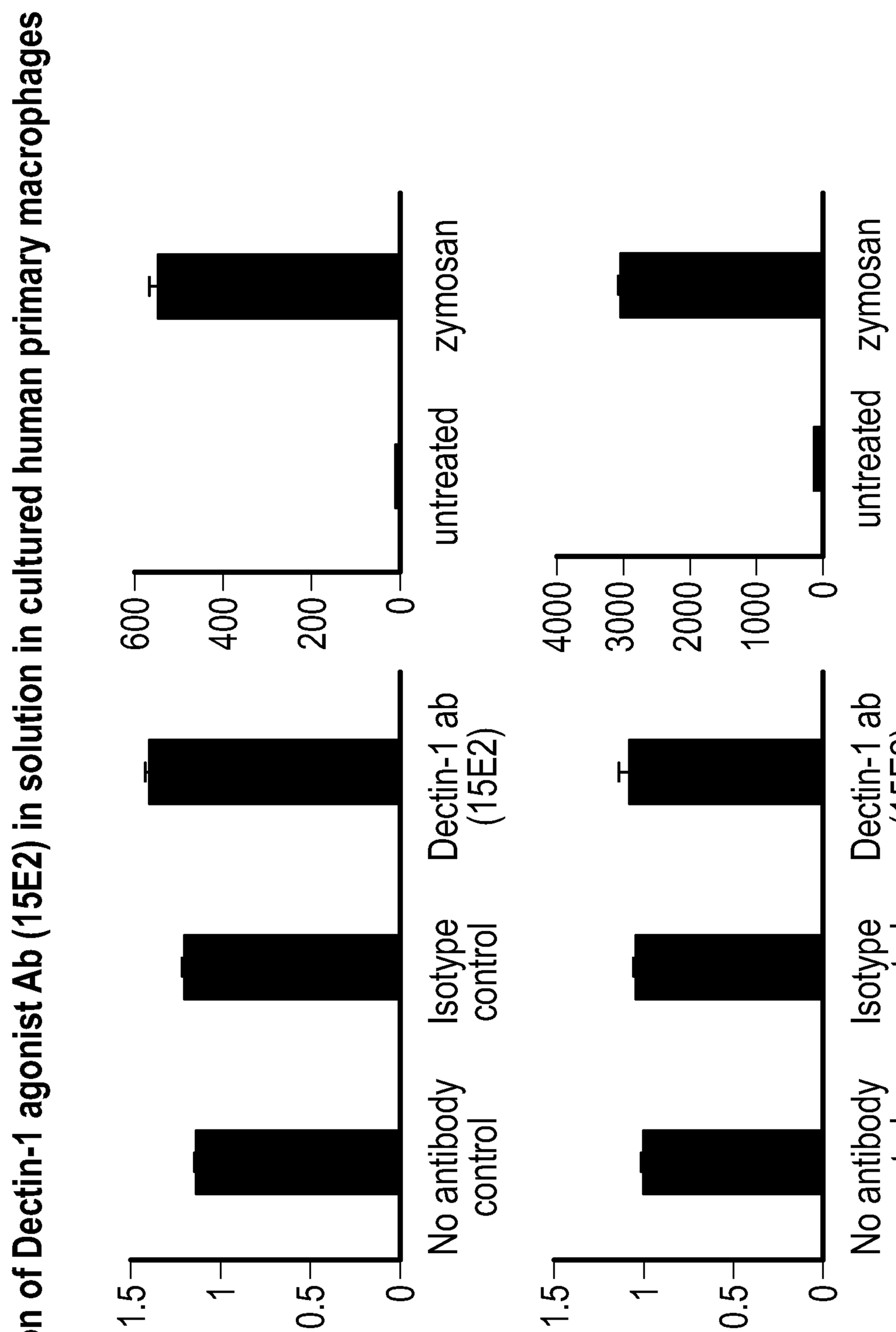

Cytokine secretion of Dectin-1 agonist Ab (15E2) in solution in cultured human primary macrophages
IL-6 secretion (fold change to no antibody control)
TNFa secretion (fold change to no antibody control)
0
0.5
1
1.5
0
1000
2000
3000
4000
0
200
400
600
No antibody control
Isotype control
Dectin-1 ab (15E2)
untreated
zymosan

FIG. 6B

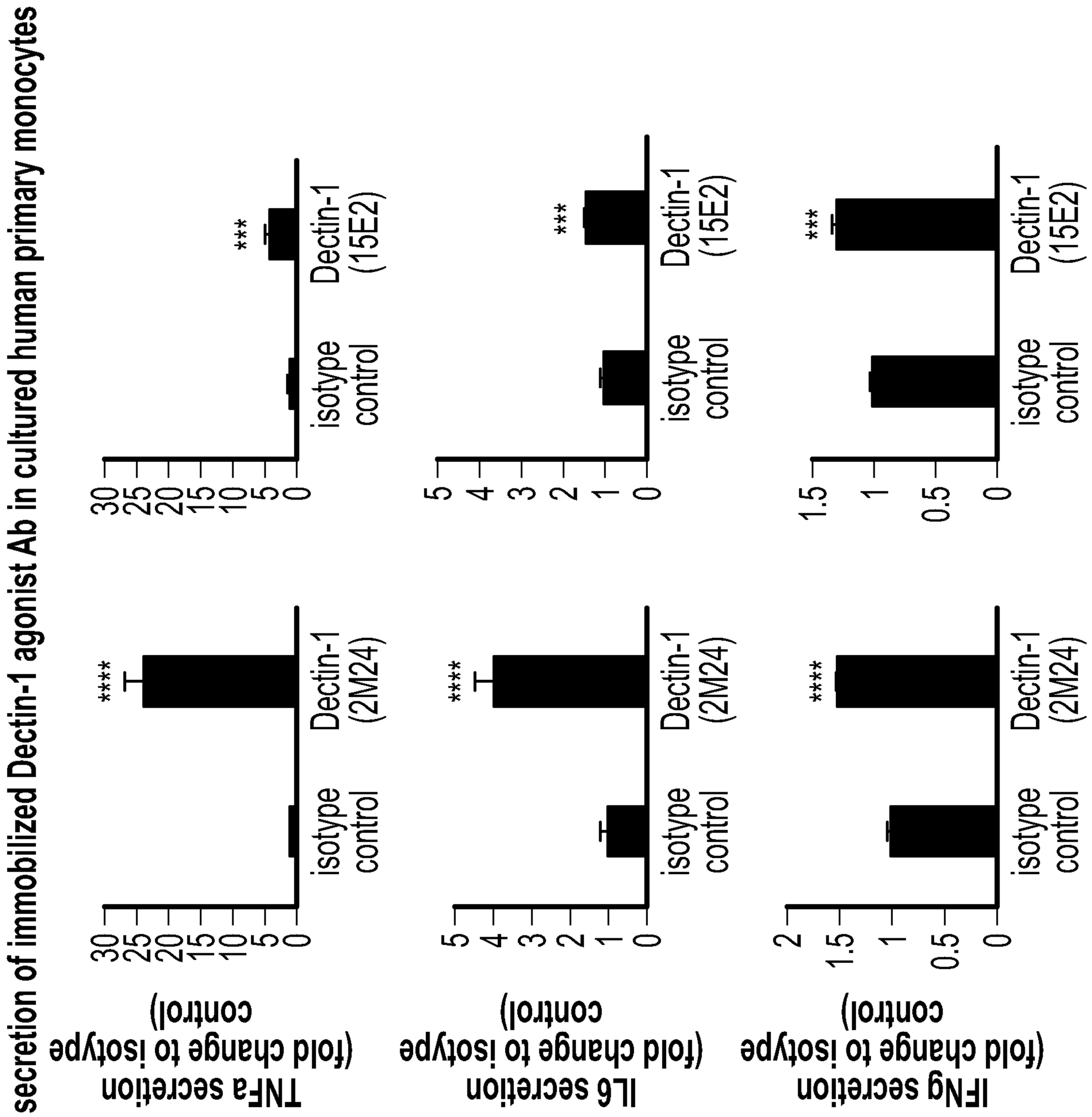

Cytokine secretion of immobilized Dectin-1 agonist Ab in cultured human primary monocytes
IFNg secretion (fold change to isotype control)
IL6 secretion (fold change to isotype control)
TNFa secretion (fold change to isotype control)
***
****
isotype control
Dectin-1 (15E2)
Dectin-1 (2M24)
0
0.5
1
1.5
2
3
4
5
10
15
20
25
30

FIG. 7A

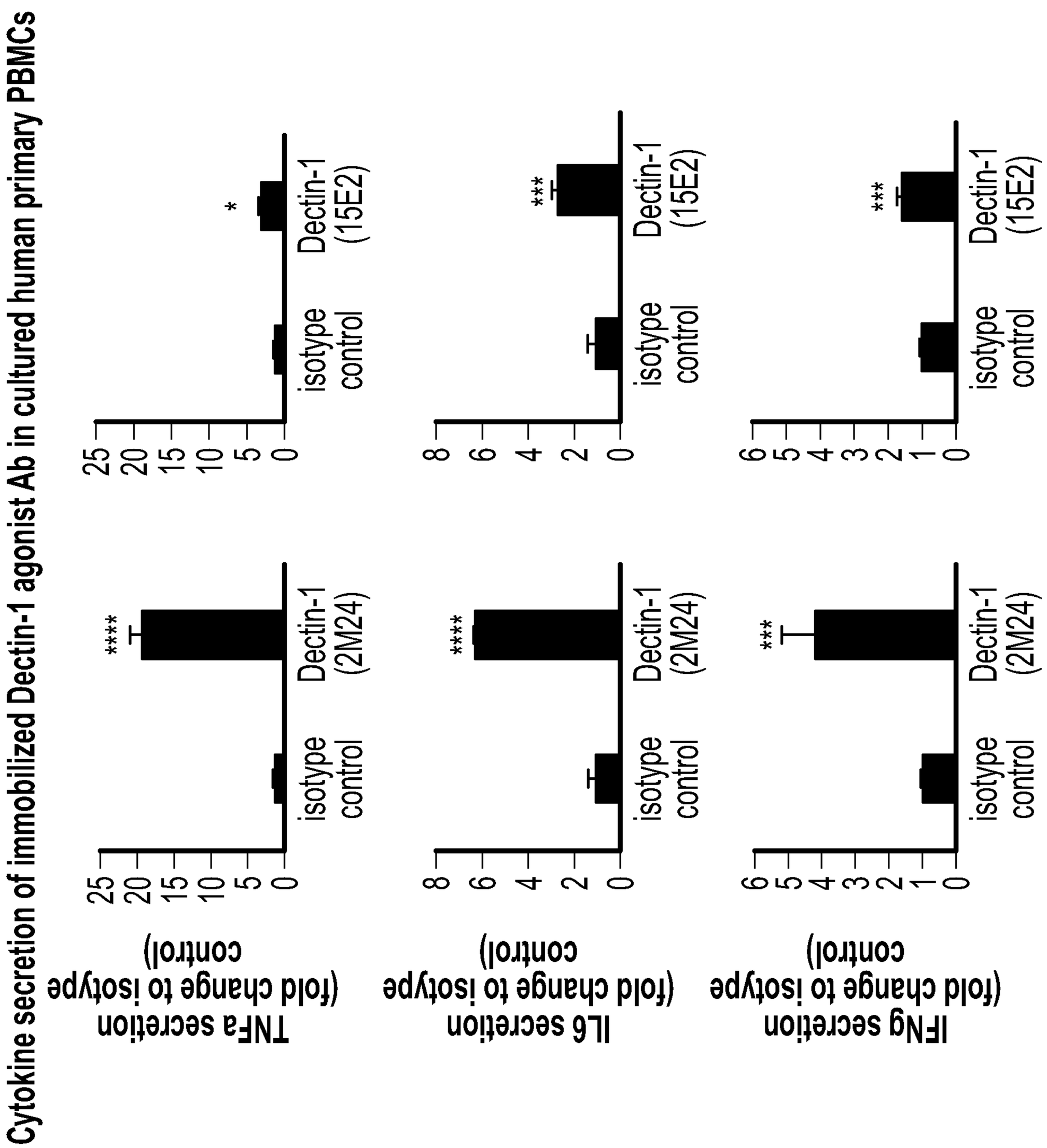

Cytokine secretion of immobilized Dectin-1 agonist Ab in cultured human primary PBMC
IFNg secretion (fold change to isotype control)
IL6 secretion (fold change to isotype control)
TNFa secretion (fold change to isotype control)
isotype control
Dectin-1 (15E2)
Dectin-1 (2M24)
*
***
****
0
2
4
5
6
8
10
15
20
25

FIG. 7B

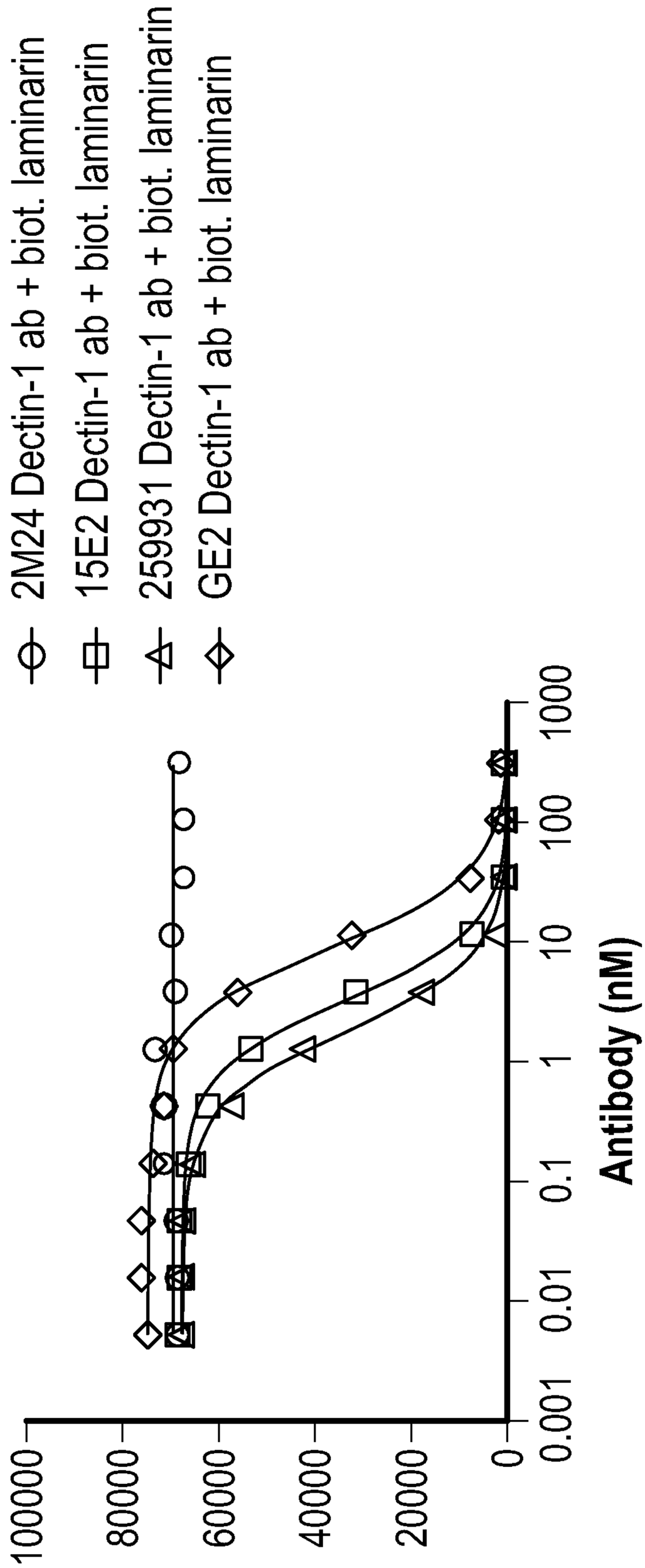

2M24 Dectin-1 ab + biot. laminarin
15E2 Dectin-1 ab + biot. laminarin
259931 Dectin-1 ab + biot. laminarin
GE2 Dectin-1 ab + biot. laminarin
MFI
100000
80000
60000
40000
20000
0
0
.001
0.01
0.1
1
10
100
1000
Antibody (nM)

FIG. 8

Dectin-1 antibody Clone	HEK-Blue hDectin-1a cells EC50 (nM)	HEK-Blue hDectin-1b cells EC50 (nM)	HEK293F hDectin-1a FL EC50 (nM))	Human monocytes EC50 (nM)	Competition with natural ligands	TNFa secretion in PBMC (fold change to isotype)	IL6 secretion in PBMC (fold change to isotype)	IFNg secretion in PBMC (fold change to isotype)	Phagocytosis
2M24	0.4	1	1.1	0.3	NO	19	6.4	4.1	YES
15E2	1.2	9.3	1.4	0.6	YES	3	2.6	1.6	YES

FIG. 9

SUBSTITUTE SHEET (RULE 26)

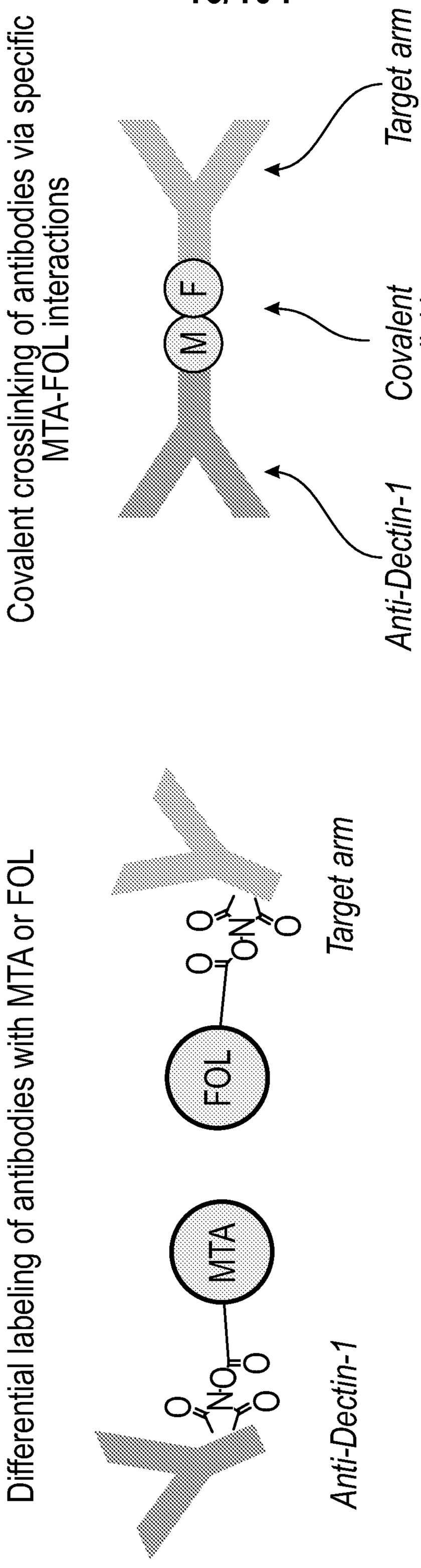
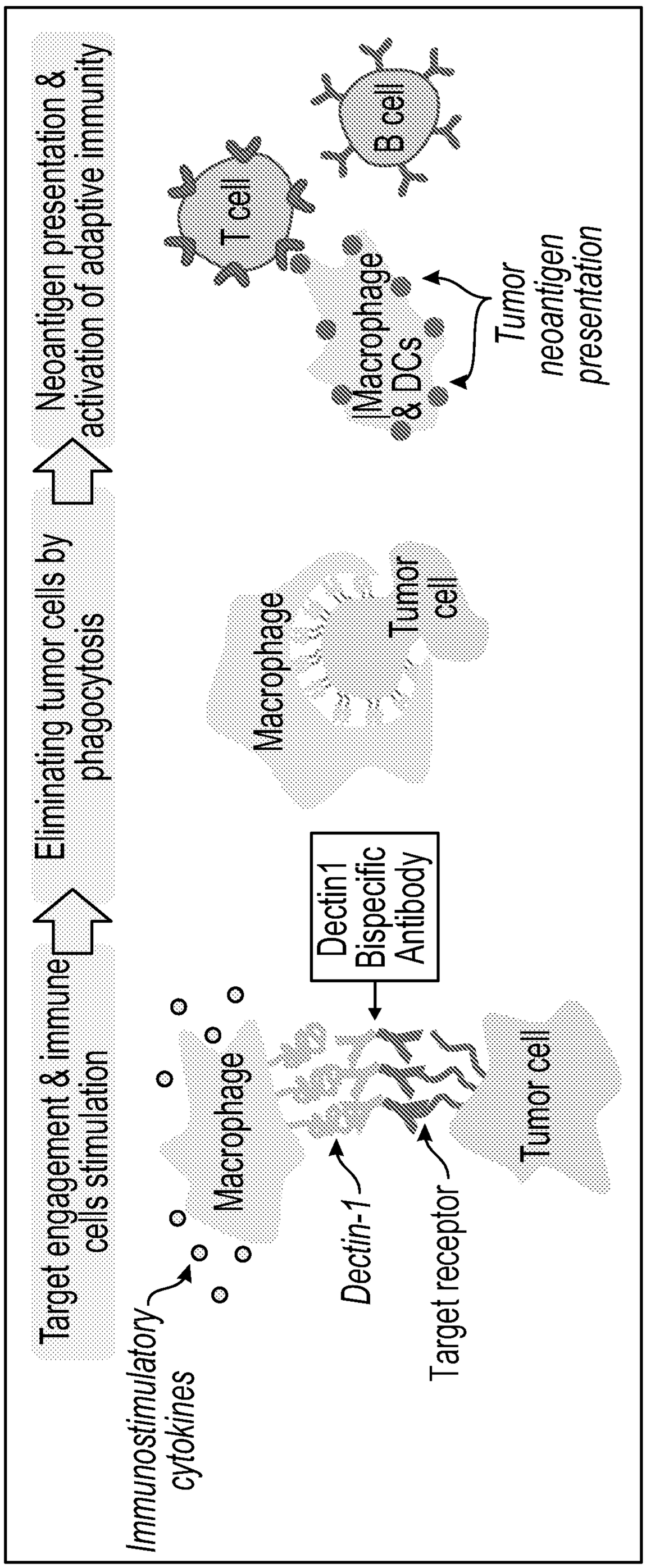


FIG. 10A

FIG. 10B

FIG. 11A



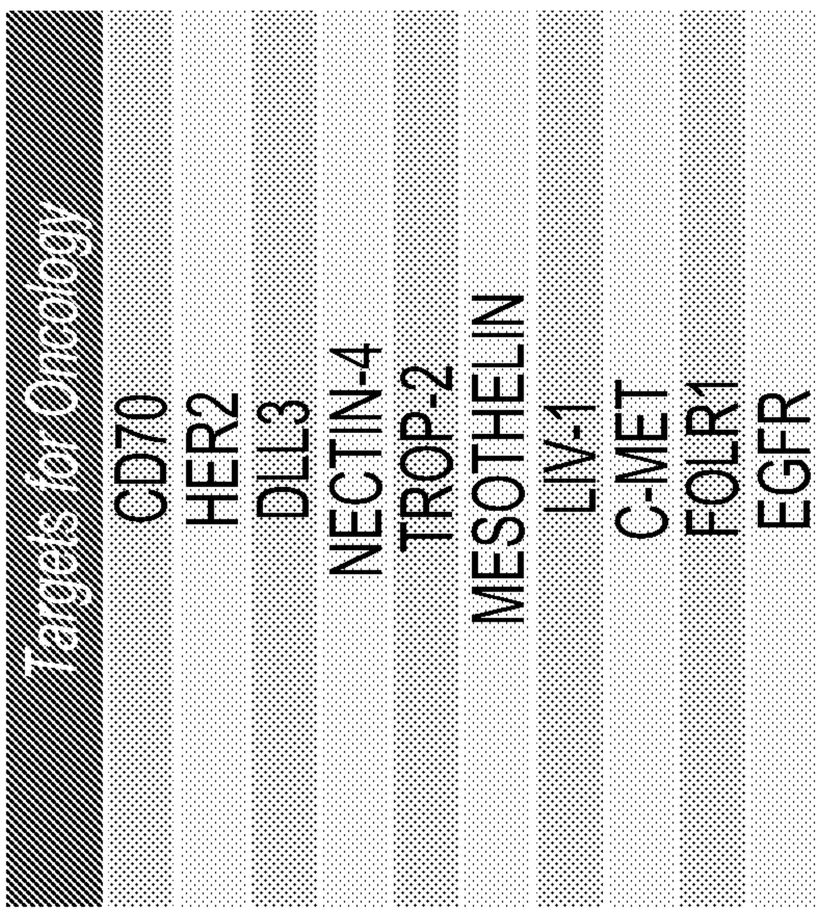


FIG. 11B

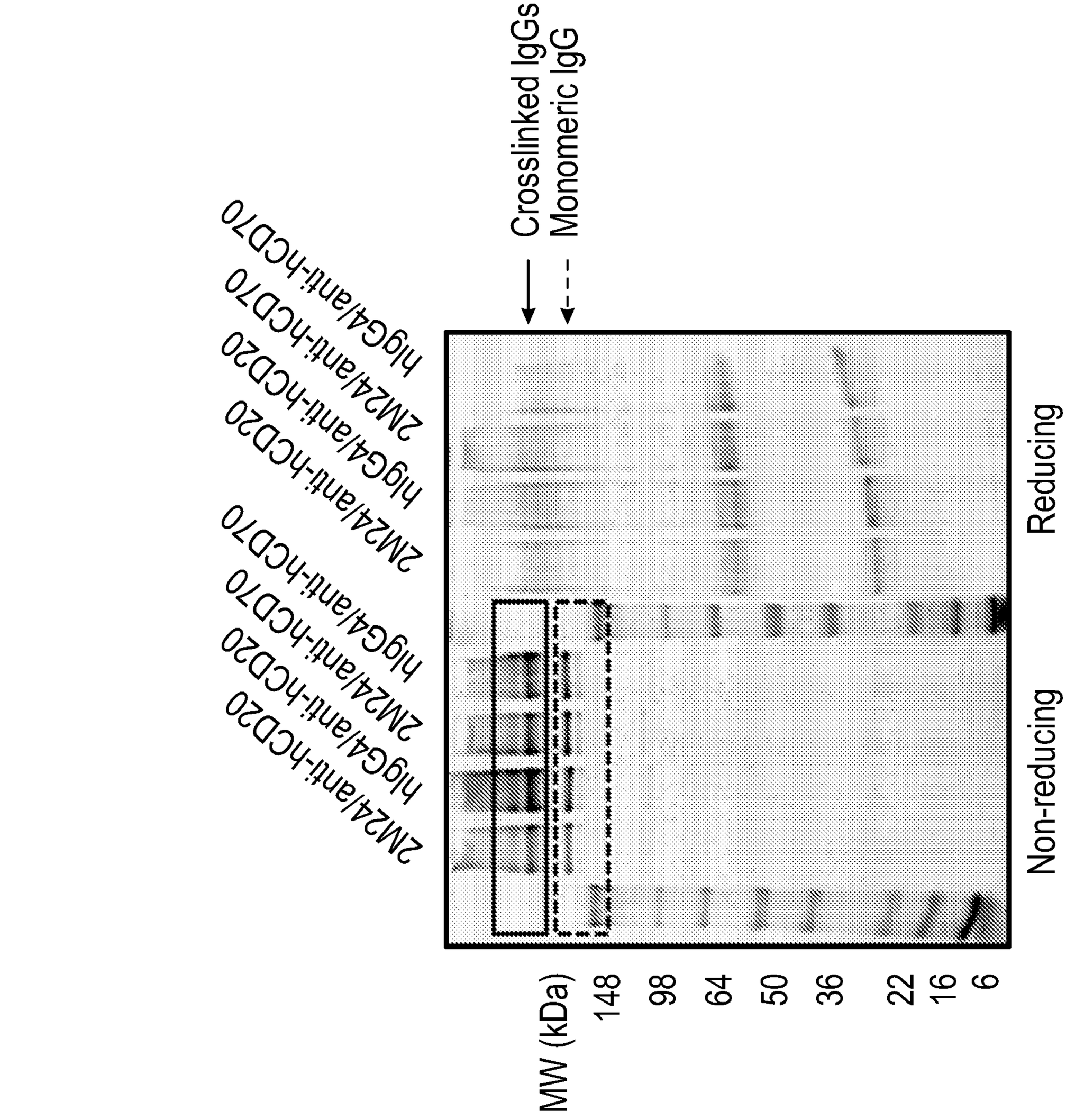

MW (kDa)
148
98
64
50
36
22
16
6
Non-reducing
Reducing
Crosslinked IgG
Monomeric IgG
2M24/anti-hCD70
hIgG4/anti-hCD20
2M24/anti-hCD20
hIgG4/anti-hCD70
2M24/anti-hCD20
hIgG4/anti-hCD70
2M24/anti-hCD20
hIgG4/anti-hCD70

FIG. 12A

EC50 concentration (nM) of 2M24/anti-hCD70 bispecific binding to cell lines	
Dectin-1 expressing HEK293 cell line	1.8nM
A498 cell line	12.34 nM
786-0 cell line	11.62 nM

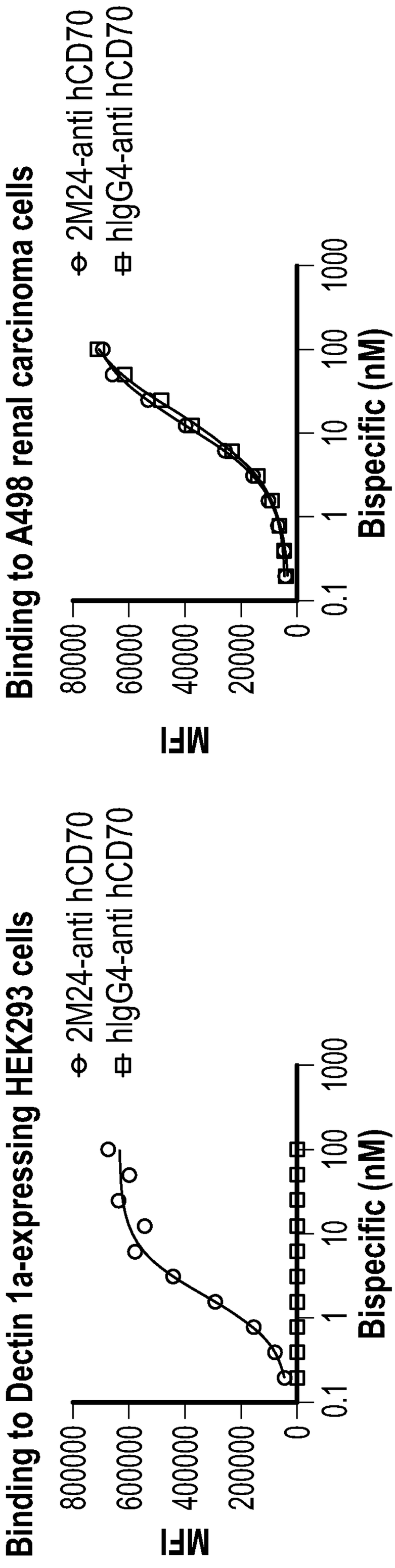


FIG. 12B

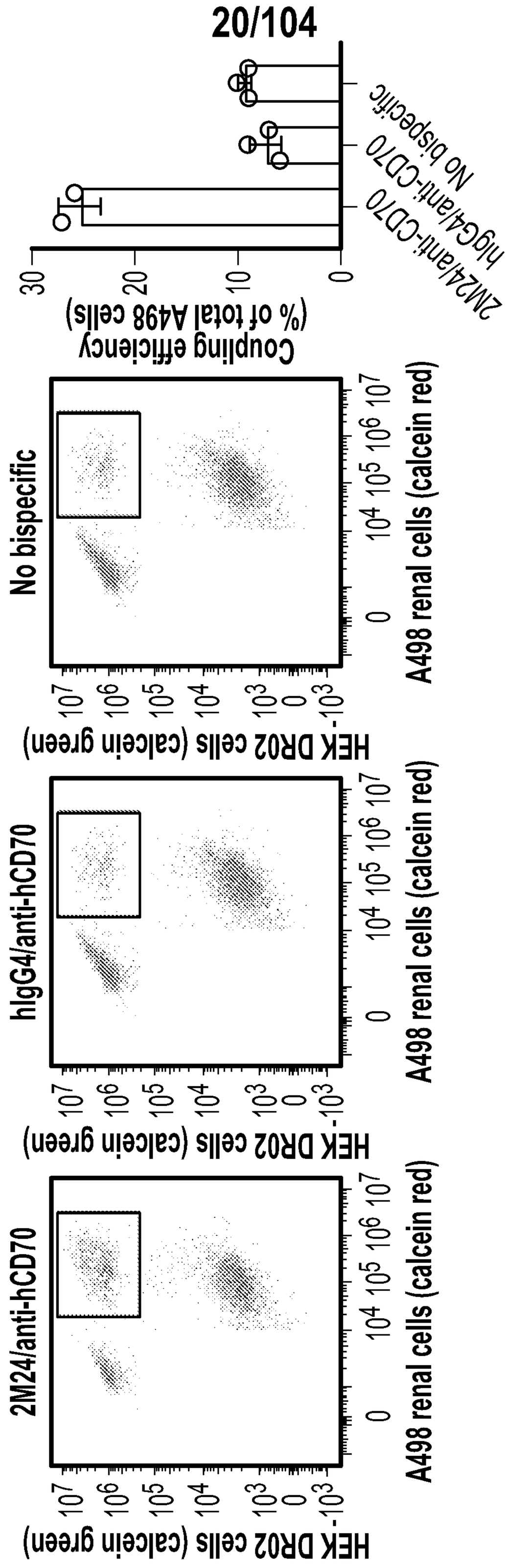

Coupling efficiency
(% of total A498 cells)
30
20
10
0
2M24/anti-CD70
hIgG4/anti-CD70
No bispecific
No bispecific
HEK DR02 cells (calcein green)
A498 renal cells (calcein red)
hIgG4/anti-hCD70
2M24/anti-hCD70

FIG. 13

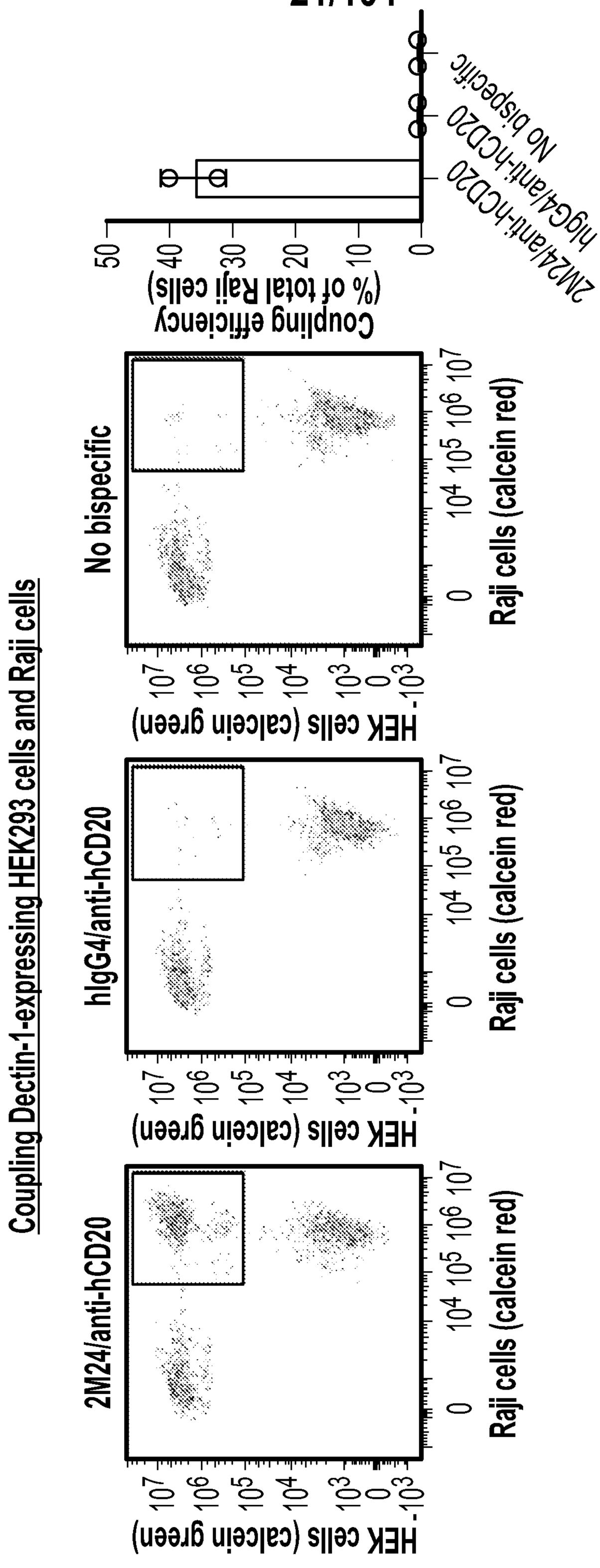

Coupling Dectin-1-expressing HEK293 cells and Raji cells
Coupling efficiency
(% of total Raji cells)
50
40
30
20
10
0
2M24/anti-hCD20
hIgG4/anti-hCD20
No bispecific
No bispecific
hIgG4/anti-hCD20
2M24/anti-hCD20
HEK cells (calcein green)
Raji cells (calcein red)
10^7
10^6
10^5
10^4
10^3
0
-10^3
0
10^4
10^5
10^6
10^7

FIG. 14A

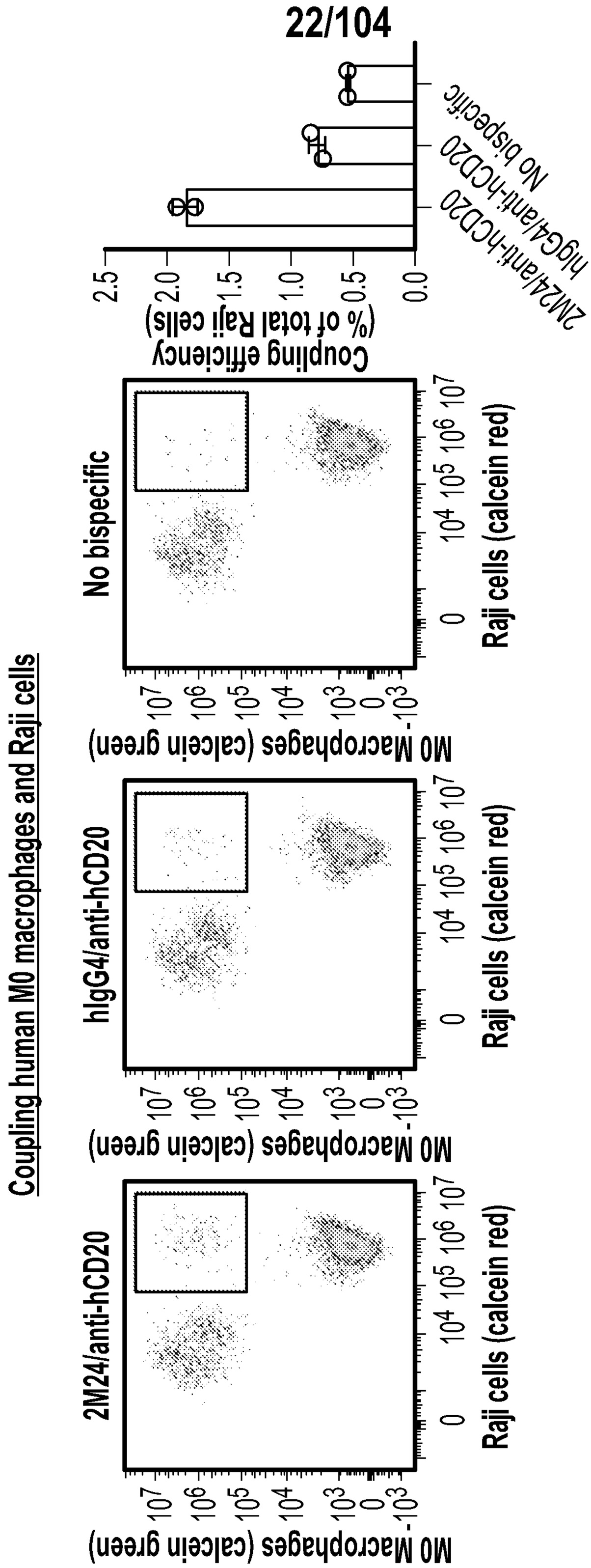

2M24/anti-hCD20
hIgG4/anti-hCD20
No bispecific
(% of total Raji cells)
2.5
2.0
1.5
1.0
0.5
0.0
Coupling efficiency
No bispecific
hIgG4/anti-hCD20
2M24/anti-hCD20
M0 Macrophages (calcein green)
Raji cells (calcein red)
10^7
10^6
10^5
10^4
10^3
0
-10^3
10^4 10^5 10^6 10^7

FIG. 14B

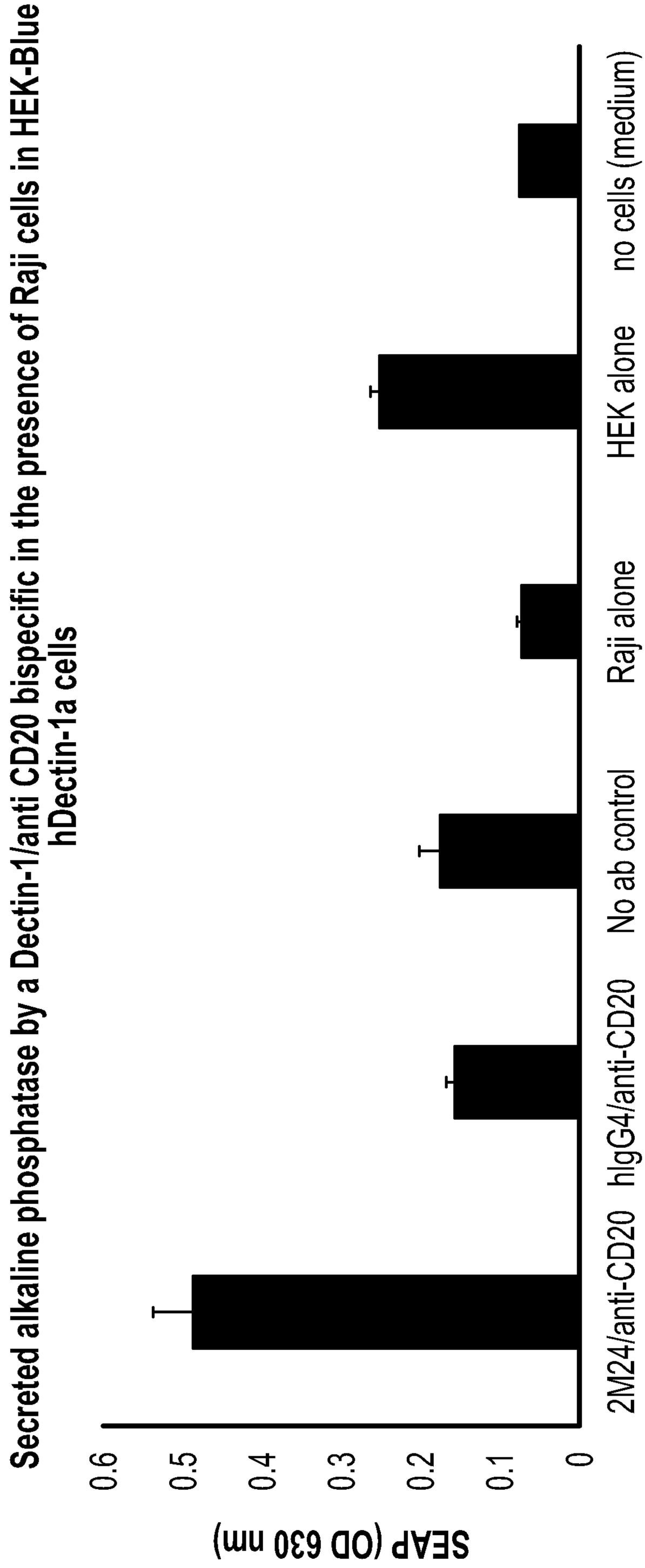

Secreted alkaline phosphatase by a Dectin-1/anti CD20 bispecific in the presence of Raji cells in HEK-Blue hDectin-1a cells
SEAP (OD 630 nm)
0.6
0.5
0.4
0.3
0.2
0.1
0
2M24/anti-CD20 hIgG4/anti-CD20
No ab control
Raji alone
HEK alone
no cells (medium)

FIG. 15

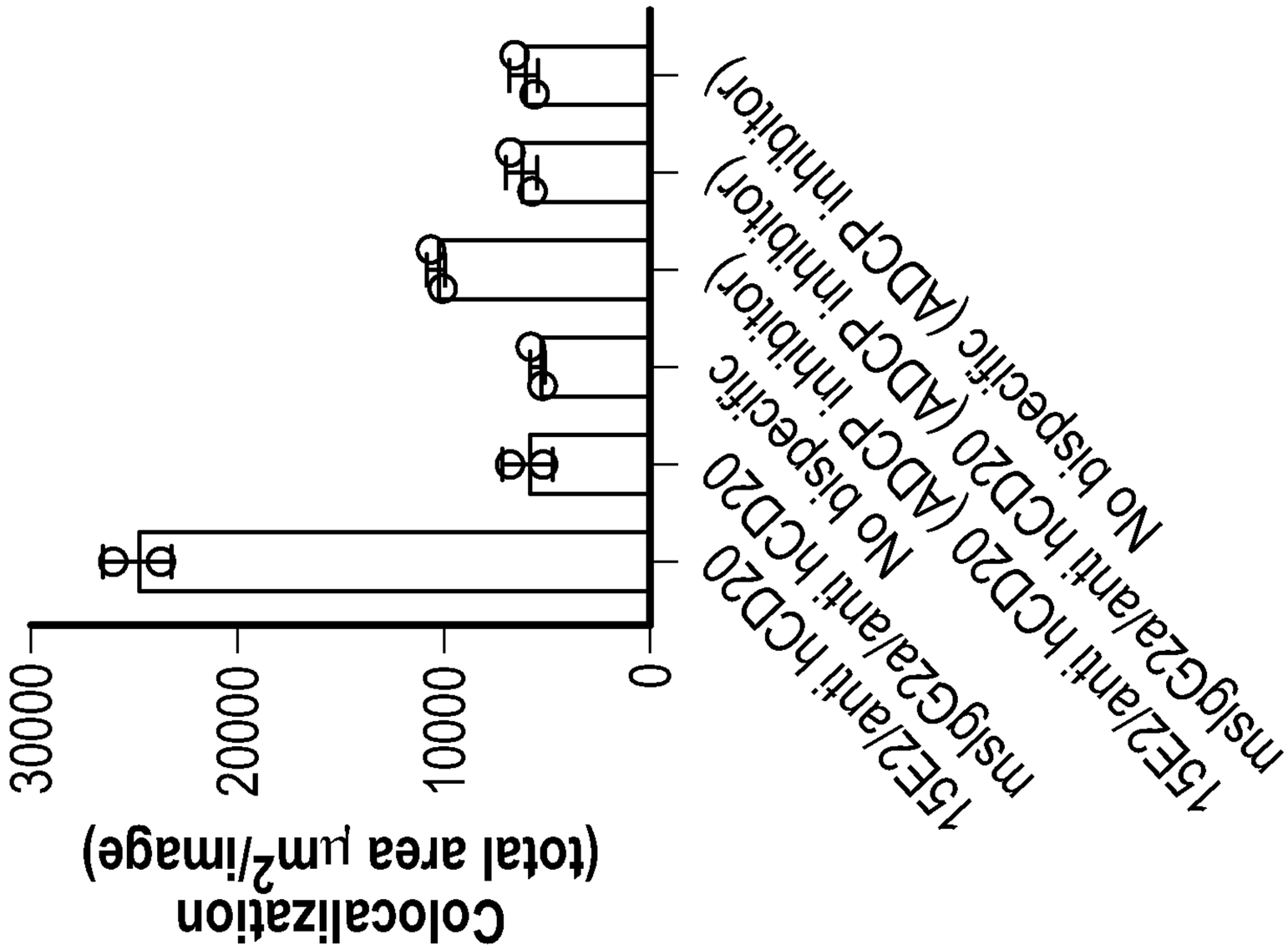

Colocalization
(total area μm²/image)
30000
20000
10000
0
15E2/anti hCD20
msIgG2a/anti hCD20
No bispecific
15E2/anti hCD20 (ADCP inhibitor)
msIgG2a/anti hCD20 (ADCP inhibitor)
No bispecific (ADCP inhibitor)
Treatment with 15E2/anti hCD20 bispecific
HEK/RAJI (time 0h)
HEK/RAJI (time 16h)
Phase contrast
Overlap fluorescence

FIG. 16

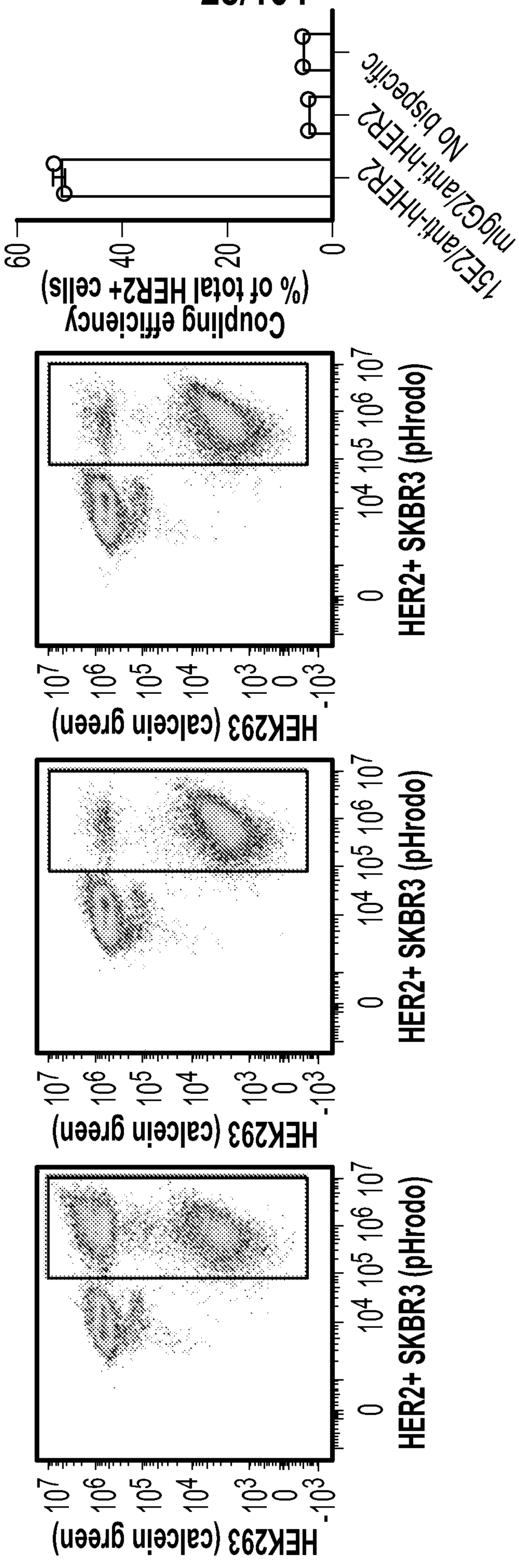

Coupling efficiency
(% of total HER2+ cells)
0
20
40
60
15E2/anti-hHER2
mIgG2/anti-hHER2
No bispecific
HEK293 (calcein green)
HER2+ SKBR3 (pHrodo)
-10^3
0
10^3
10^4
10^5
10^6
10^7

FIG. 1

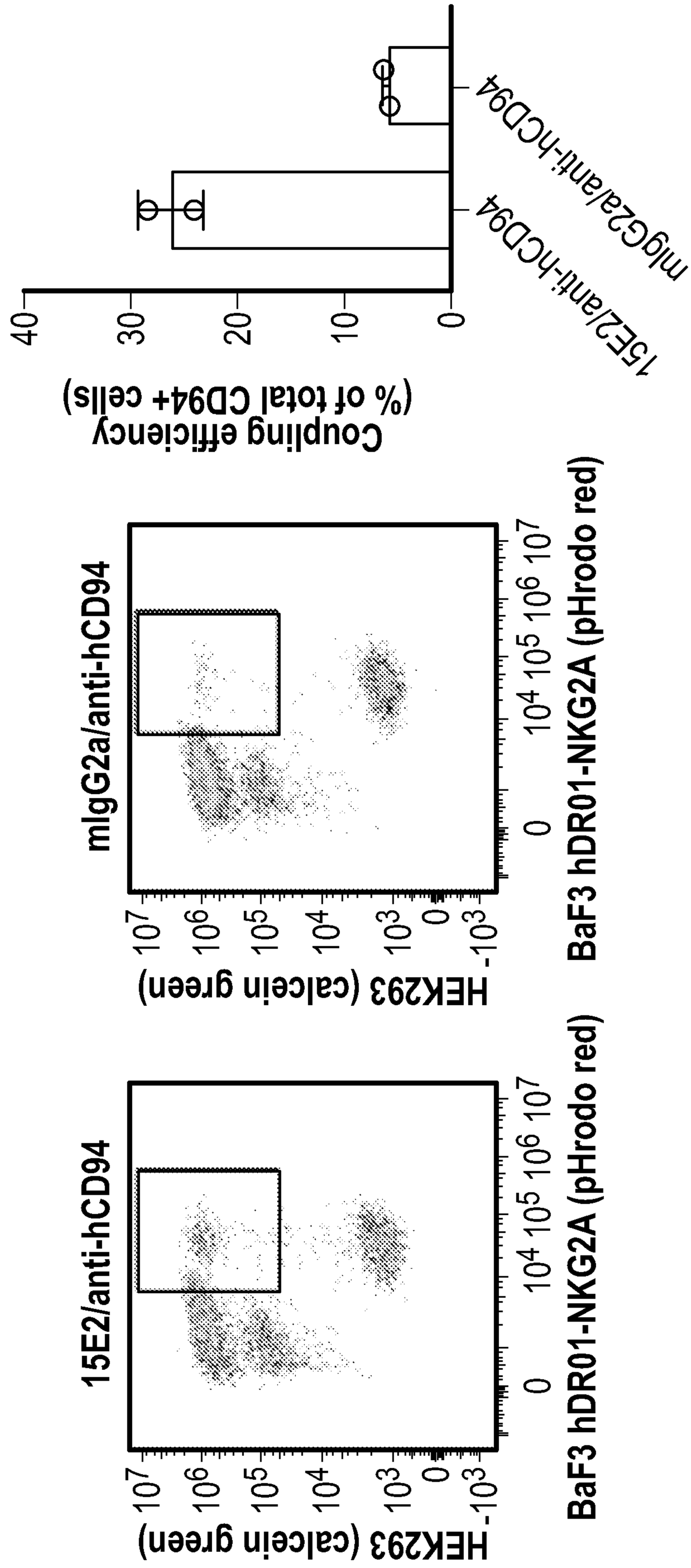

15E2/anti-hCD94
mIgG2a/anti-hCD94
Coupling efficiency
(% of total CD94+ cells)
0
10
20
30
40
mIgG2a/anti-hCD94
15E2/anti-hCD94
HEK293 (calcein green)
BaF3 hDR01-NKG2A (pHrodo red)
-10^3
0
10^3
10^4
10^5
10^6
10^7

FIG. 18

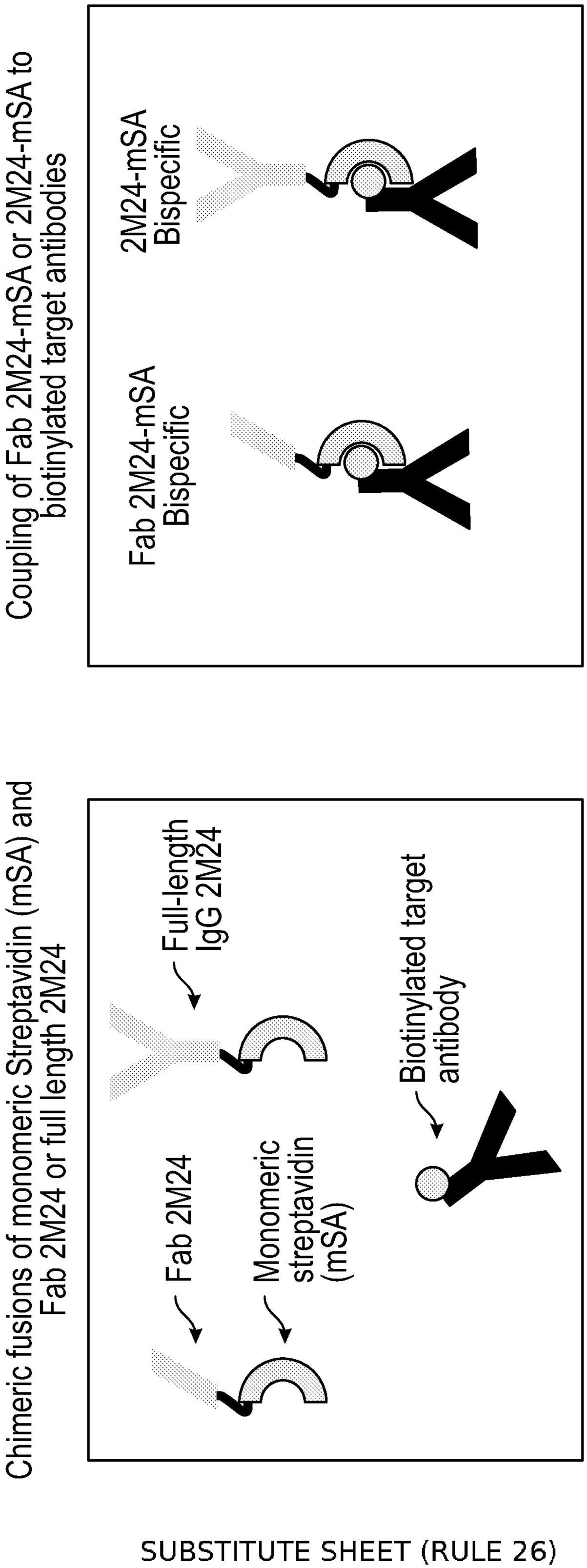


FIG. 19B

FIG. 19A

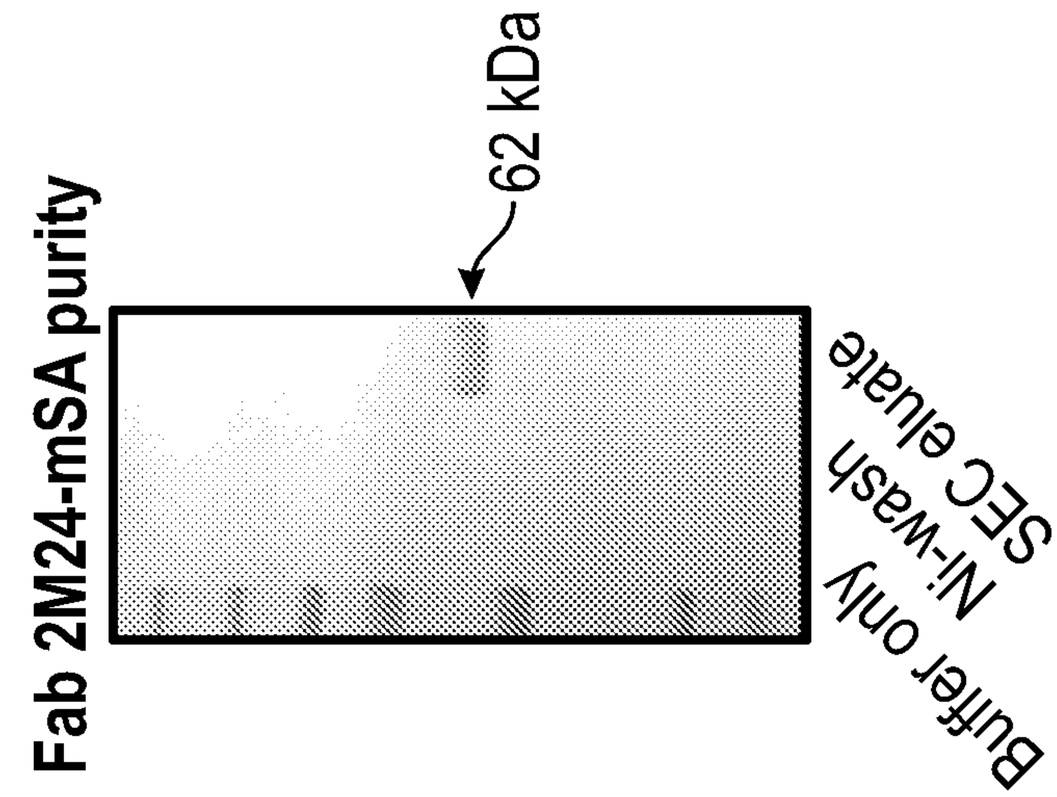


FIG. 20B

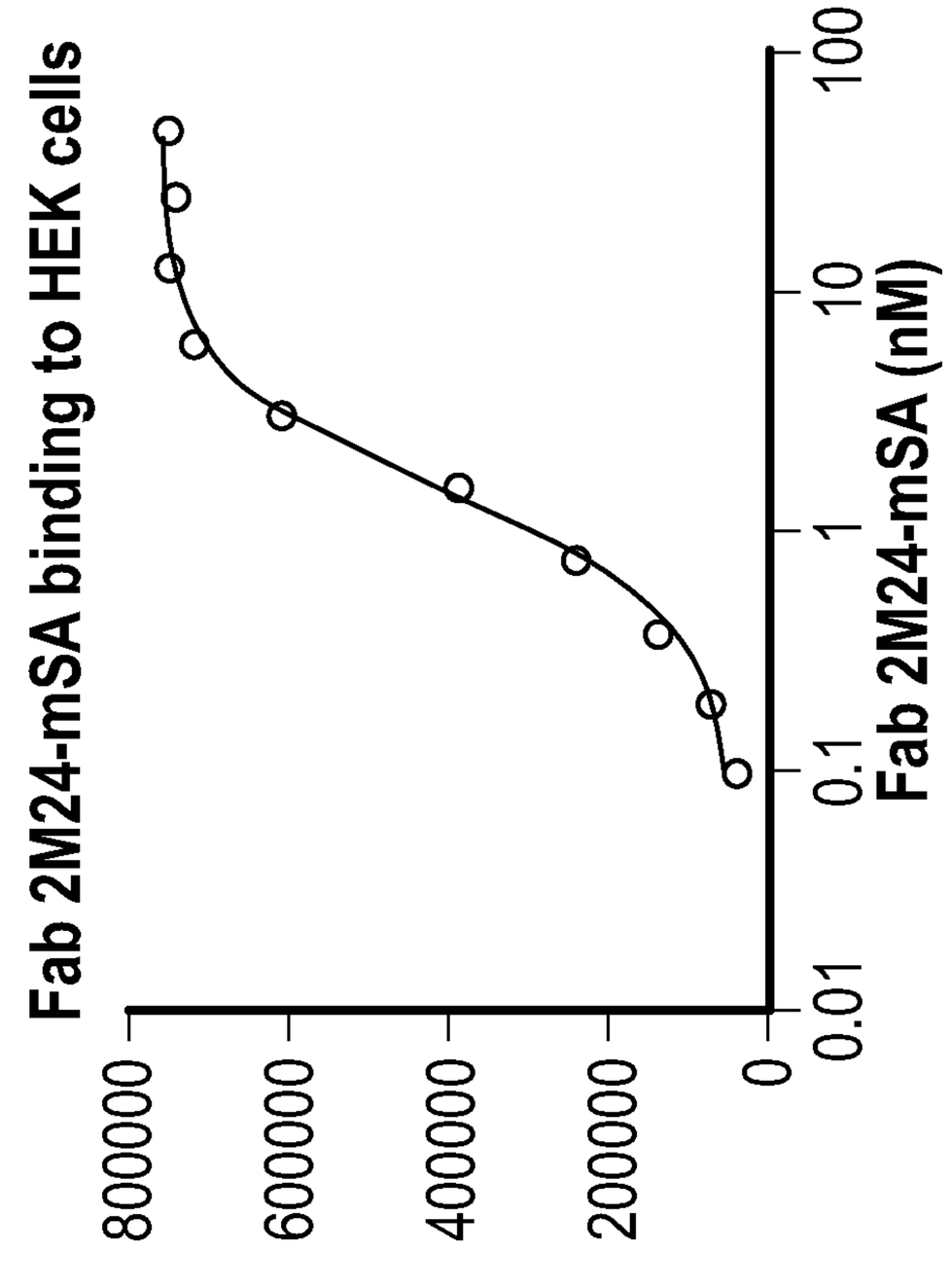


FIG. 20C

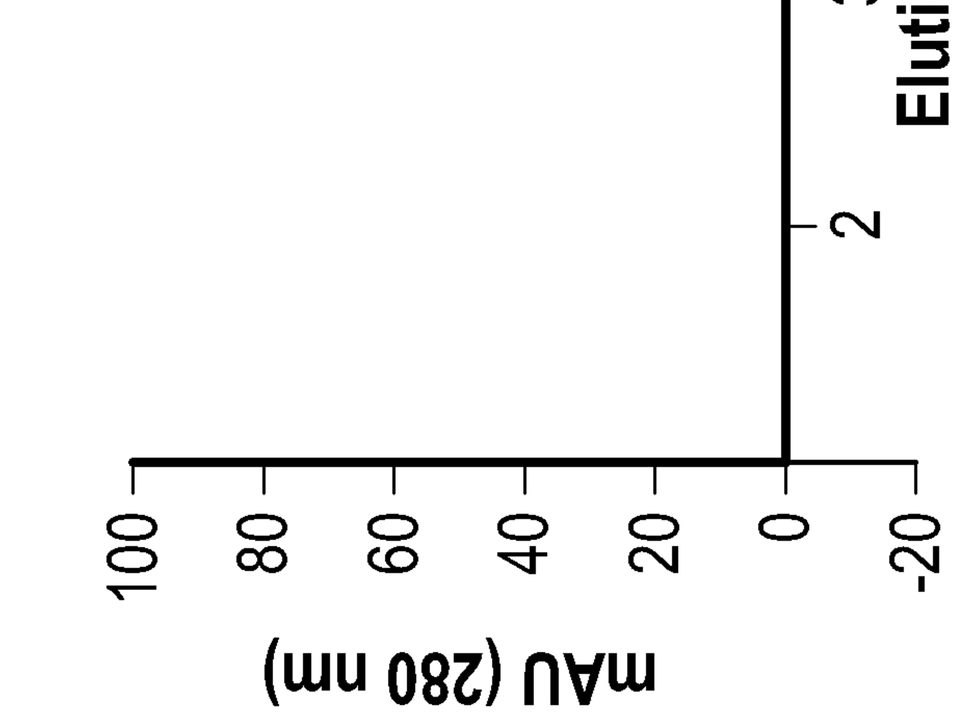


FIG. 20A

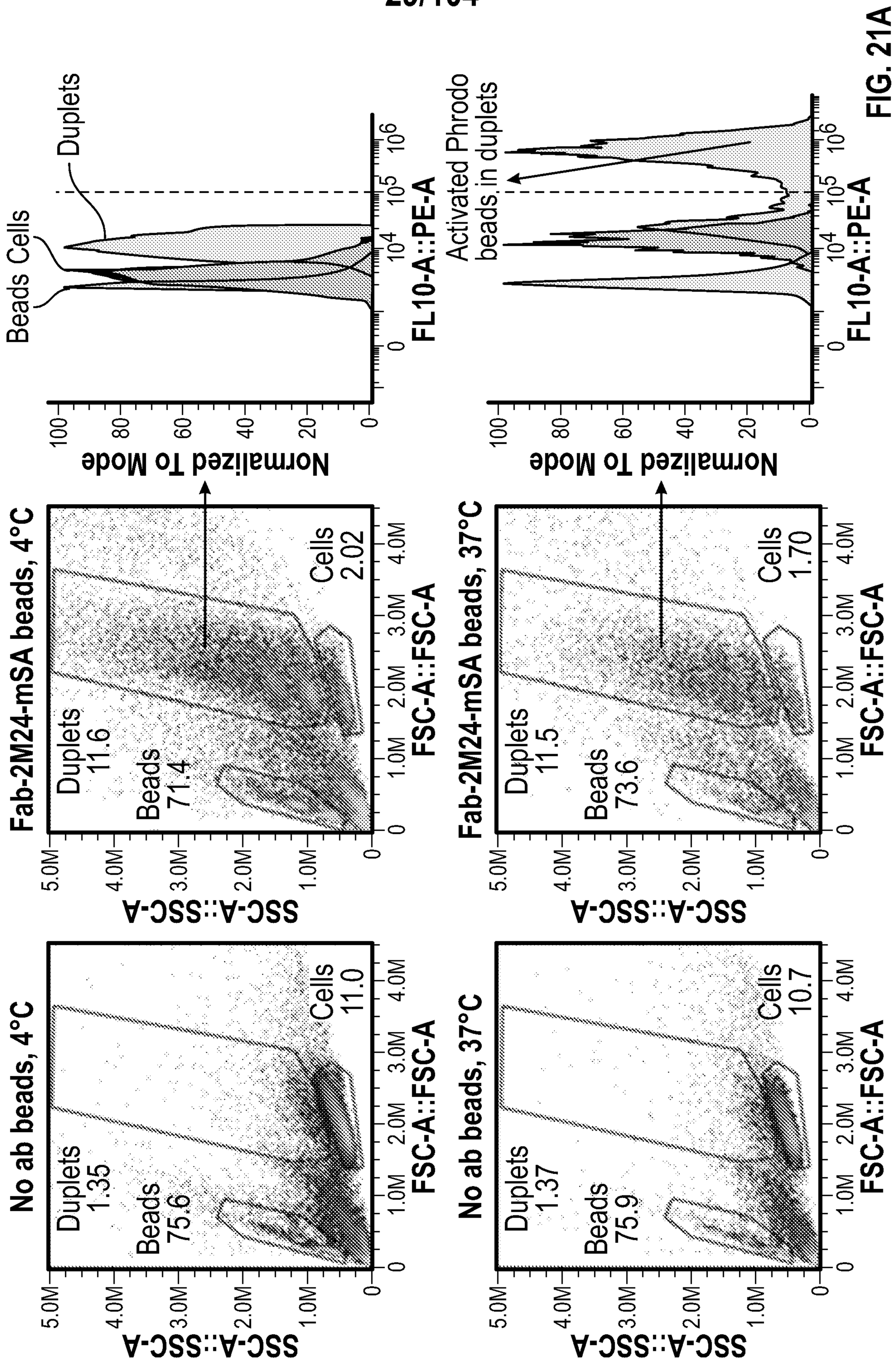

Fab-2M24-mSA beads, 4°C
Duplets
11.6
Beads
71.4
Cells
2.02
SSC-A::SSC-A
FSC-A::FSC-A
Fab-2M24-mSA beads, 37°C
Duplets
11.5
Beads
73.6
Cells
1.70
SSC-A::SSC-A
FSC-A::FSC-A
No ab beads, 4°C
Duplets
1.35
Beads
75.6
Cells
11.0
SSC-A::SSC-A
FSC-A::FSC-A
No ab beads, 37°C
Duplets
1.37
Beads
75.9
Cells
10.7
SSC-A::SSC-A
FSC-A::FSC-A
Beads Cells
Duplets
Normalized To Mode
FL10-A::PE-A
Activated Phrodo beads in duplets

FIG. 21A

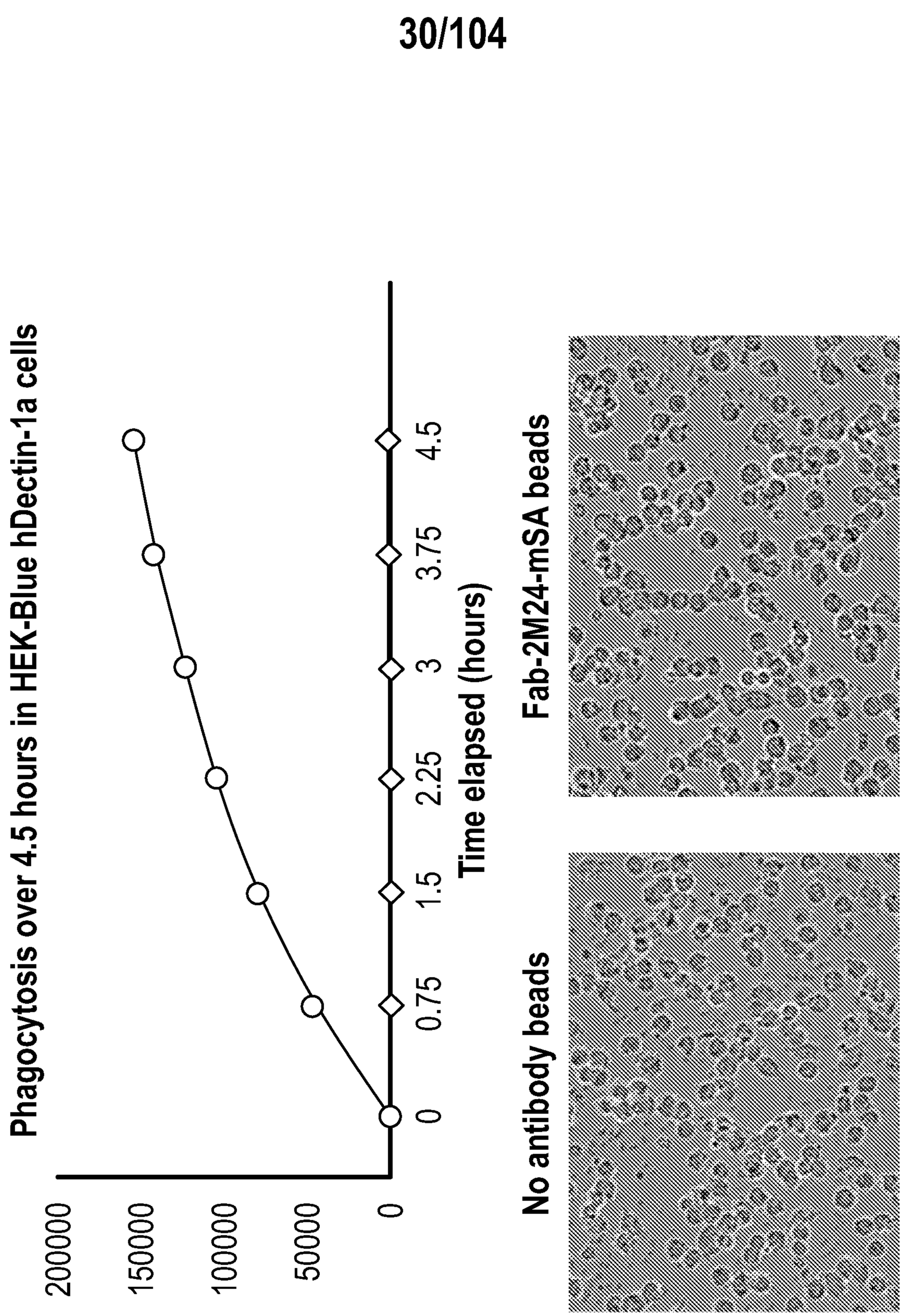

Phagocytosis over 4.5 hours in HEK-Blue hDectin-1a cells
red integrated intensity
200000
150000
100000
50000
0
0
0.75
1.5
2.25
3
3.75
4.5
Time elapsed (hours)
No antibody beads
Fab-2M24-mSA beads

FIG. 21B

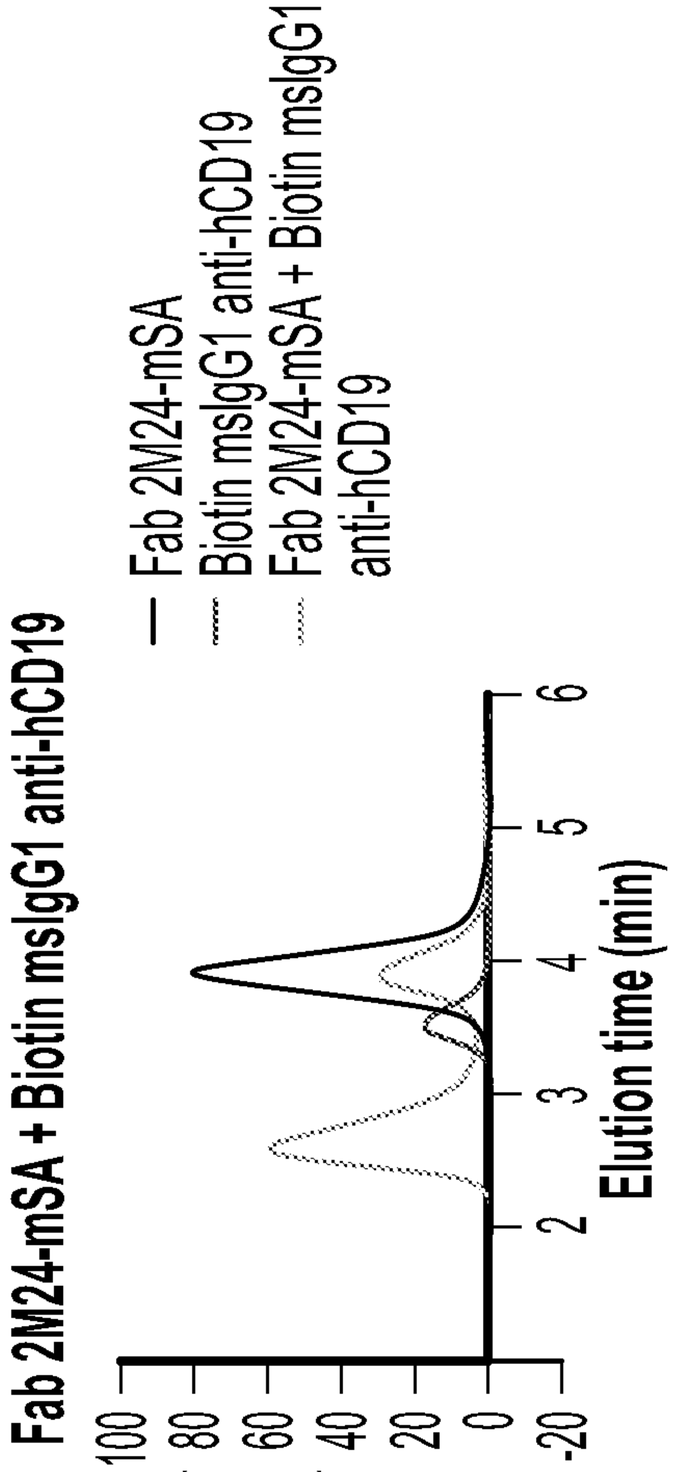


FIG. 22B

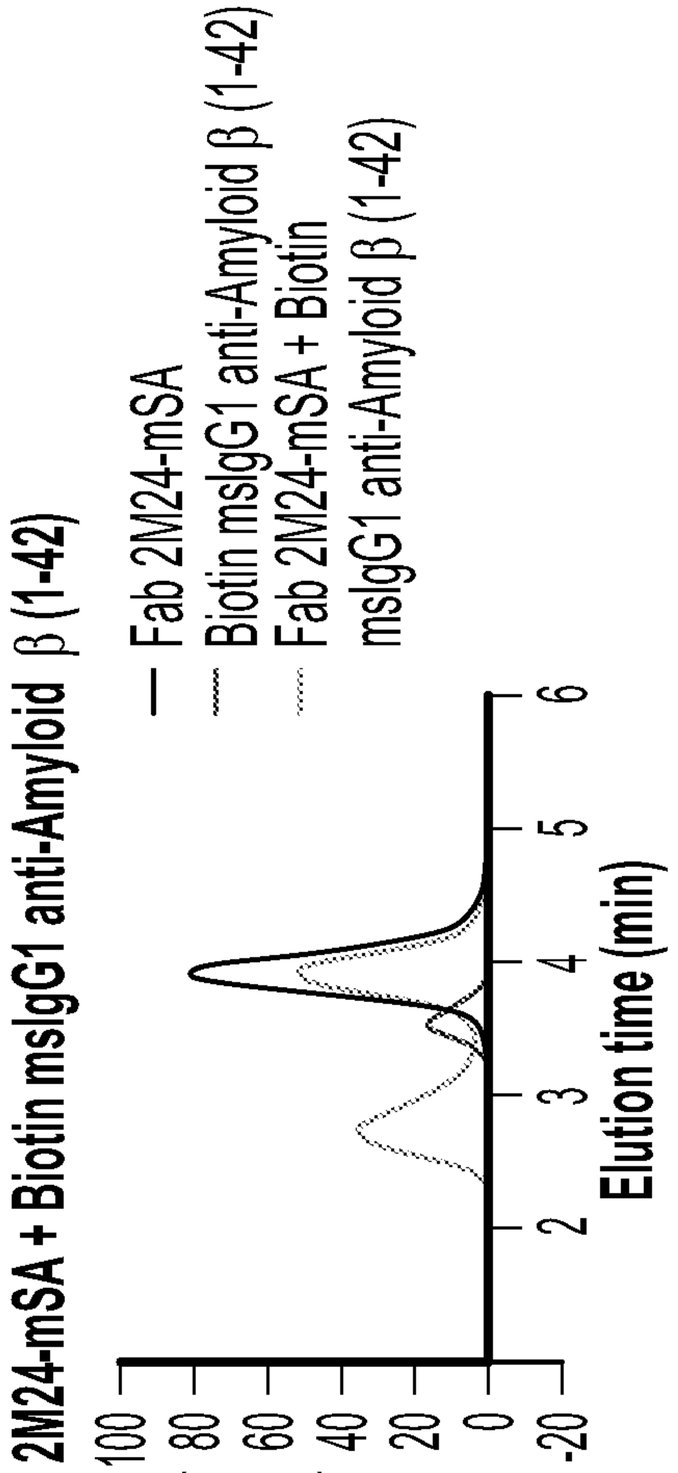


FIG. 22D

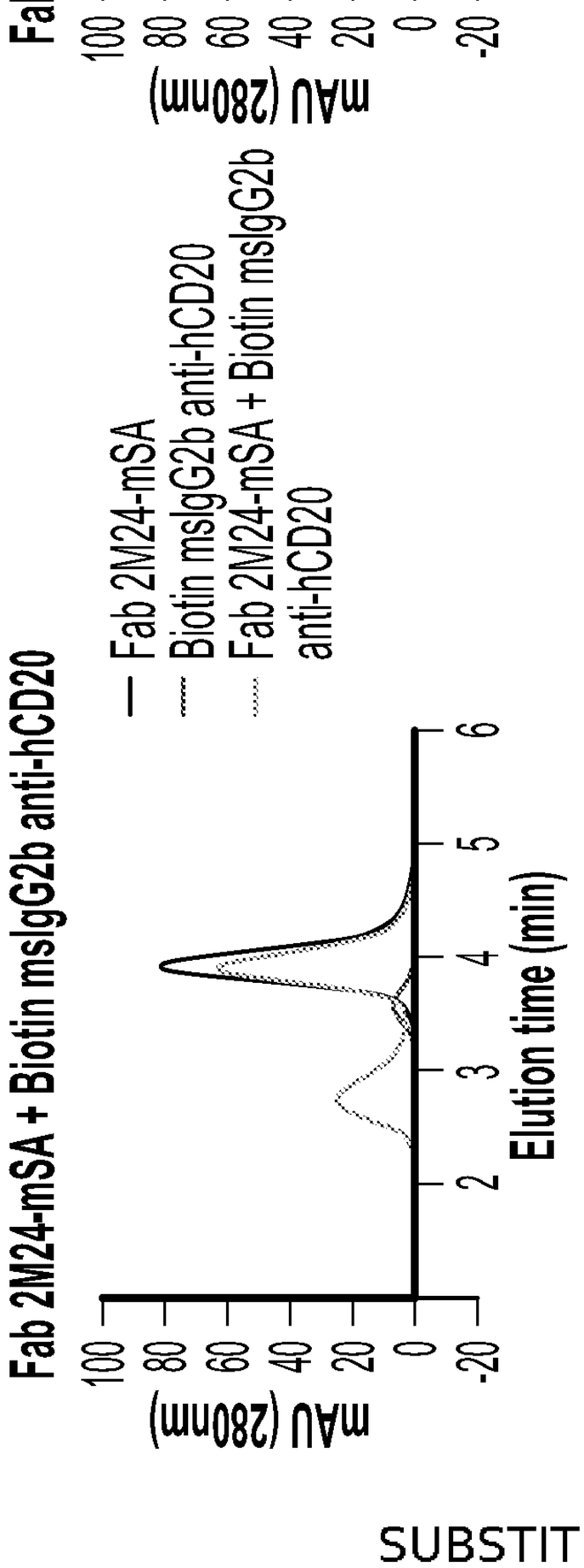


FIG. 22A

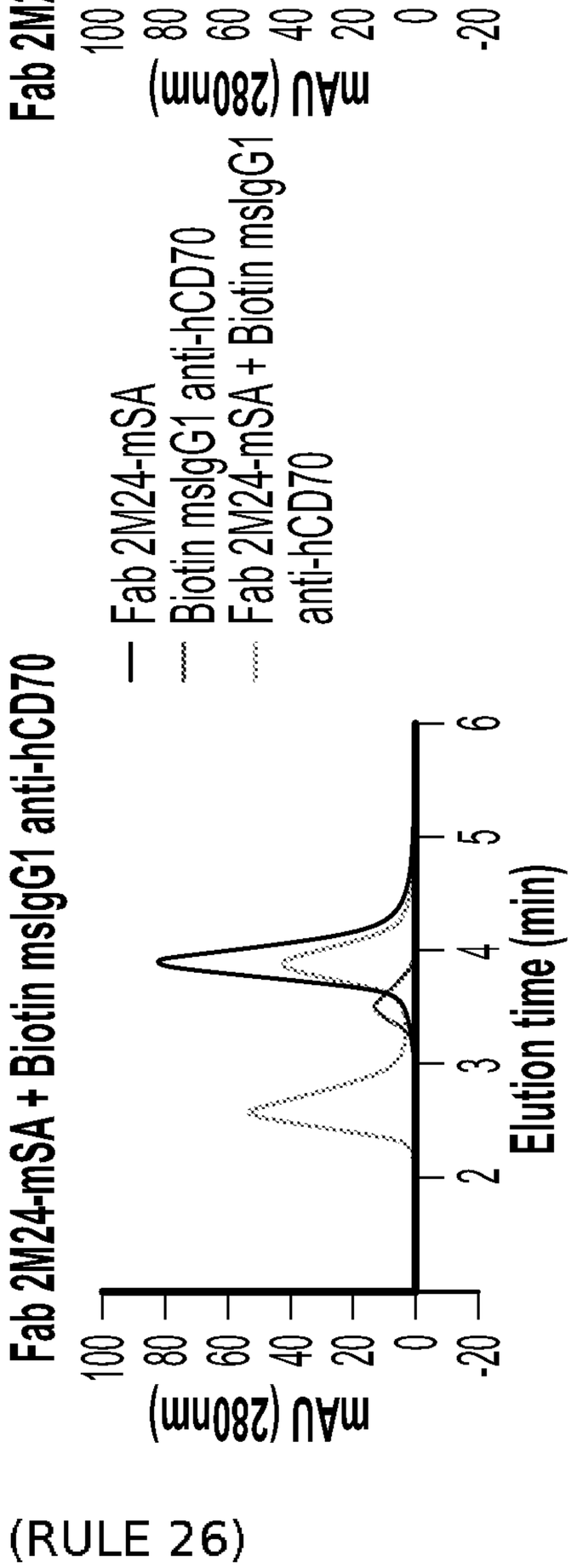
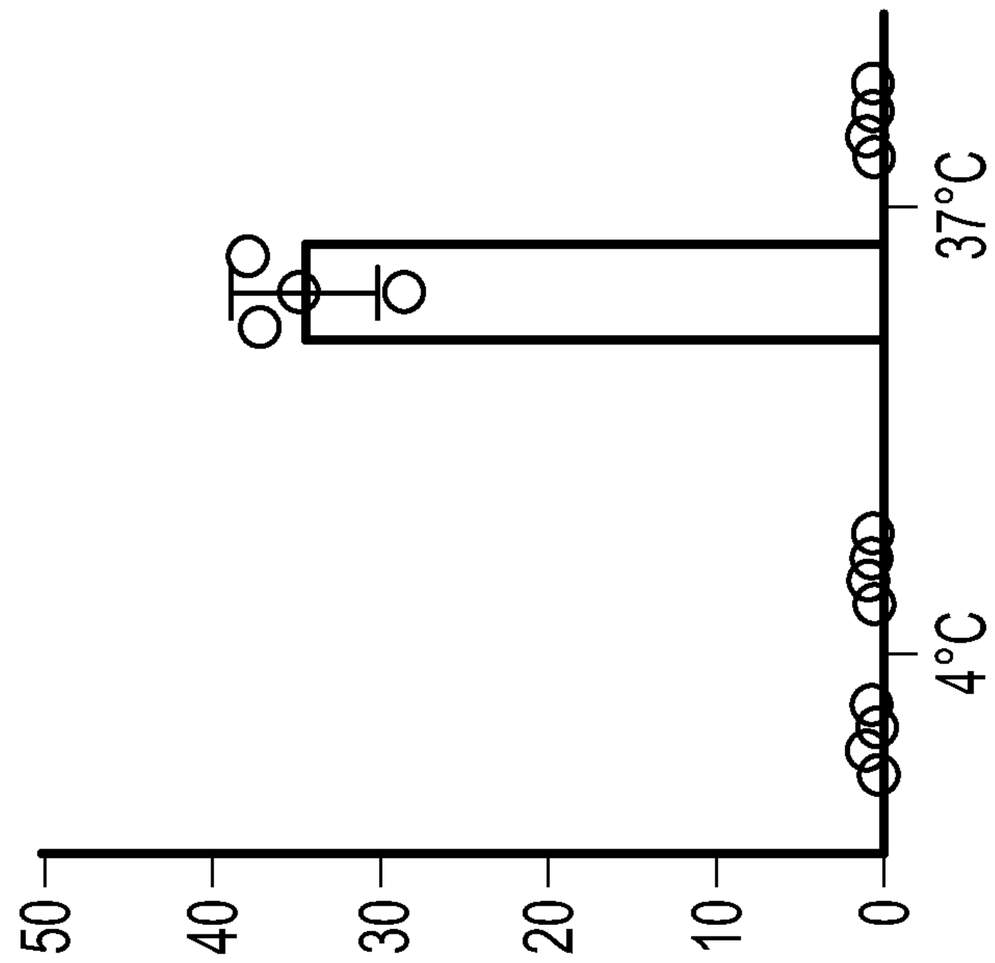
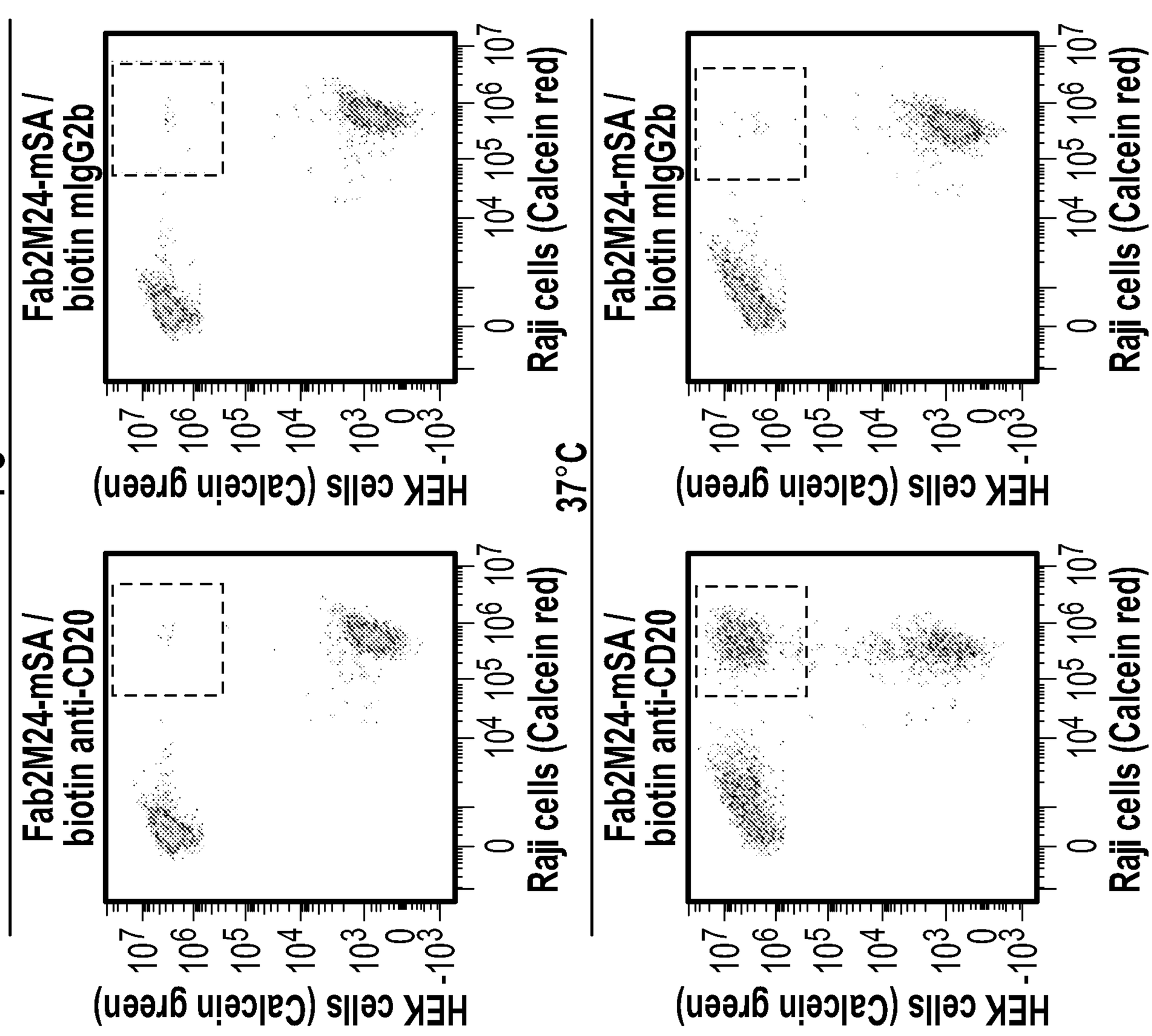


FIG. 22C

FIG. 23


37°C
4°C
50
40
30
20
10
0
Coupling efficiency
(% of total Raji cells)


4°C
37°C
Fab2M24-mSA / biotin mIgG2b
Fab2M24-mSA / biotin anti-CD20
HEK cells (Calcein green)
Raji cells (Calcein red)
10^7
10^6
10^5
10^4
10^3
0
-10^3
0
10^4
10^5
10^6
10^7

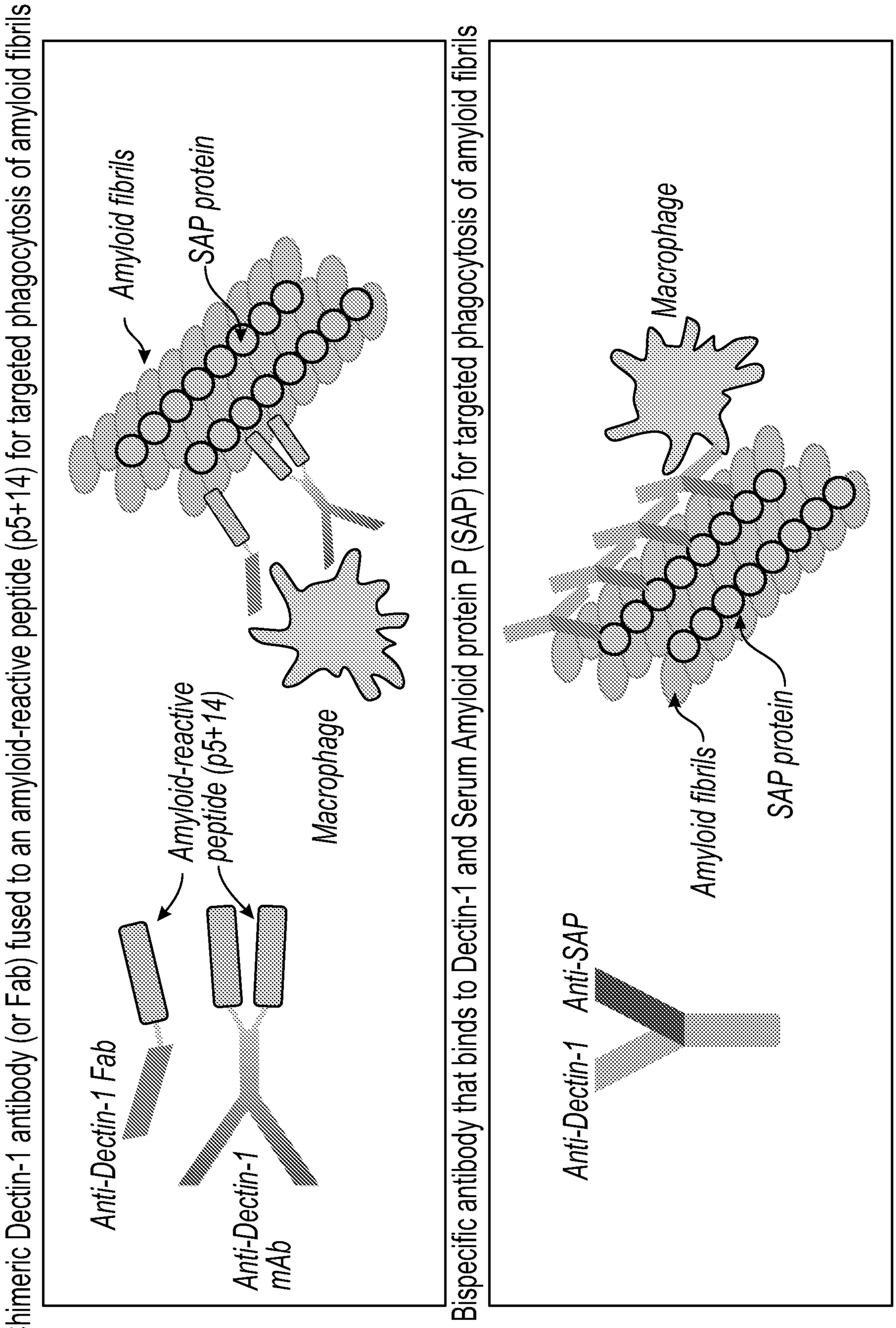

Chimeric Dectin-1 antibody (or Fab) fused to an amyloid-reactive peptide (p5+14) for targeted phagocytosis of amyloid fibrils
Anti-Dectin-1 Fab
Amyloid-reactive peptide (p5+14)
Anti-Dectin-1 mAb
Macrophage
Bispecific antibody that binds to Dectin-1 and Serum Amyloid protein P (SAP) for targeted phagocytosis of amyloid fibrils
Anti-Dectin-1
Anti-SAP
Macrophage
Amyloid fibrils
SAP protein

FIG. 24

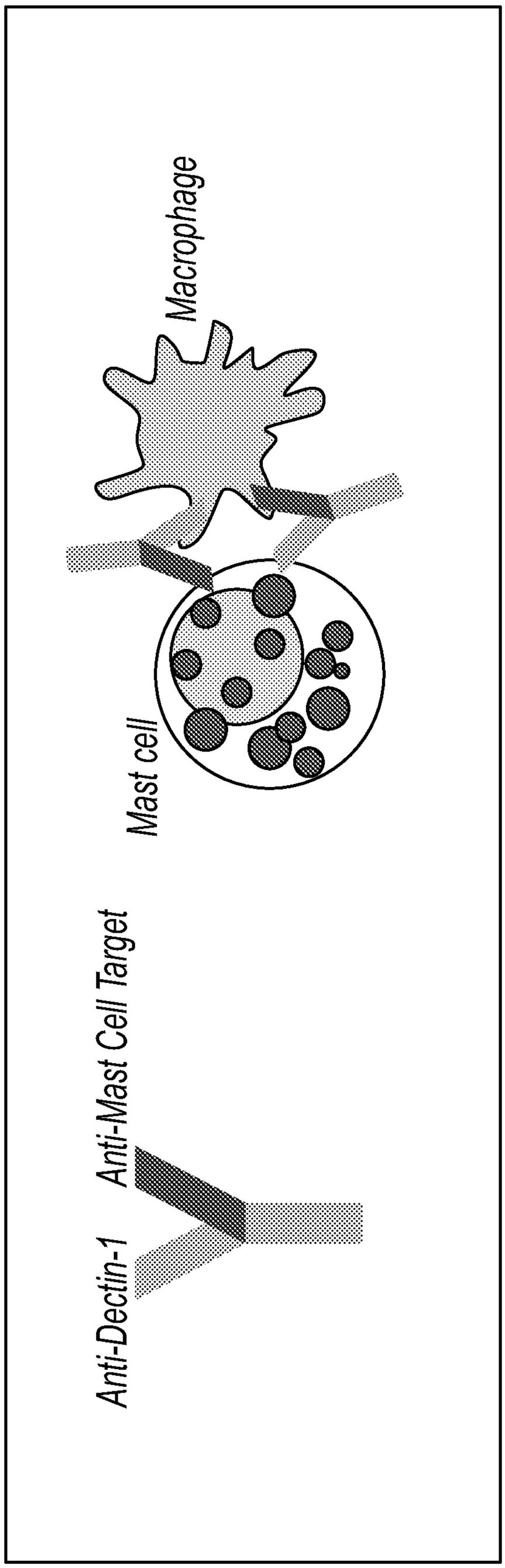


FIG. 25A

FIG. 25B

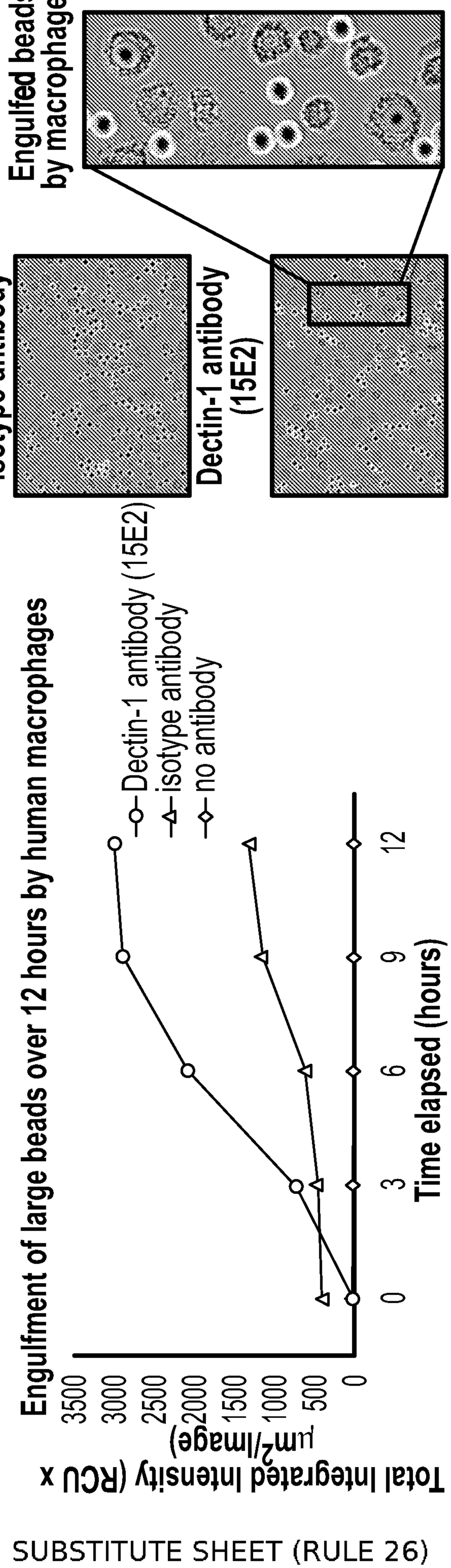

Engulfed beads by macrophages
Isotype antibody
Dectin-1 antibody (15E2)
Engulfment of large beads over 12 hours by human macrophages
Dectin-1 antibody (15E2)
isotype antibody
no antibody
Total Integrated Intensity (RCU x μm2/Image)
Time elapsed (hours)
0
3
6
9
12
500
1000
1500
2000
2500
3000
3500

FIG. 26

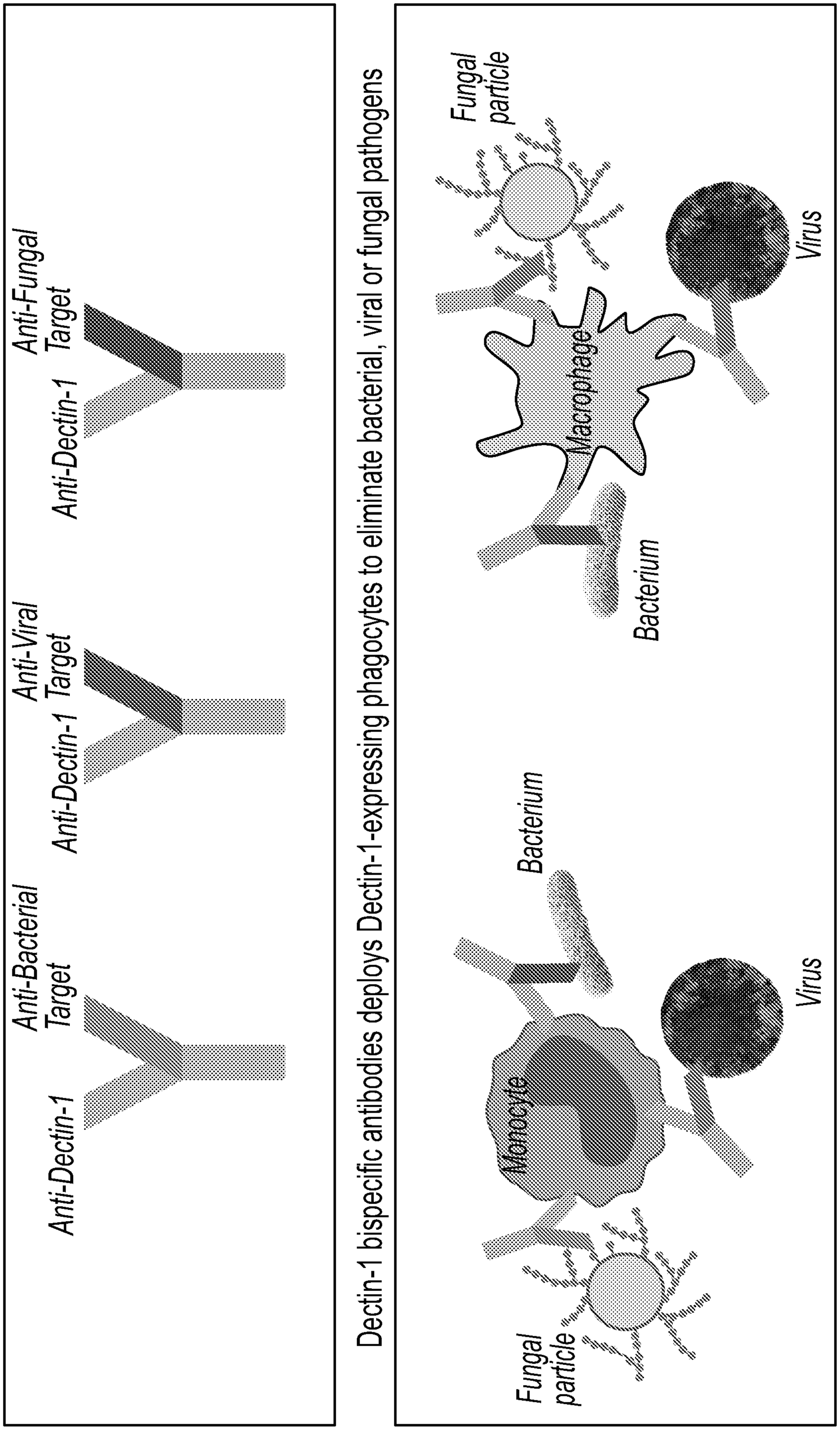

Bispecific(anti-Dectin-1/anti-microbialtarget) against bacteria, viruses, and fungi
Anti-Dectin-1
Anti-Bacterial Target
Anti-Dectin-1
Anti-Viral Target
Anti-Dectin-1
Anti-Fungal Target
Dectin-1 bispecific antibodies deploys Dectin-1-expressing phagocytes to eliminate bacterial, viral or fungal pathogens
Monocyte
Bacterium
Virus
Fungal particle
Macrophage
Bacterium
Virus
Fungal particle

FIG. 27

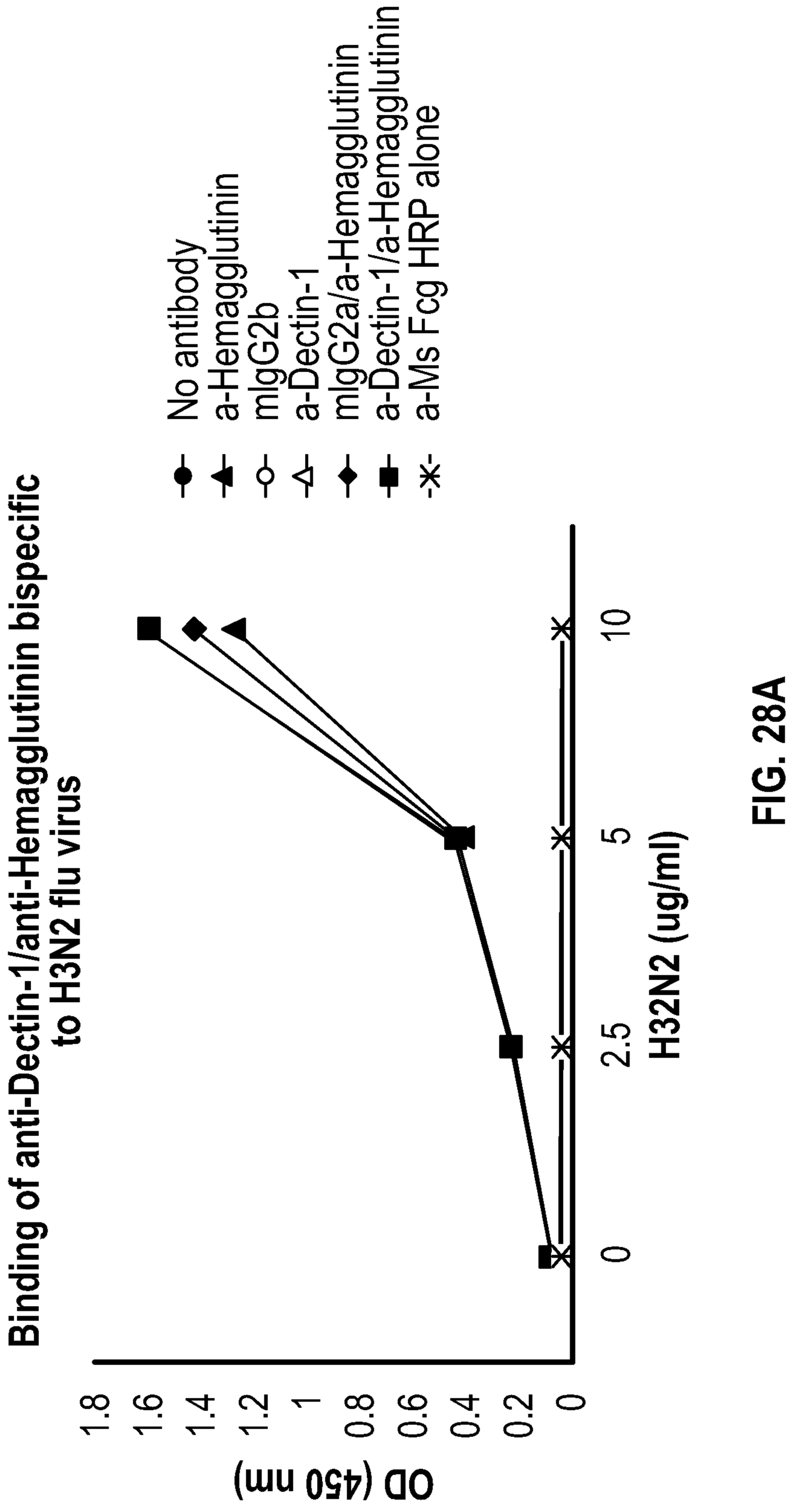

Binding of anti-Dectin-1/anti-Hemagglutinin bispecific to H3N2 flu virus
OD (450 nm)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
H32N2 (ug/ml)
0
2.5
5
10
No antibody
a-Hemagglutinin
mIgG2b
a-Dectin-1
mIgG2a/a-Hemagglutinin
a-Dectin-1/a-Hemagglutinin
a-Ms Fcg HRP alone

FIG. 28A

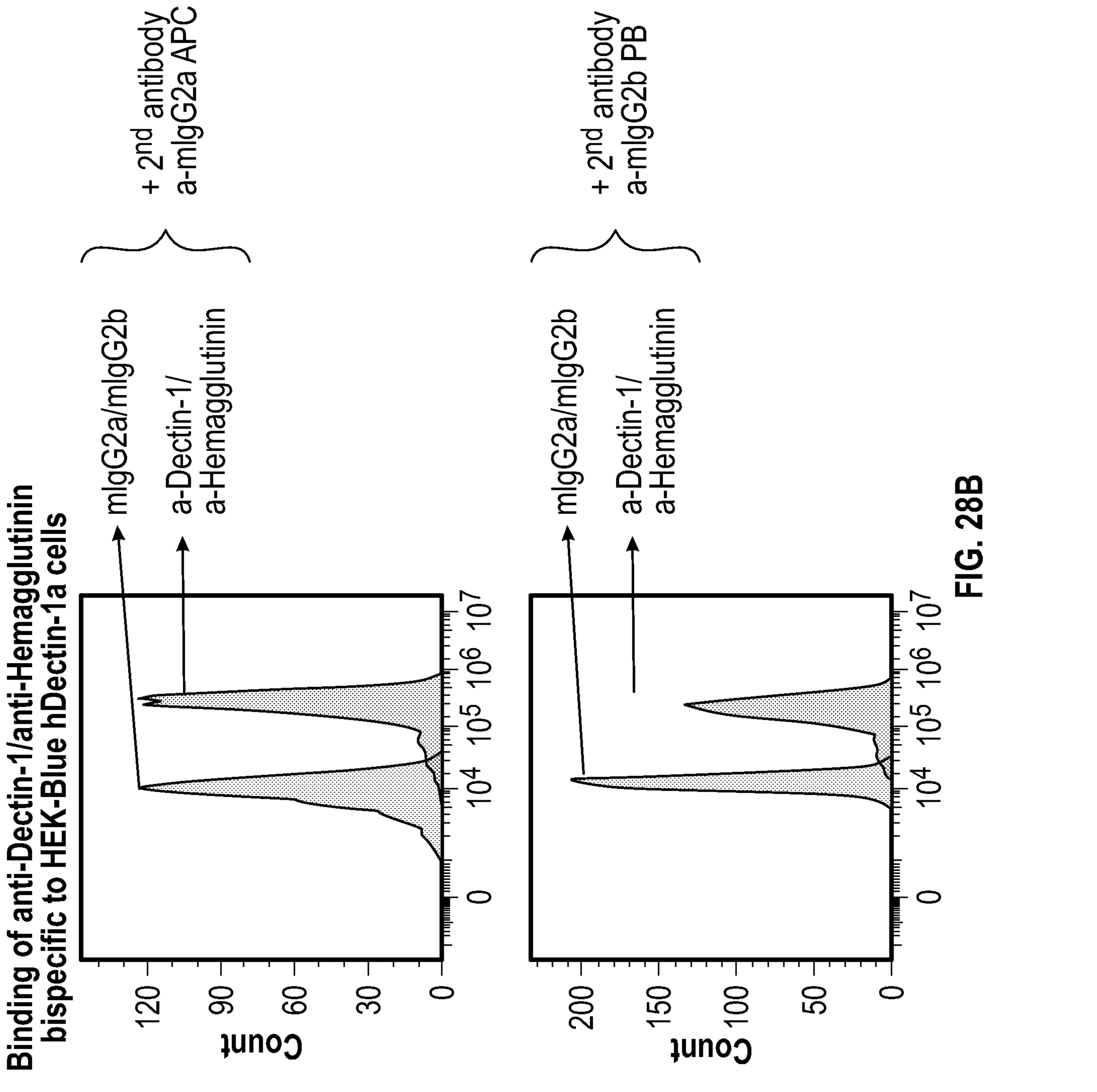

Binding of anti-Dectin-1/anti-Hemagglutinin bispecific to HEK-Blue hDectin-1a cells
Count
120
90
60
30
0
mIgG2a/mIgG2b
a-Dectin-1/
a-Hemagglutinin
+ 2nd antibody
a-mIgG2a AP
0
10^4
10^5
10^6
10^7
Count
200
150
100
50
0
mIgG2a/mIgG2b
a-Dectin-1/
a-Hemagglutinin
+ 2nd antibody
a-mIgG2b PB
0
10^4
10^5
10^6
10^7

FIG. 28B

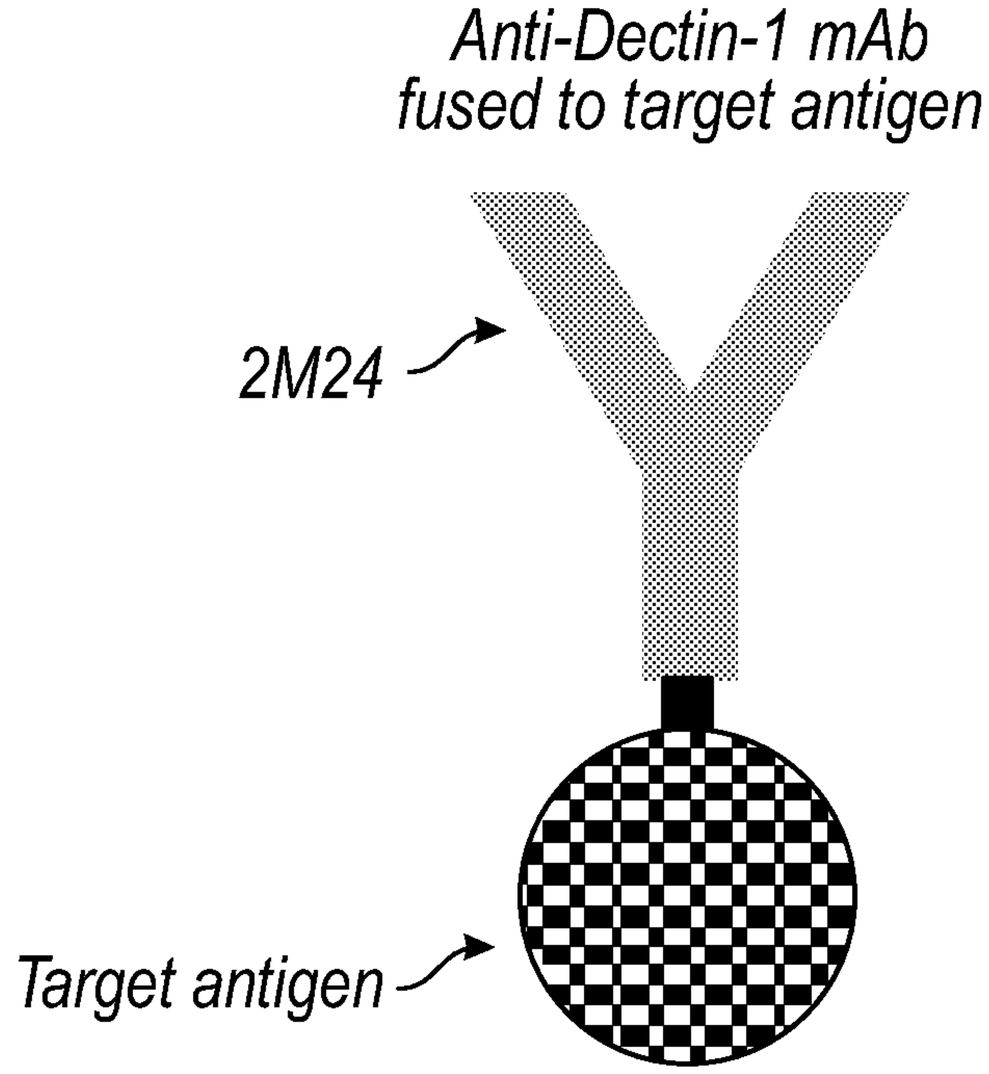

Anti-Dectin-1 mAb
fused to target antigen
2M24
Target antigen

FIG. 29A

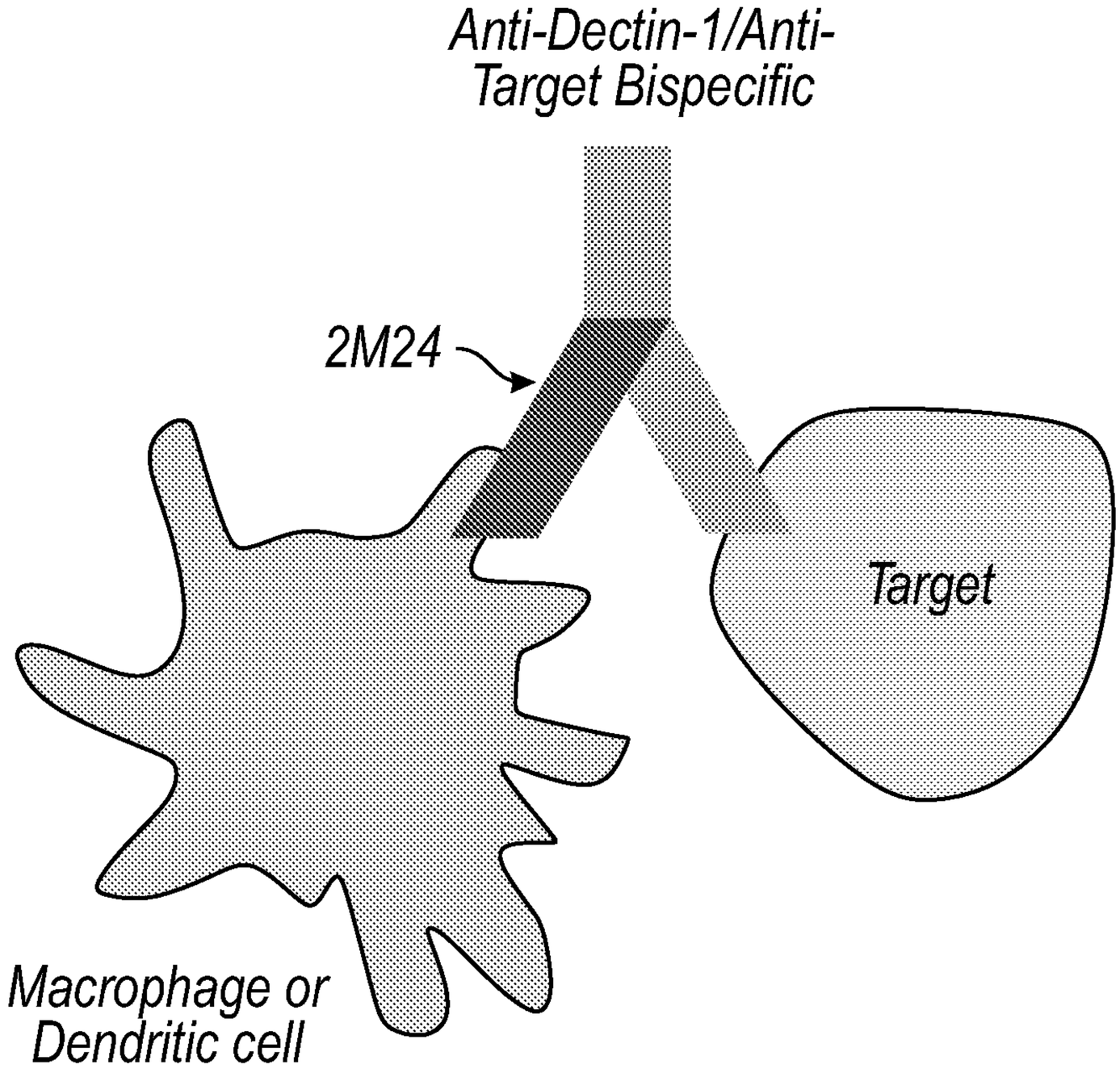

Anti-Dectin-1/Anti-
Target Bispecific
2M24
Target
Macrophage or
Dendritic cell

FIG. 29B

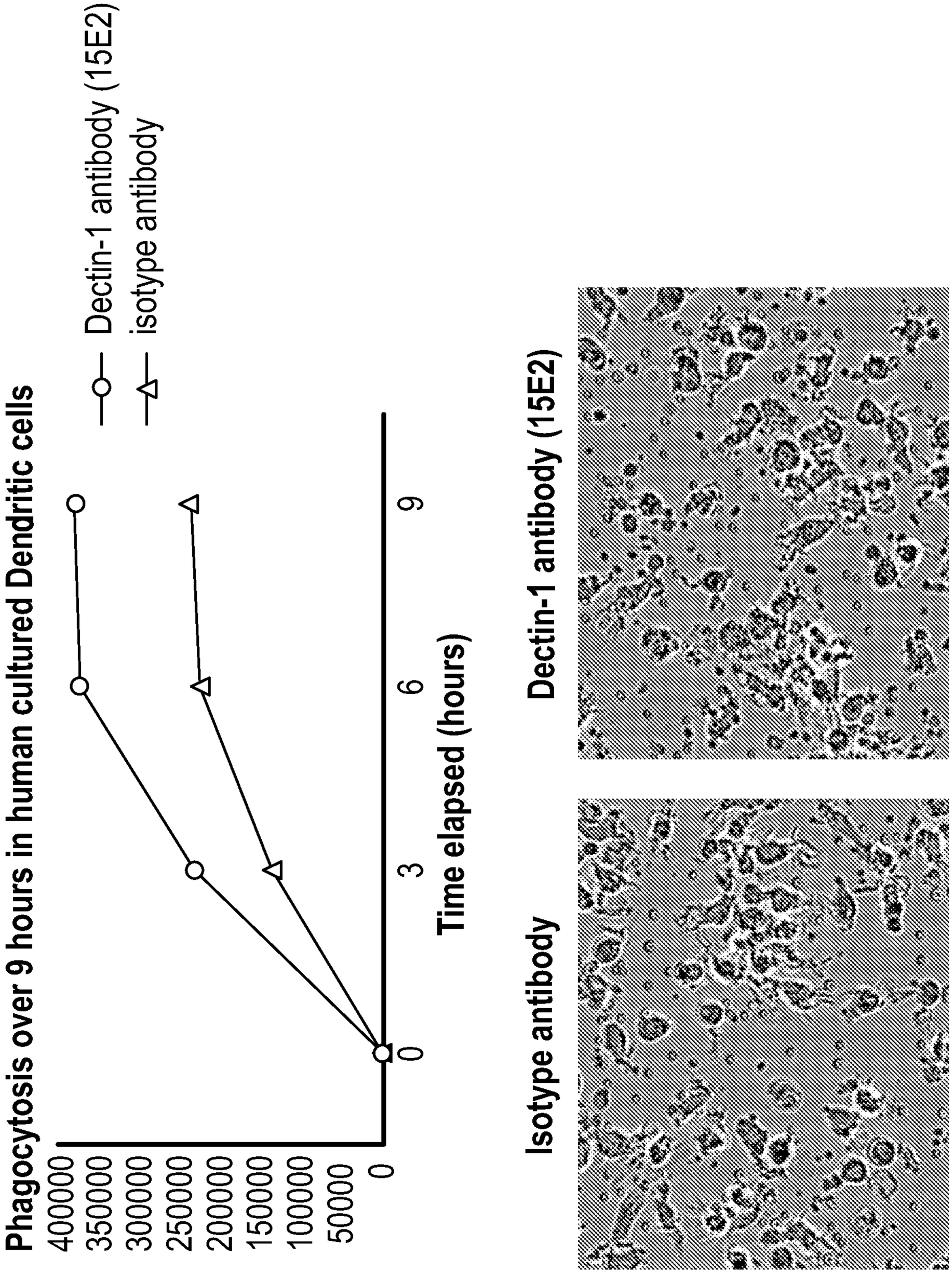

Phagocytosis over 9 hours in human cultured Dendritic cells
Total Integrated Intensity (RCU x μm²/image)
400000
350000
300000
250000
200000
150000
100000
50000
0
0
3
6
9
Time elapsed (hours)
Dectin-1 antibody (15E2)
isotype antibody
Dectin-1 antibody (15E2)
Isotype antibody

FIG. 30

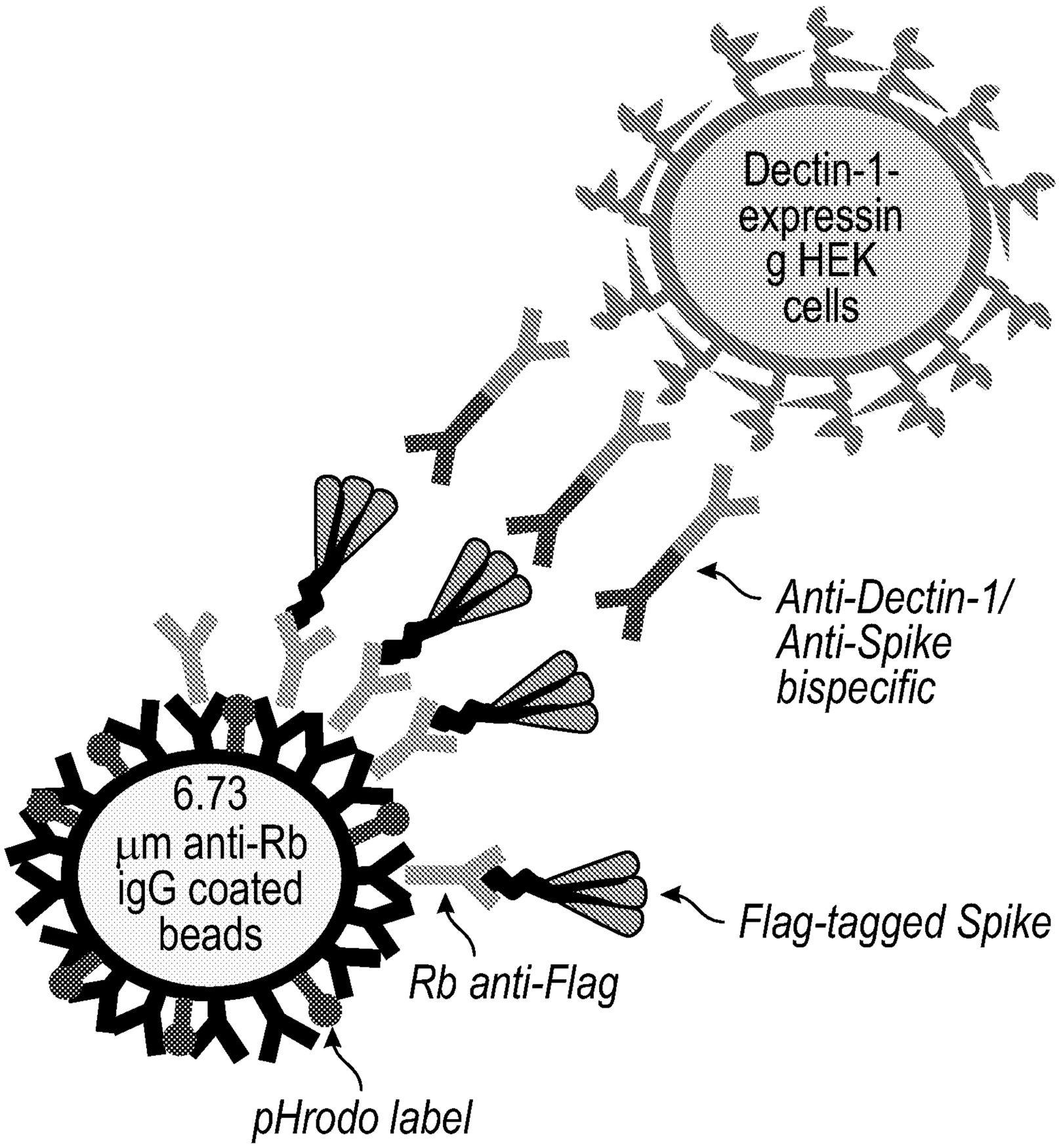

Dectin-1-expressing HEK cells
Anti-Dectin-1/ Anti-Spike bispecific
6.73 µm anti-Rb igG coated beads
Flag-tagged Spike
Rb anti-Flag
pHrodo label

FIG. 31A

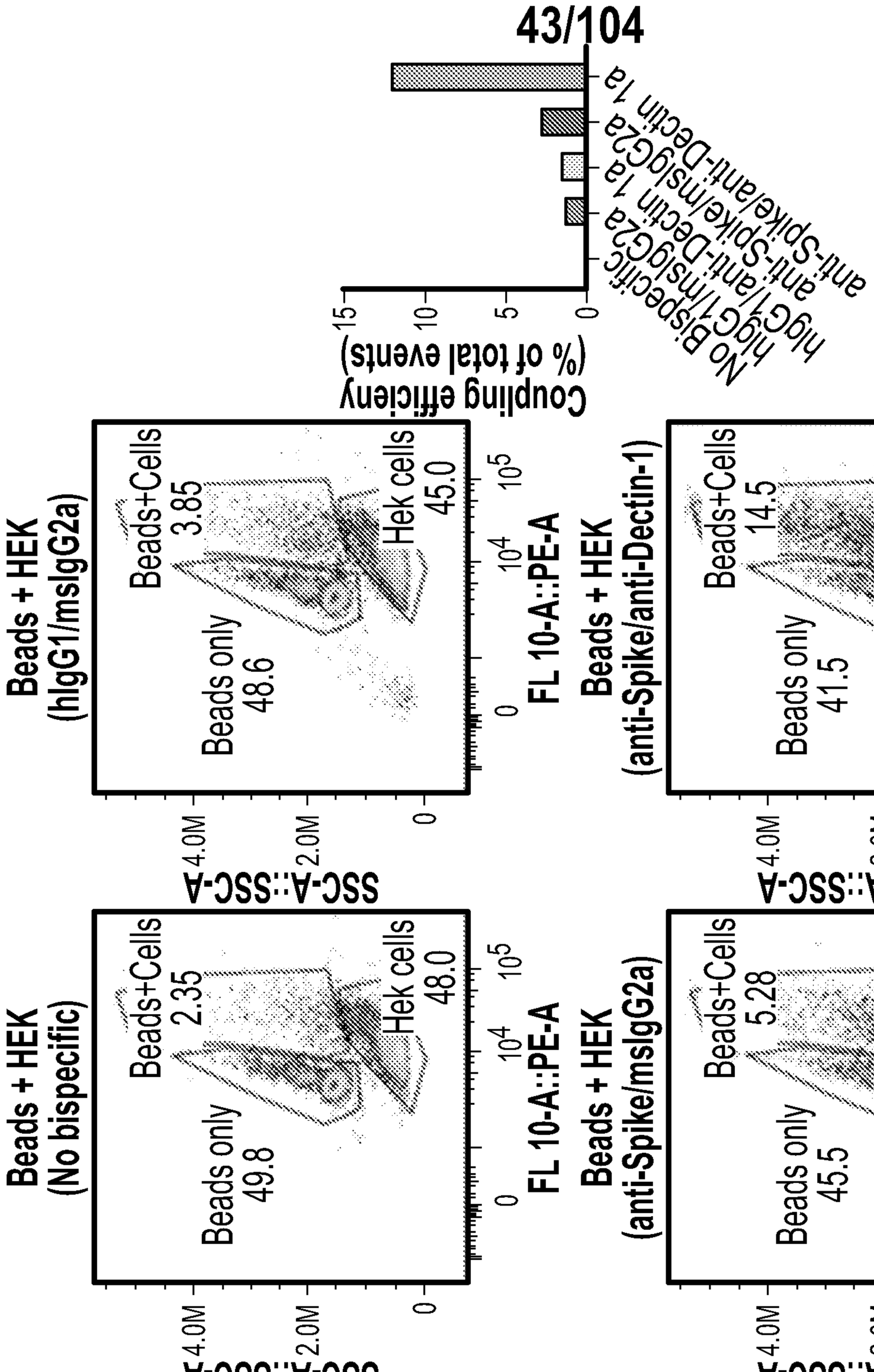

Coupling efficiency
(% of total events)
15
10
5
0
No Bispecific
hIgG1/msIgG2a
hIgG1/anti-Dectin 1a
anti-Spike/msIgG2a
anti-Spike/anti-Dectin 1a
Beads + HEK
(hIgG1/msIgG2a)
Beads+Cells
3.85
Beads only
48.6
Hek cells
45.0
SSC-A::SSC-A
FL 10-A::PE-A
Beads + HEK
(anti-Spike/anti-Dectin-1)
Beads+Cells
14.5
Beads only
41.5
Hek cells
42.8
Beads + HEK
(No bispecific)
Beads+Cells
2.35
Beads only
49.8
Hek cells
48.0
Beads + HEK
(anti-Spike/msIgG2a)
Beads+Cells
5.28
Beads only
45.5
Hek cells
47.0
Beads only
Beads+Cells
0.18
Beads only
99.3
Hek cells
0.040
Beads + HEK
(hIgG1/anti-Dectin-1)
Beads+Cells
3.90
Beads only
47.4
Hek cells
47.4
4.0M
2.0M
0
10^4
10^5

FIG. 31B

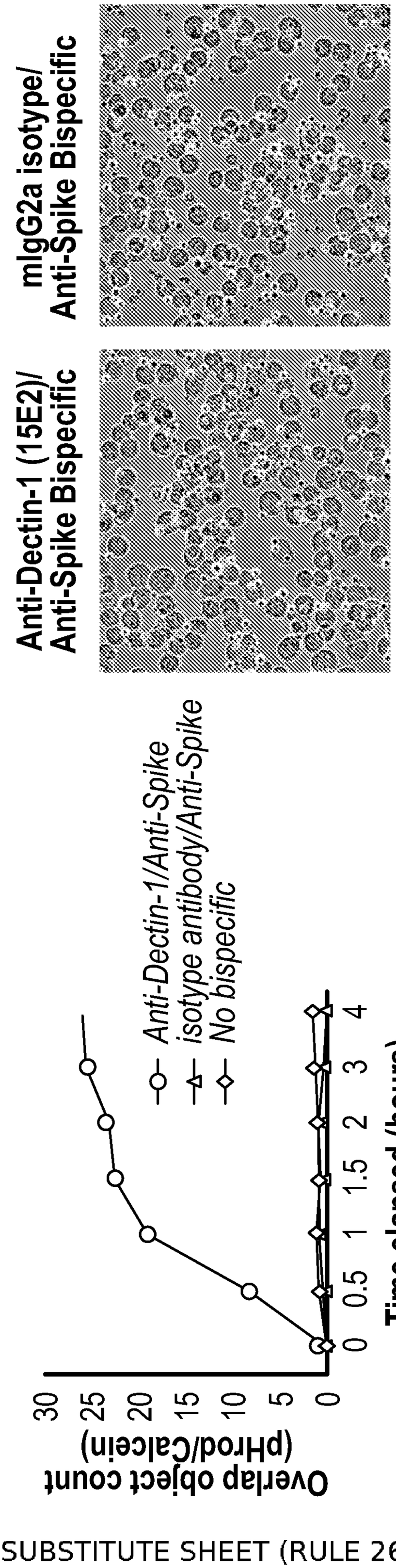

mIgG2a isotype/
Anti-Spike Bispecific
Anti-Dectin-1 (15E2)/
Anti-Spike Bispecific
Anti-Dectin-1/Anti-Spike
isotype antibody/Anti-Spike
No bispecific
Overlap object count
(pHrod/Calcein)
30
25
20
15
10
5
0
Time elapsed (hours)
0
0.5
1
1.5
2
3
4

FIG. 31C

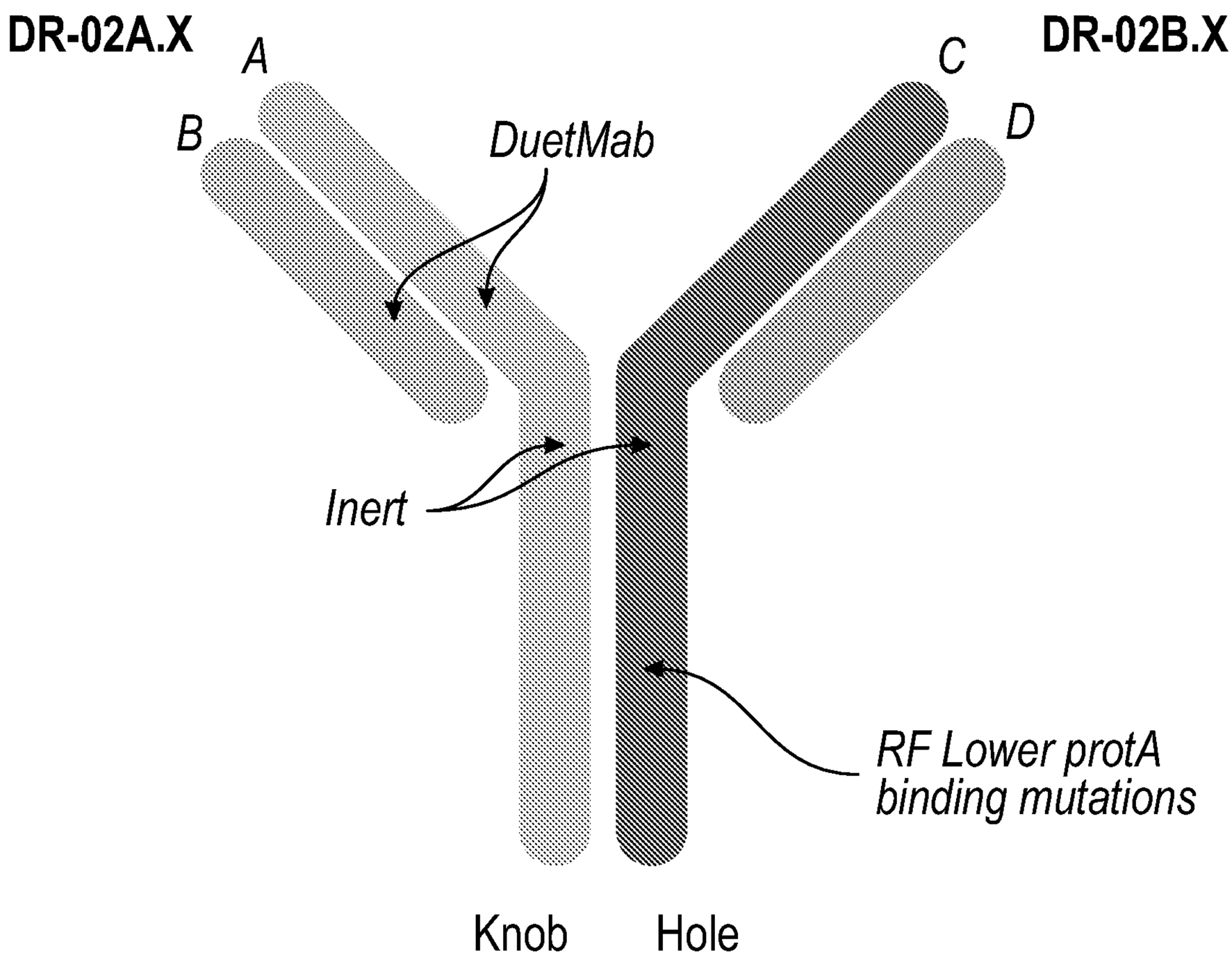

DR-02A.X
A
B
DuetMab
C
D
DR-02B.X
Inert
RF Lower protA
binding mutations
Knob
Hole

FIG. 32A

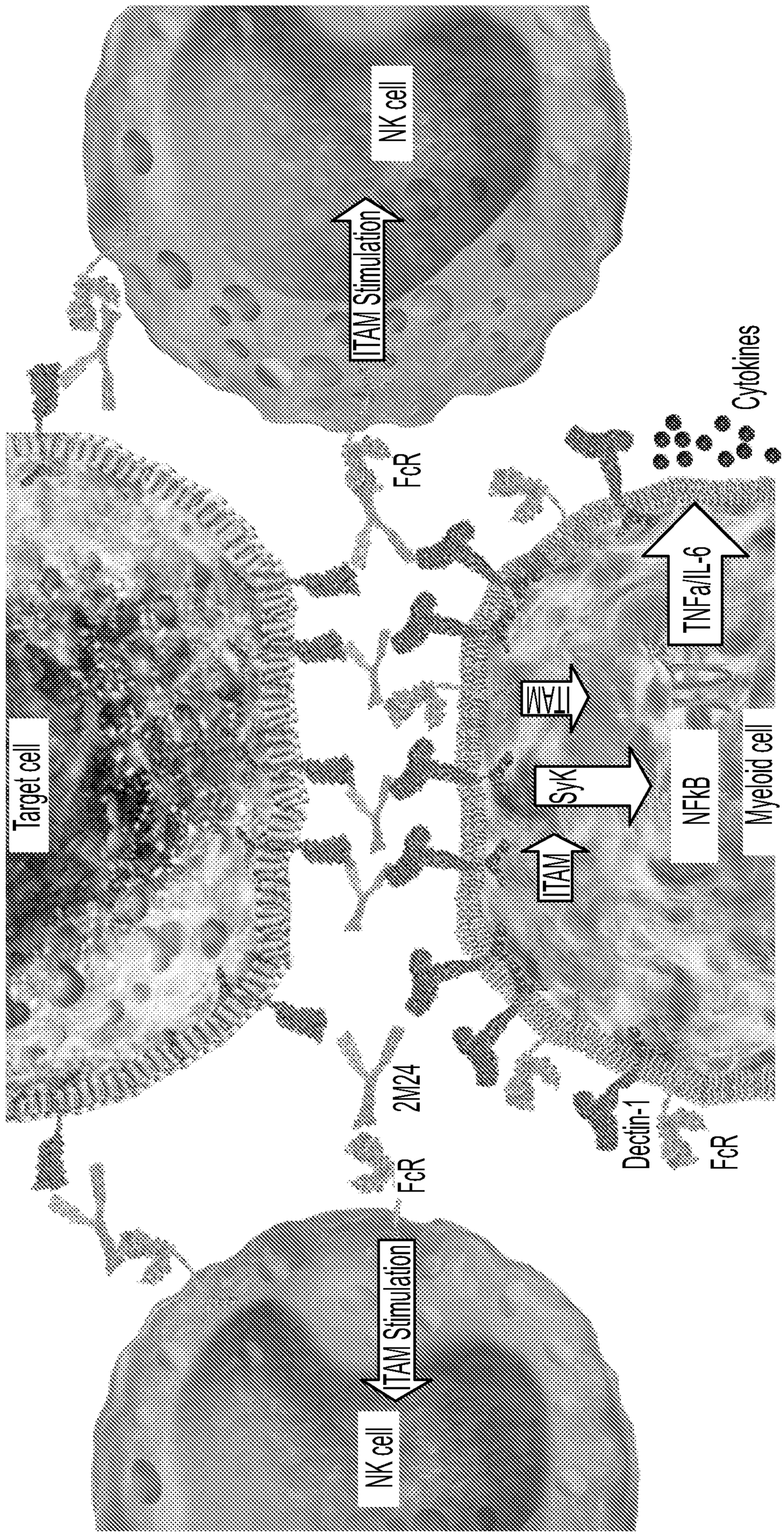

NK cell
ITAM Stimulation
FcR
Cytokines
TNFa/IL-6
Target cell
ITAM
SyK
NFkB
Myeloid cell
2M24
Dectin-1
FcR
ITAM Stimulation
NK cell

FIG. 32B

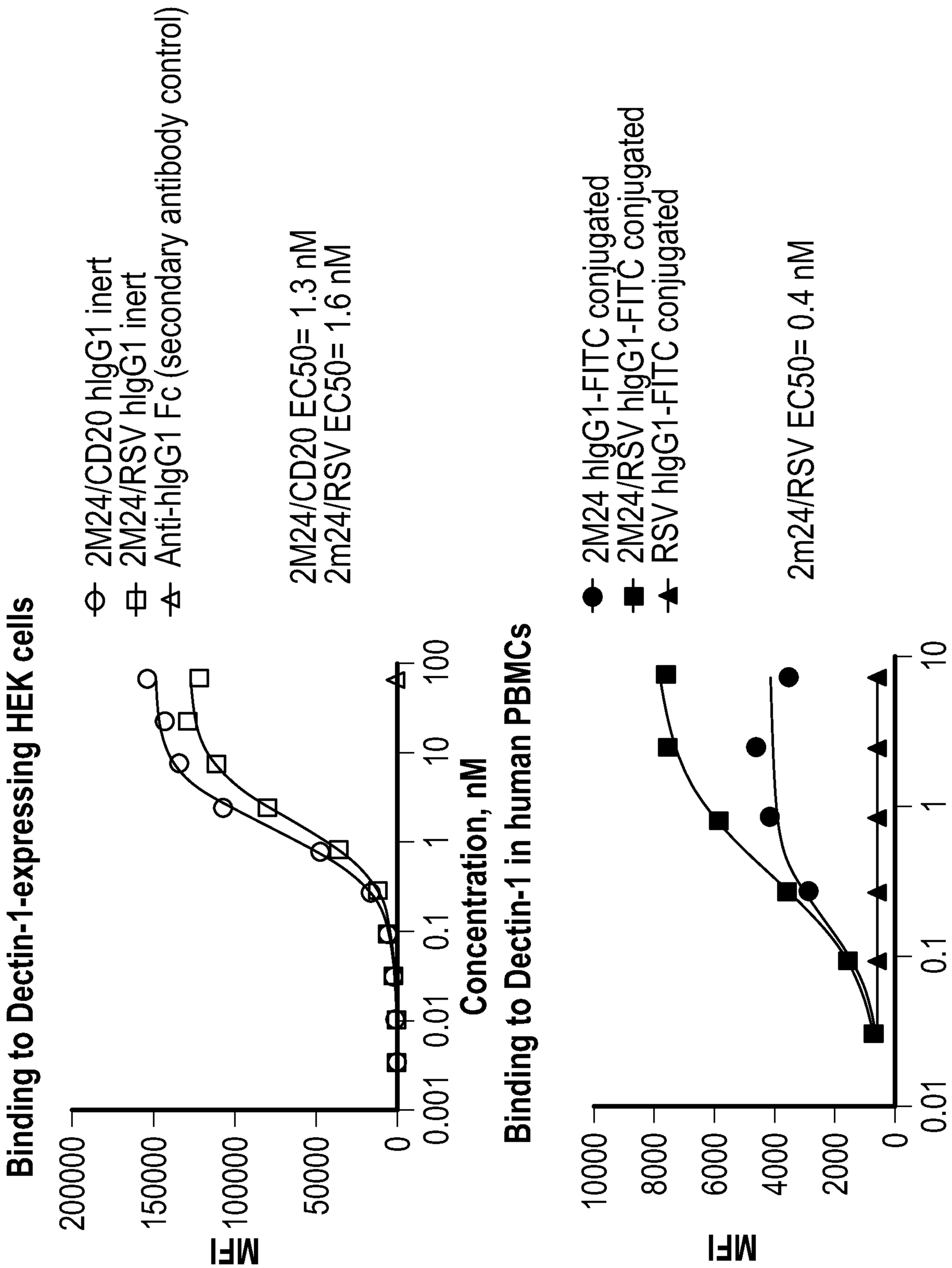

Binding to Dectin-1-expressing HEK cells (no control)
2M24/CD20 hIgG1 inert
2M24/RSV hIgG1 inert
Anti-hIgG1 Fc (secondary antibody control)
MFI
200000
150000
100000
50000
0
0.001
0.01
0.1
1
10
100
Concentration, nM
2M24/CD20 EC50= 1.3 nM
2m24/RSV EC50= 1.6 nM
Binding to Dectin-1 in human PBMCs
2M24 hIgG1-FITC conjugated
2M24/RSV hIgG1-FITC conjugated
RSV hIgG1-FITC conjugated
MFI
10000
8000
6000
4000
2000
0
0.01
0.1
1
10
Antibody (nM)
2m24/RSV EC50= 0.4 nM

FIG. 33A

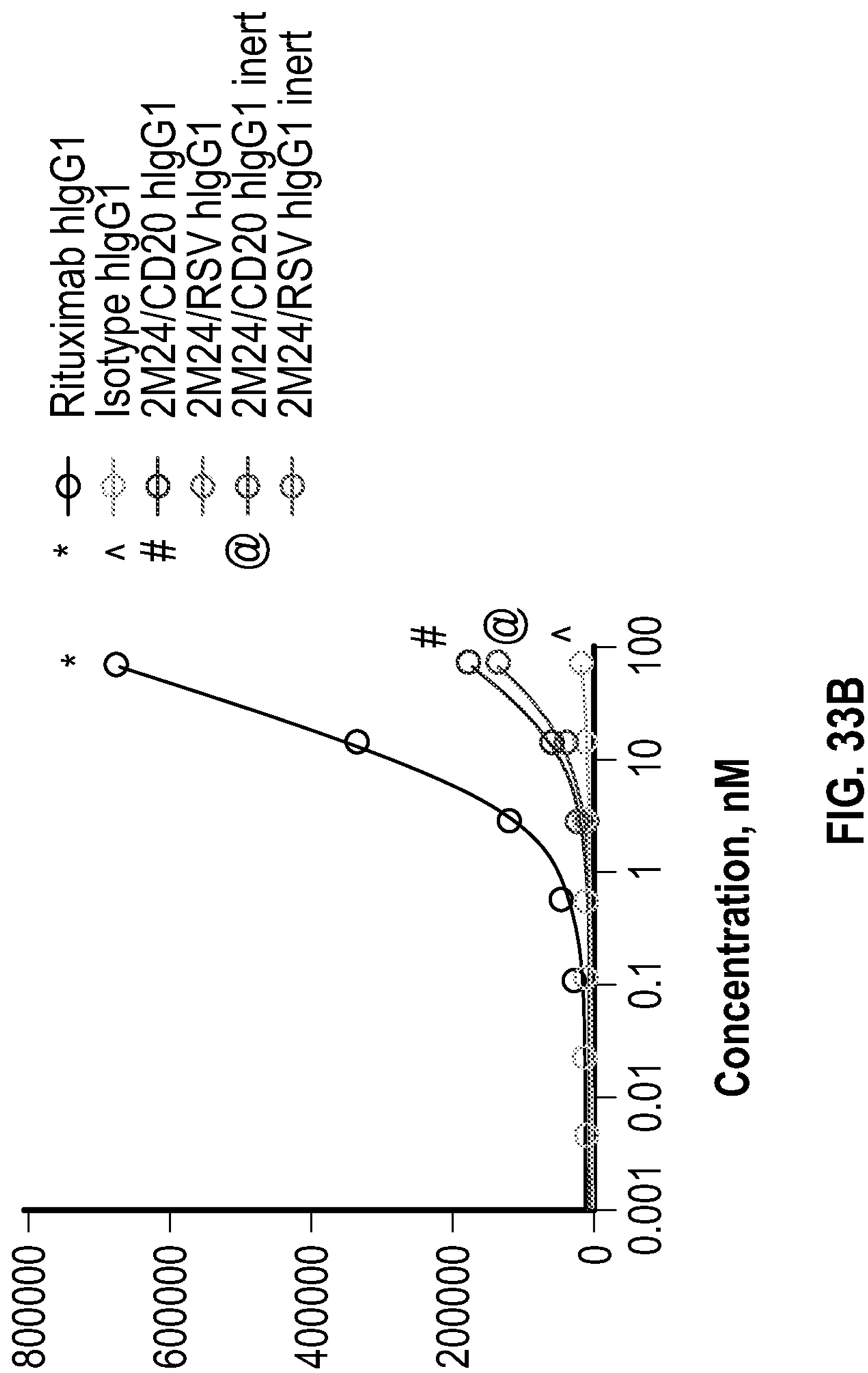

All events/Raji cells
MFI
8000
6000
4000
2000
0
0.001
0.01
0.1
1
10
100
Concentration, nM
* Rituximab hIgG1
^ Isotype hIgG1
2M24/CD20 hIgG1
2M24/RSV hIgG1
@ 2M24/CD20 hIgG1 inert
2M24/RSV hIgG1 inert

FIG. 33B

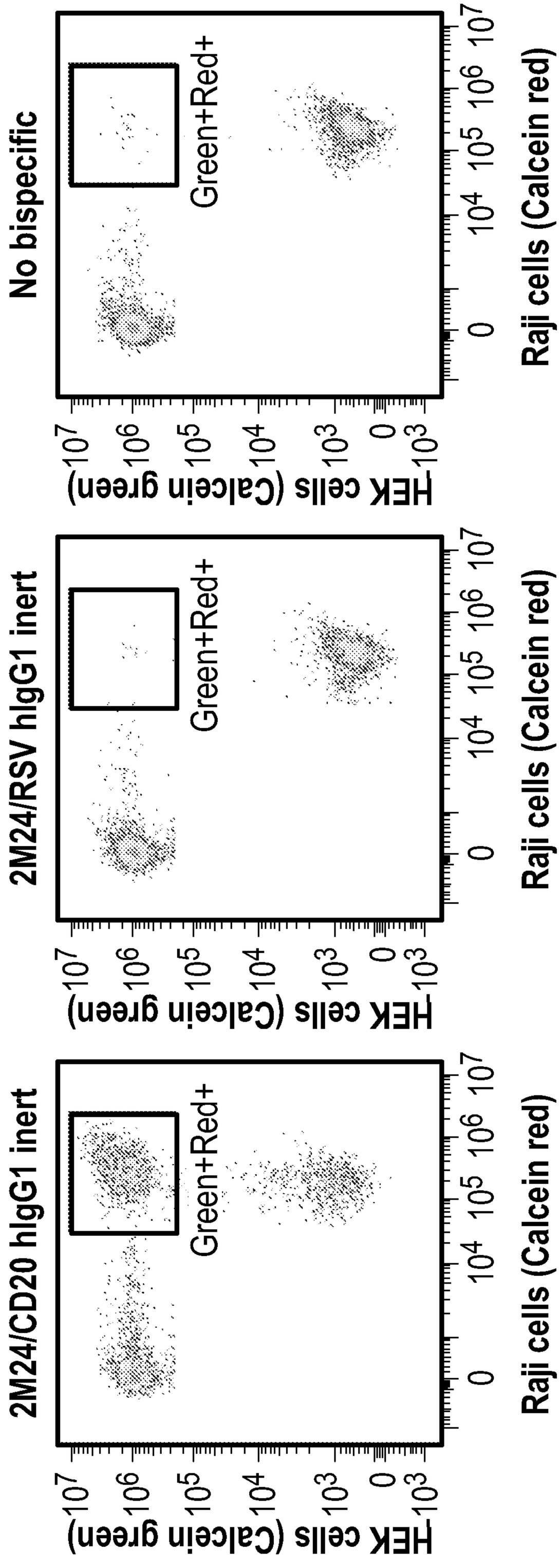

No bispecific
2M24/RSV hIgG1 inert
2M24/CD20 hIgG1 inert
Green+Red+
HEK cells (Calcein green)
Raji cells (Calcein red)
10^7
10^6
10^5
10^4
10^3
0

FIG. 34A

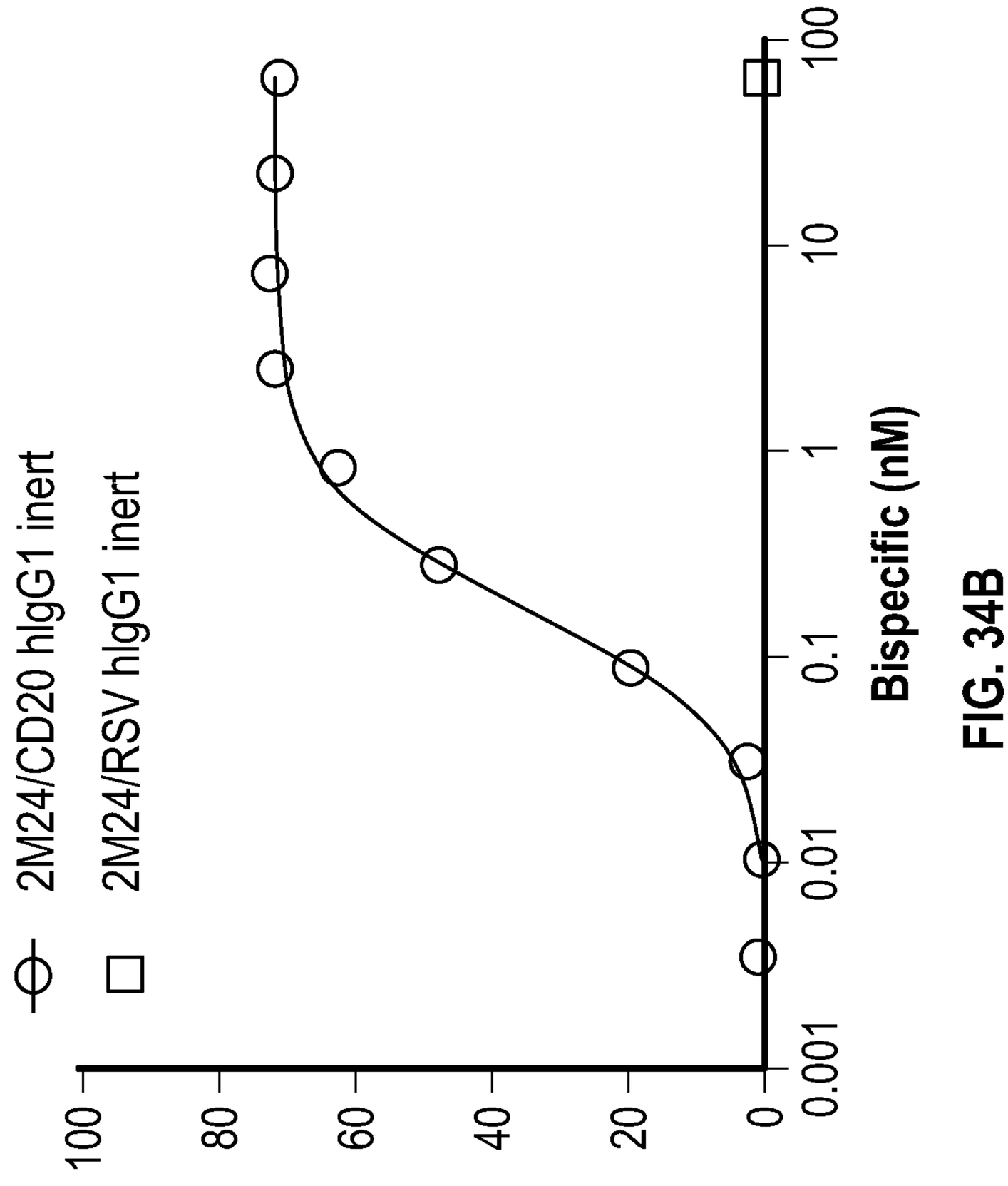

Coupling efficiency
(% of total Raji cells)
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
Bispecific (nM)
2M24/CD20 hIgG1 inert
2M24/RSV hIgG1 inert

FIG. 34B

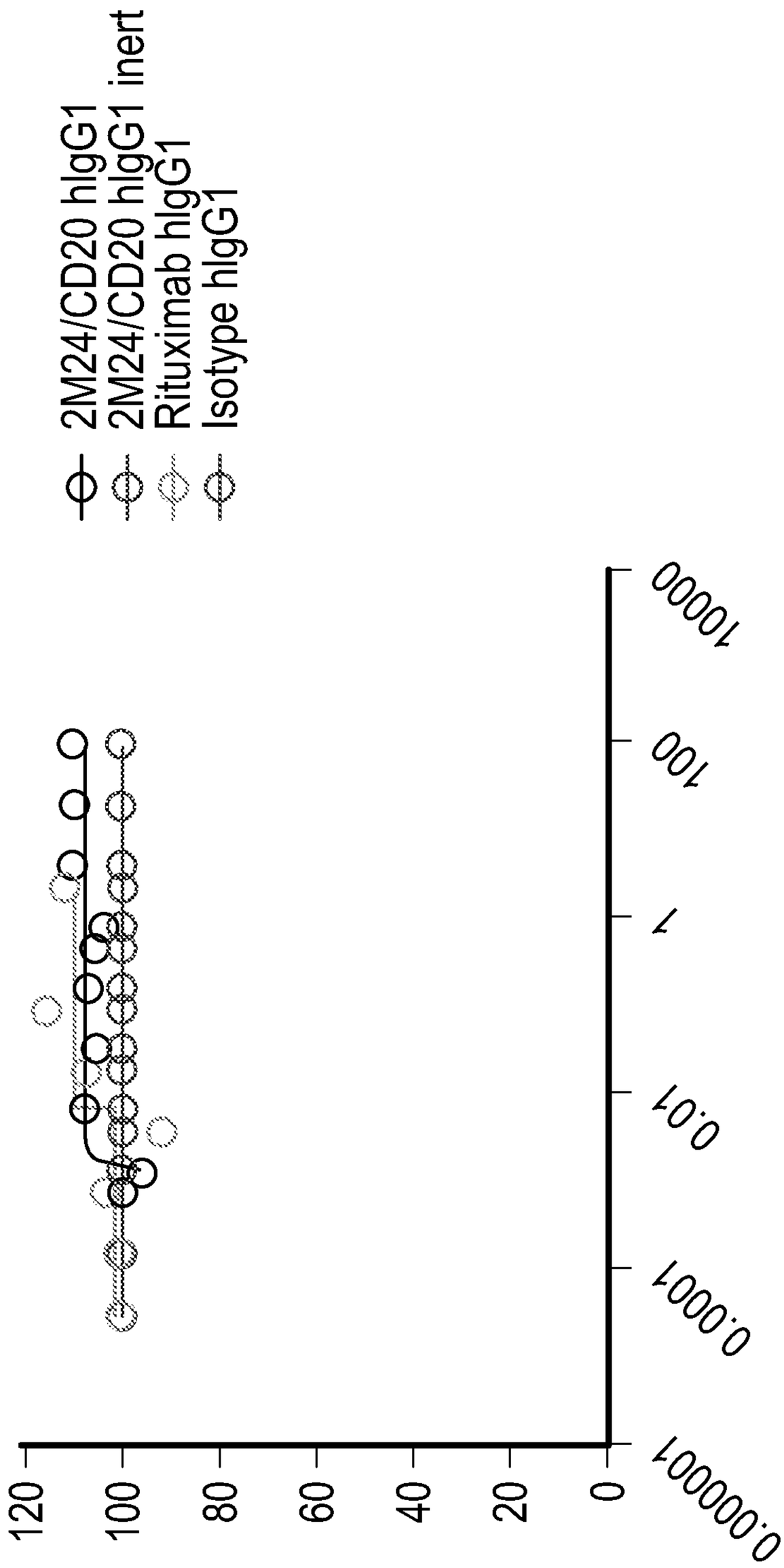

2M24/CD20 hIgG1
2M24/CD20 hIgG1 inert
Rituximab hIgG1
Isotype hIgG1
Donor 76
Single/Live/CD14+cells
(% of isotype control)
120
100
80
60
40
20
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
Concentration (nM)

FIG. 35A

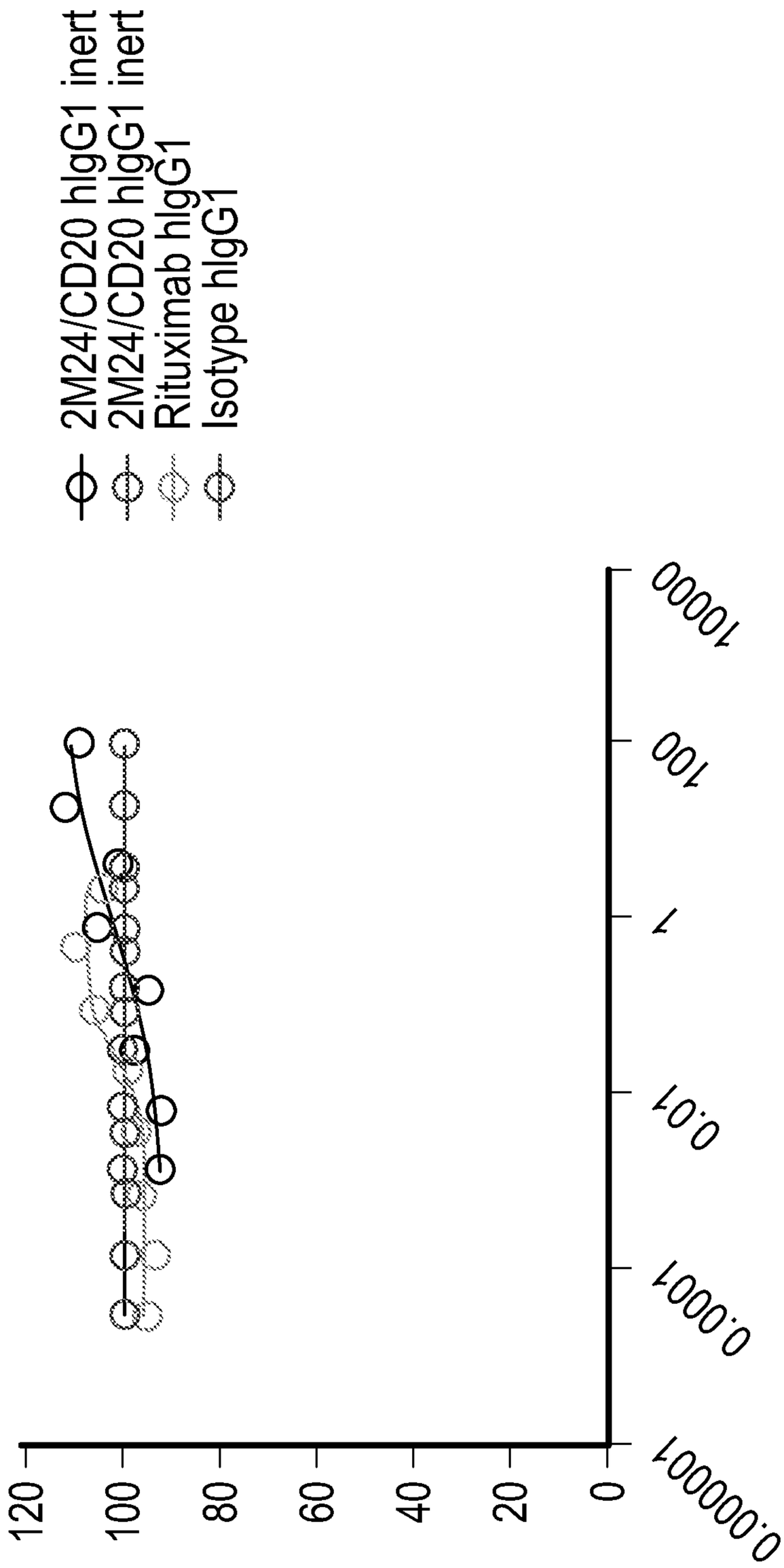

2M24/CD20 hIgG1 inert
2M24/CD20 hIgG1 inert
Rituximab hIgG1
Isotype hIgG1
Donor 77
Single/Live/CD14+cells
(% of isotype control)
120
100
80
60
40
20
0
0.00001
0.0001
0.001
0.01
1
100
10000
Concentration (nM)

FIG. 35B

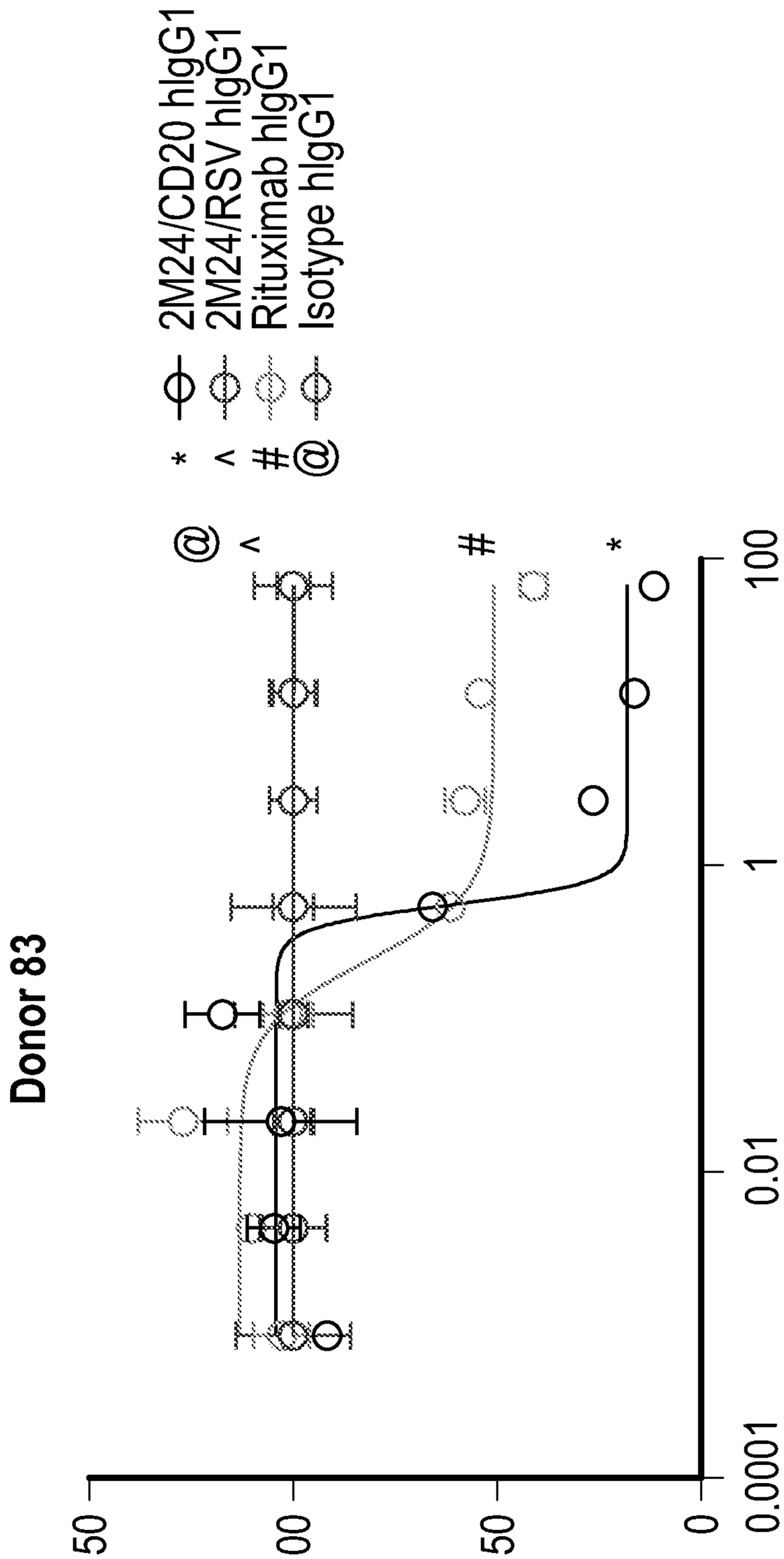

2M24/CD20 hIgG1
2M24/RSV hIgG1
Rituximab hIgG1
Isotype hIgG1
Donor 83
Live/CD19+ cells
(% of isotype control)
150
100
50
0
Antibody (nM)
100
1
0.01
0.0001

FIG. 36A

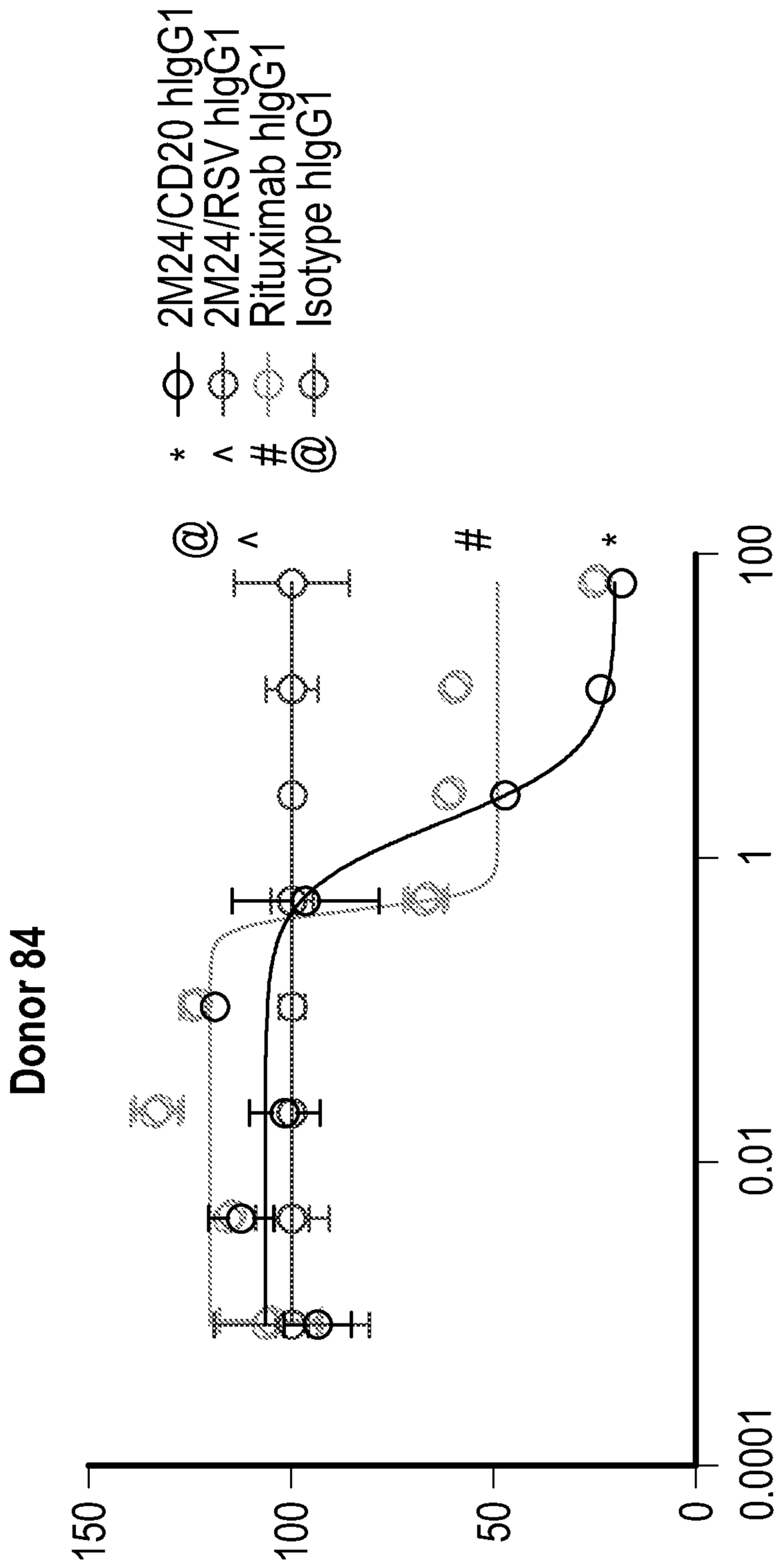

Donor 84
Live/CD19+ cells
(% of isotype control)
150
100
50
0
0.0001
0.01
1
100
Antibody (nM)
2M24/CD20 hIgG1
2M24/RSV hIgG1
Rituximab hIgG1
Isotype hIgG1
*
<
#
@

FIG. 36B

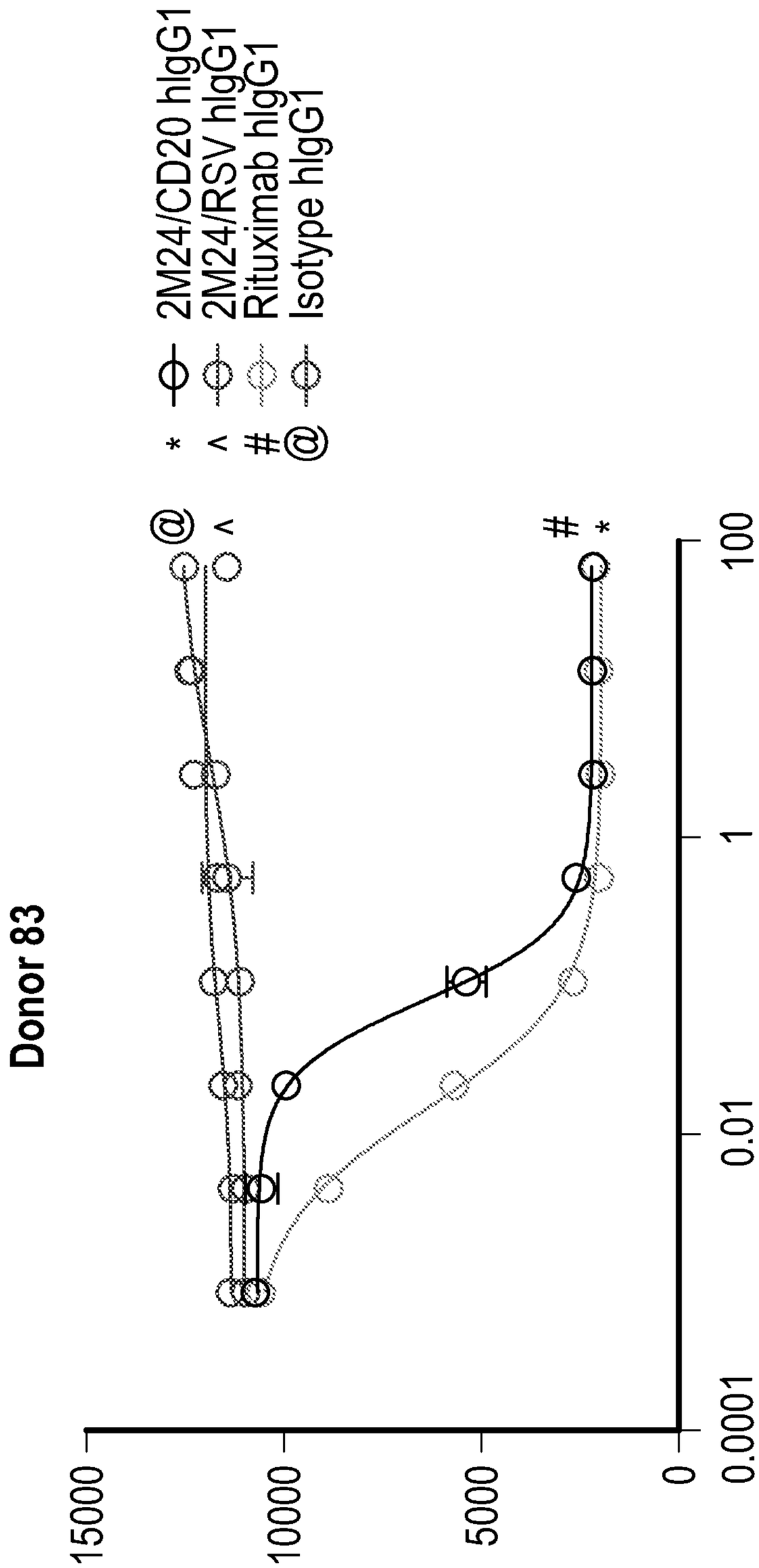

Donor 83
CD19 (MFI)
15000
10000
5000
0
0.0001
0.01
1
100
Antibody (nM)
* 2M24/CD20 hIgG1
^ 2M24/RSV hIgG1
Rituximab hIgG1
@ Isotype hIgG1
*
#
^
@

FIG. 37A

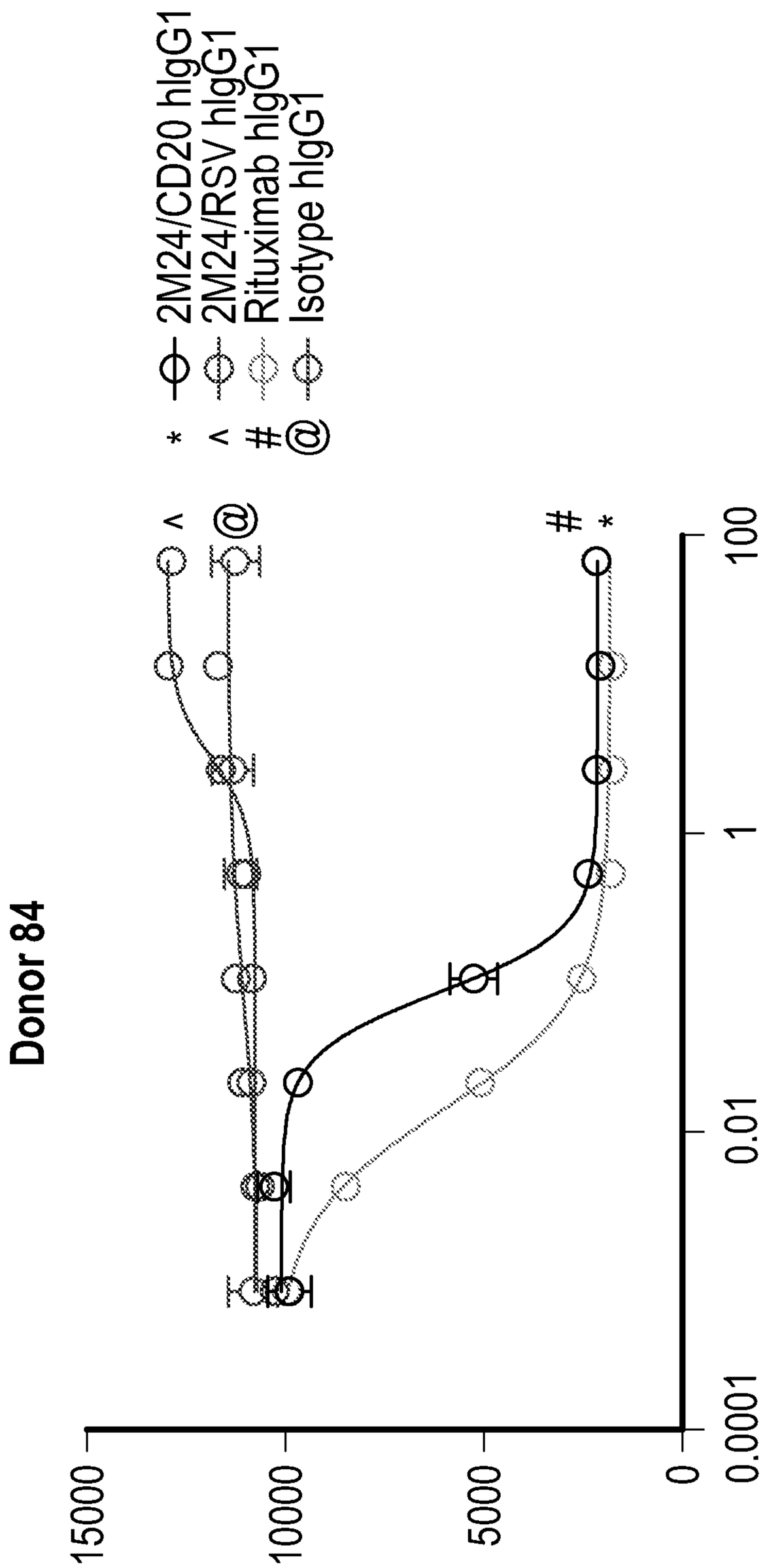

Donor 84
CD19 (MFI)
15000
10000
5000
0
0.0001
0.01
1
100
Antibody (nM)
* 2M24/CD20 hIgG1
< 2M24/RSV hIgG1
Rituximab hIgG1
@ Isotype hIgG1

FIG. 37B

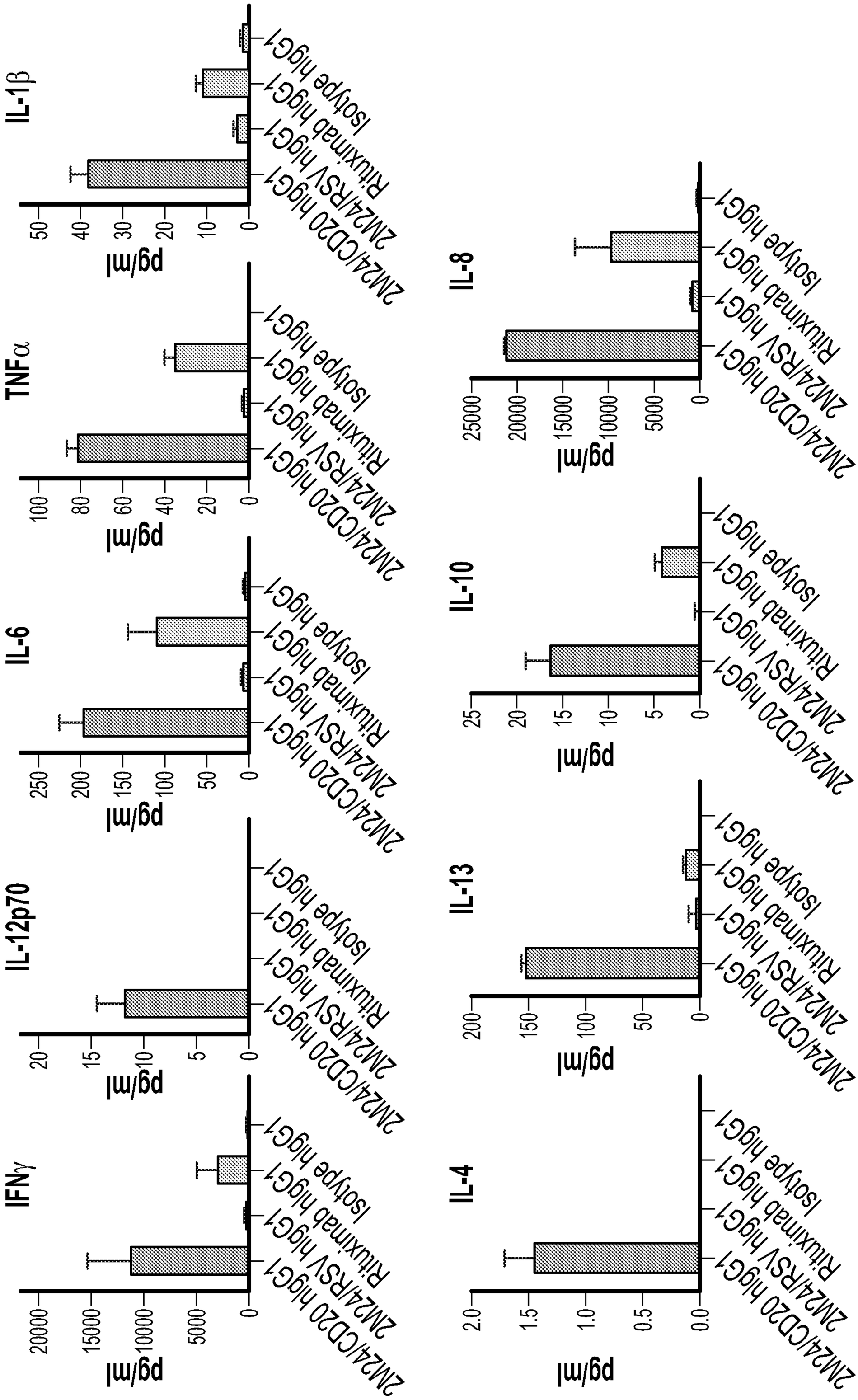

IL-1β
pg/ml
0
10
20
30
40
50
2M24/CD20 hIgG1
2M24/RSV hIgG1
Rituximab hIgG1
Isotype hIgG1
TNFα
pg/ml
0
20
40
60
80
100
IL-6
pg/ml
0
50
100
150
200
250
IL-12p70
pg/ml
0
5
10
15
20
IFNγ
pg/ml
0
5000
10000
15000
20000
IL-8
pg/ml
0
5000
10000
15000
20000
25000
IL-10
pg/ml
0
5
10
15
20
25
IL-13
pg/ml
0
50
100
150
200
IL-4
pg/ml
0.0
0.5
1.0
1.5
2.0

FIG. 38

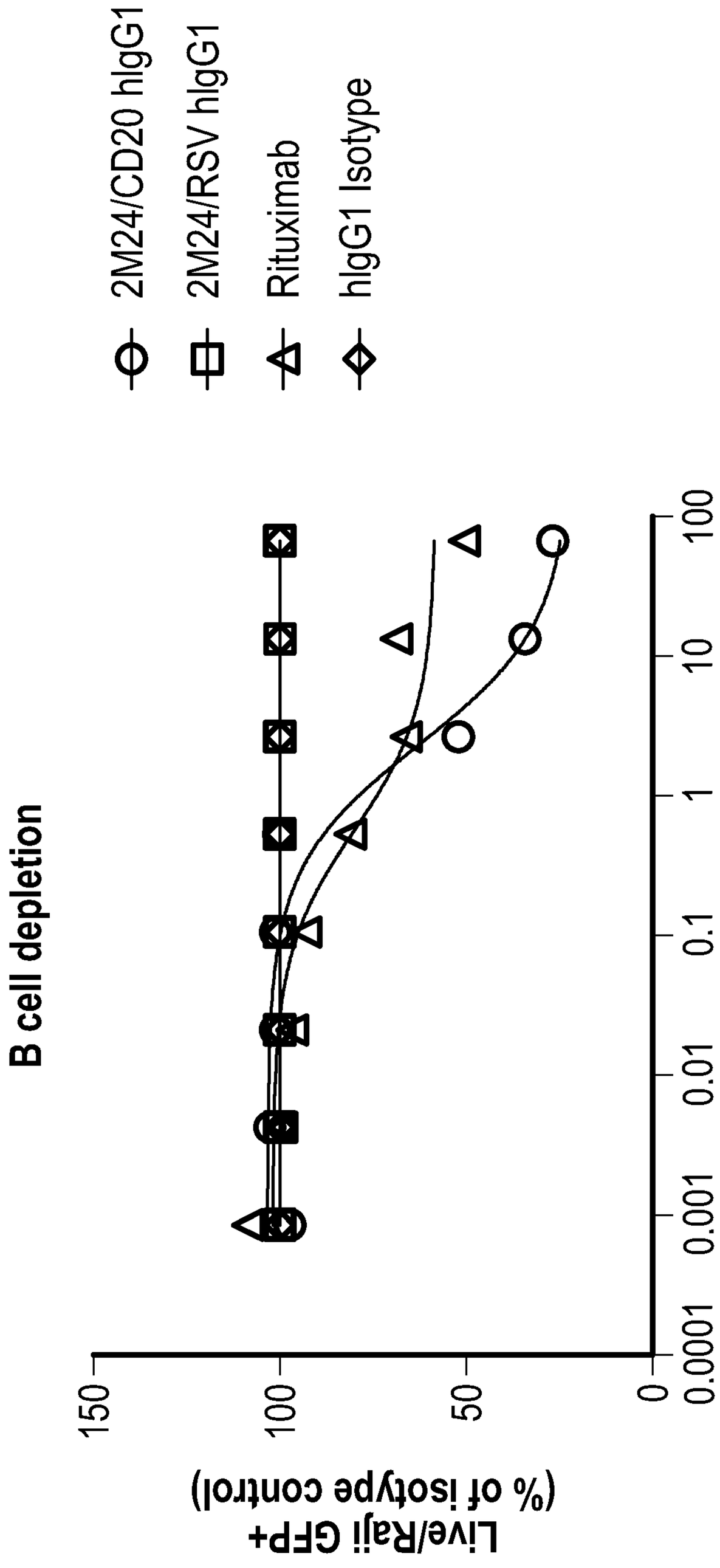

2M247/CD20 hIgG1
2M247/RSV hIgG1
Rituximab
hIgG1 Isotype
B cell depletion
150
100
50
0
Live/Raji GFP+
(% of isotype control)
0.0001
0.001
0.01
0.1
1
10
100
Concentration (nM)

FIG. 39A

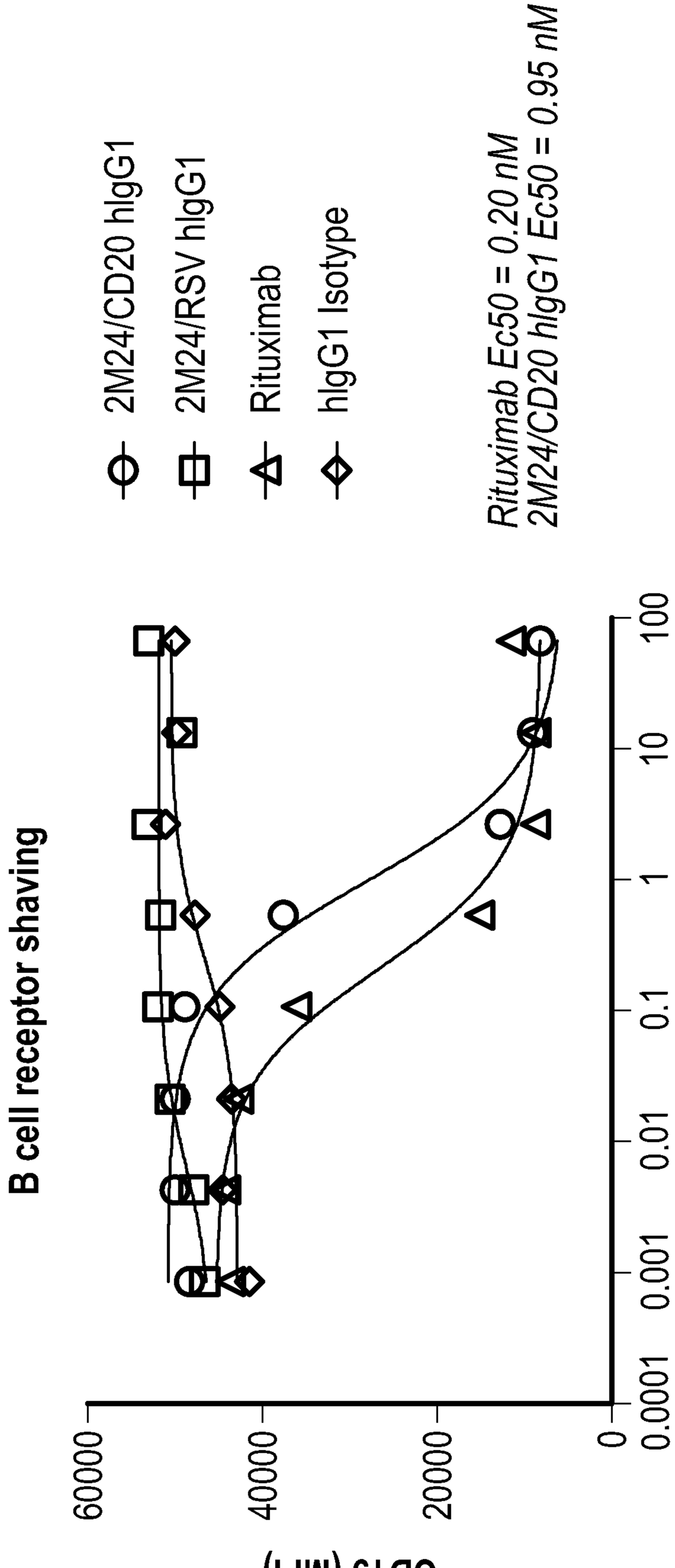

2M24/CD20 hIgG1
2M24/RSV hIgG1
Rituximab
hIgG1 Isotype
Rituximab Ec50 = 0.20 nM
2M24/CD20 hIgG1 Ec50 = 0.95 nM
B cell receptor shaving
CD19 (MFI)
60000
40000
20000
0
0.001
0.01
0.1
1
10
100
Concentration (nM)

FIG. 39B

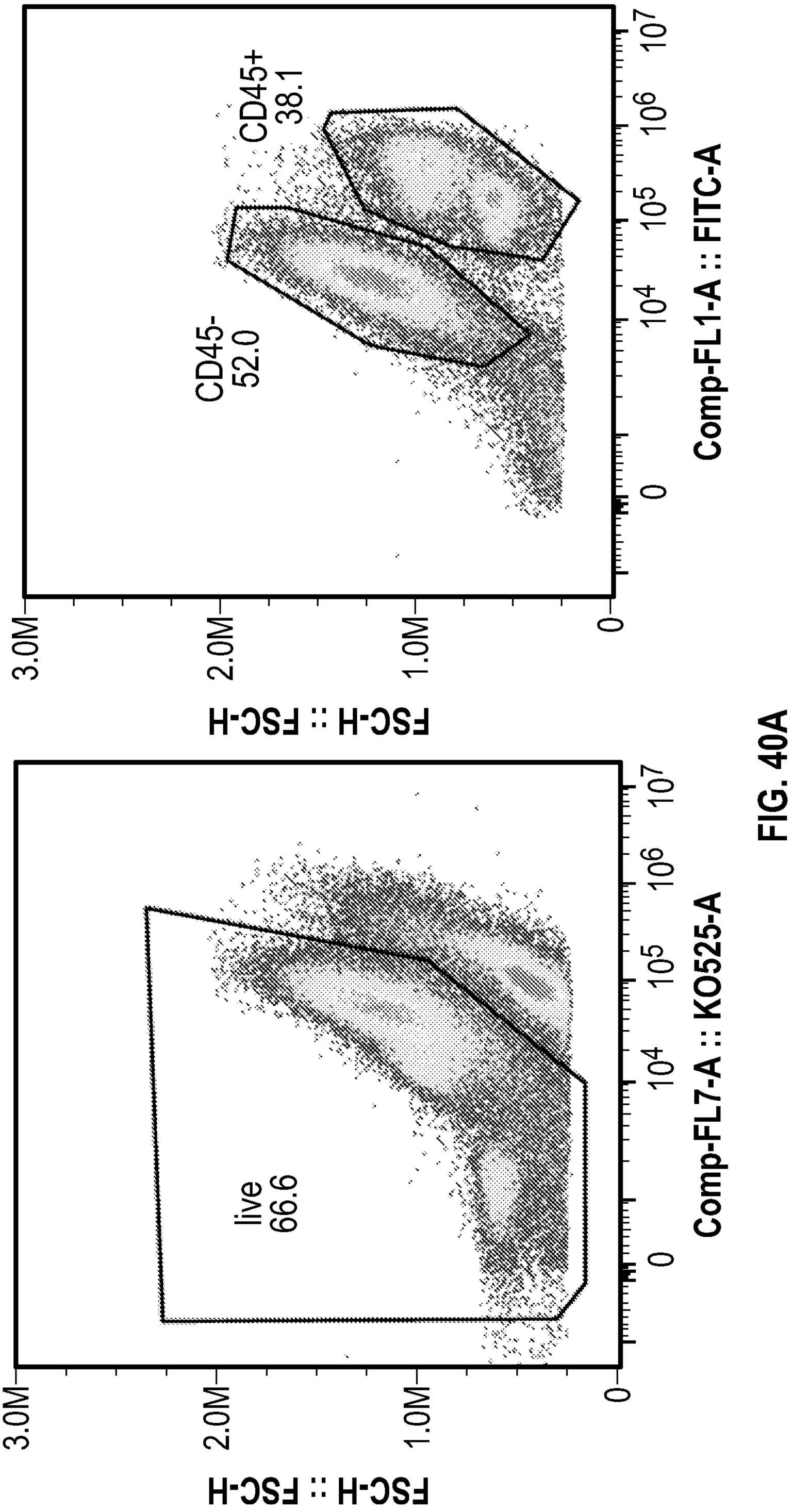

CD45+/CD45- cells
CD45+
38.1
CD45-
52.0
3.0M
2.0M
1.0M
0
0
10^4
10^5
10^6
10^7
Comp-FL1-A :: FITC-A
FSC-H :: FSC-H
Single/Live cells
live
66.6
3.0M
2.0M
1.0M
0
0
10^4
10^5
10^6
10^7
Comp-FL7-A :: KO525-A
FSC-H :: FSC-H

FIG. 40A

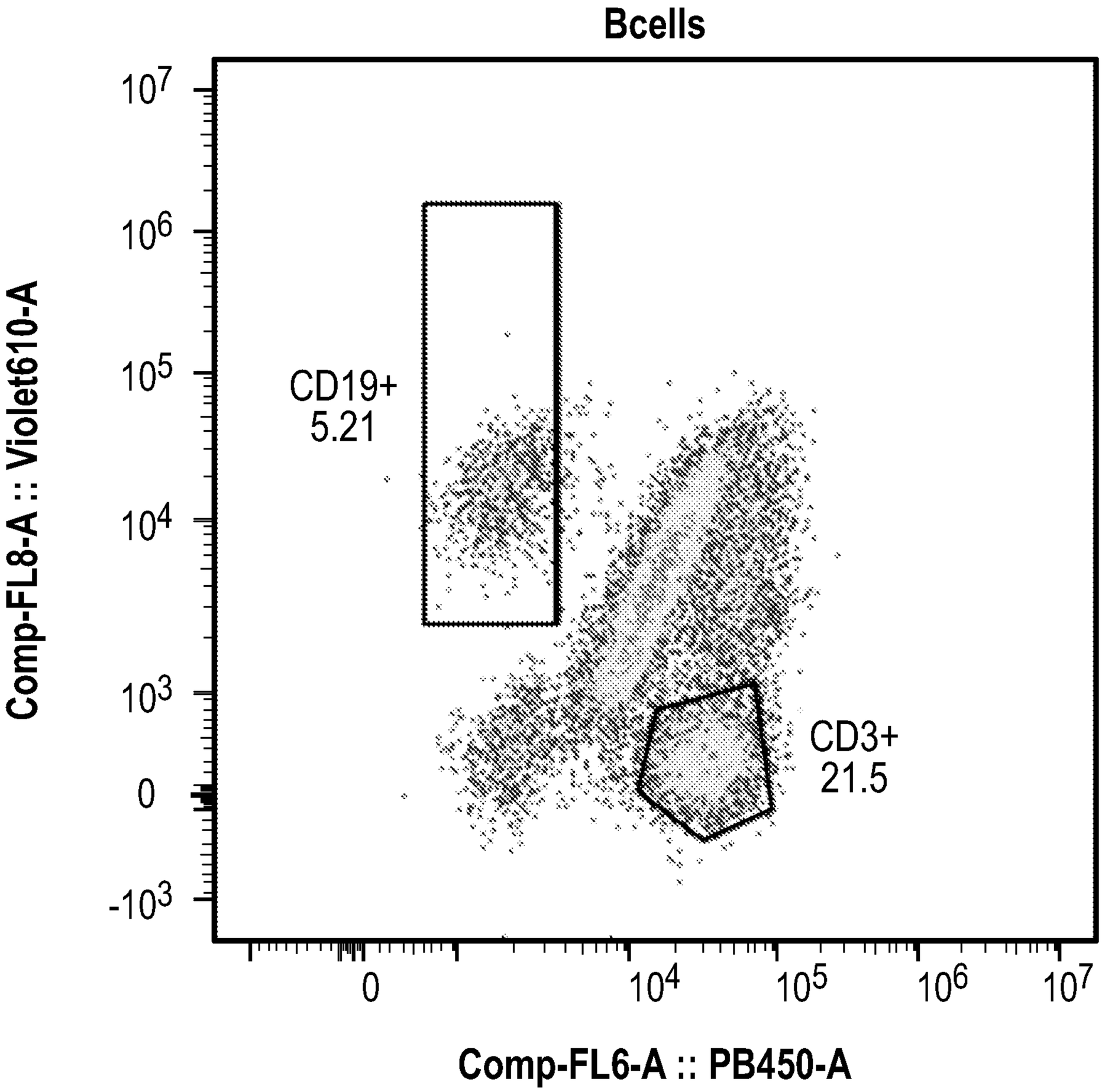

Bcells
CD19+
5.21
CD3+
21.5
Comp-FL8-A :: Violet610-A
Comp-FL6-A :: PB450-A
10^7
10^6
10^5
10^4
10^3
0
-10^3
0
10^4
10^5
10^6
10^7

FIG. 40B

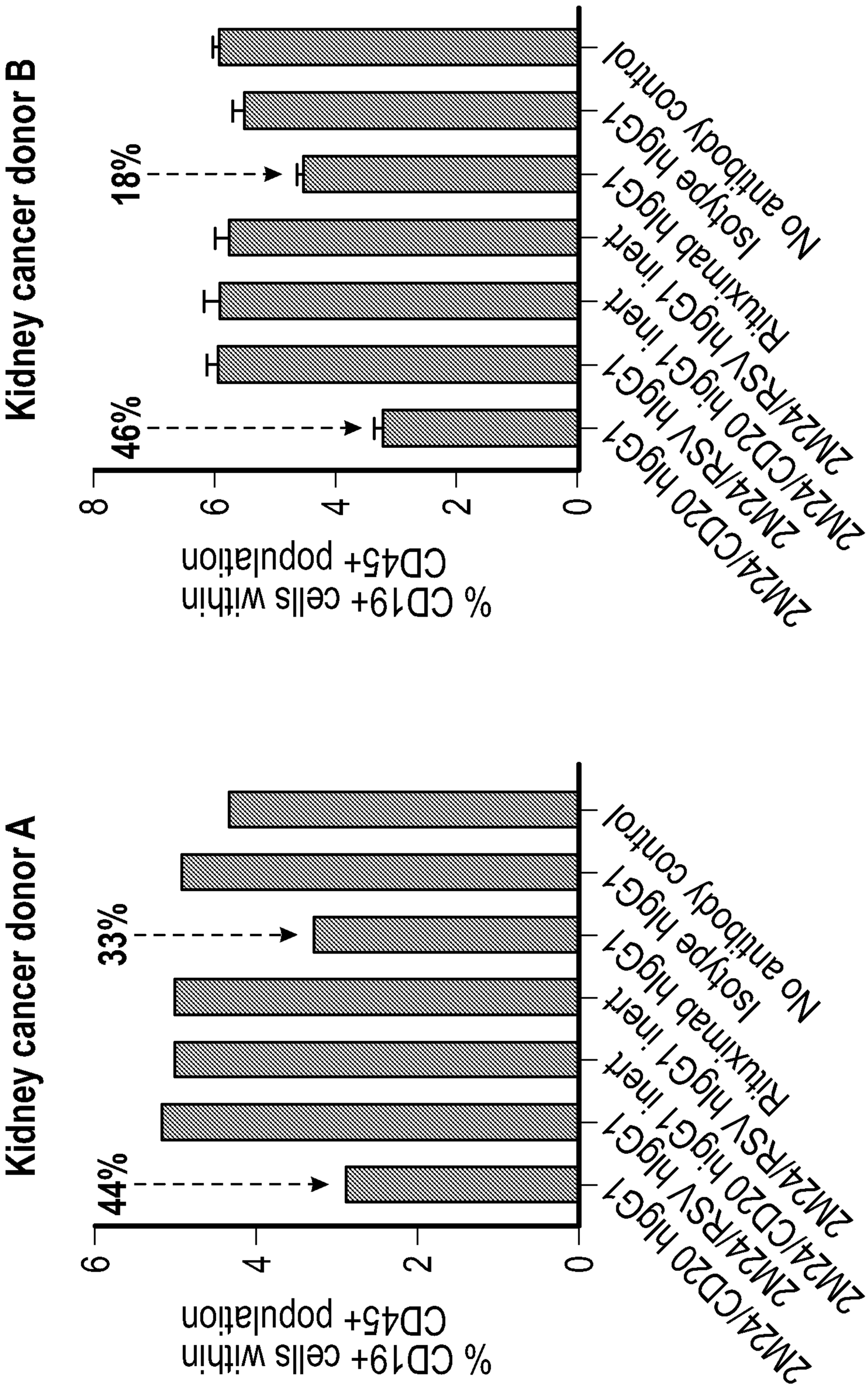

Kidney cancer donor B
% CD19+ cells within CD45+ population
0
2
4
6
8
46%
18%
2M24/CD20 hIgG1
2M24/RSV hIgG1
2M24/CD20 hIgG1 inert
2M24/RSV hIgG1 inert
Rituximab hIgG1 inert
Isotype hIgG1
No antibody control
Kidney cancer donor A
% CD19+ cells within CD45+ population
0
2
4
6
44%
33%
2M24/CD20 hIgG1
2M24/RSV hIgG1
2M24/CD20 hIgG1 inert
2M24/RSV hIgG1 inert
Rituximab hIgG1 inert
Isotype hIgG1
No antibody control

FIG. 40C

SUBSTITUTE SHEET (RULE 26)

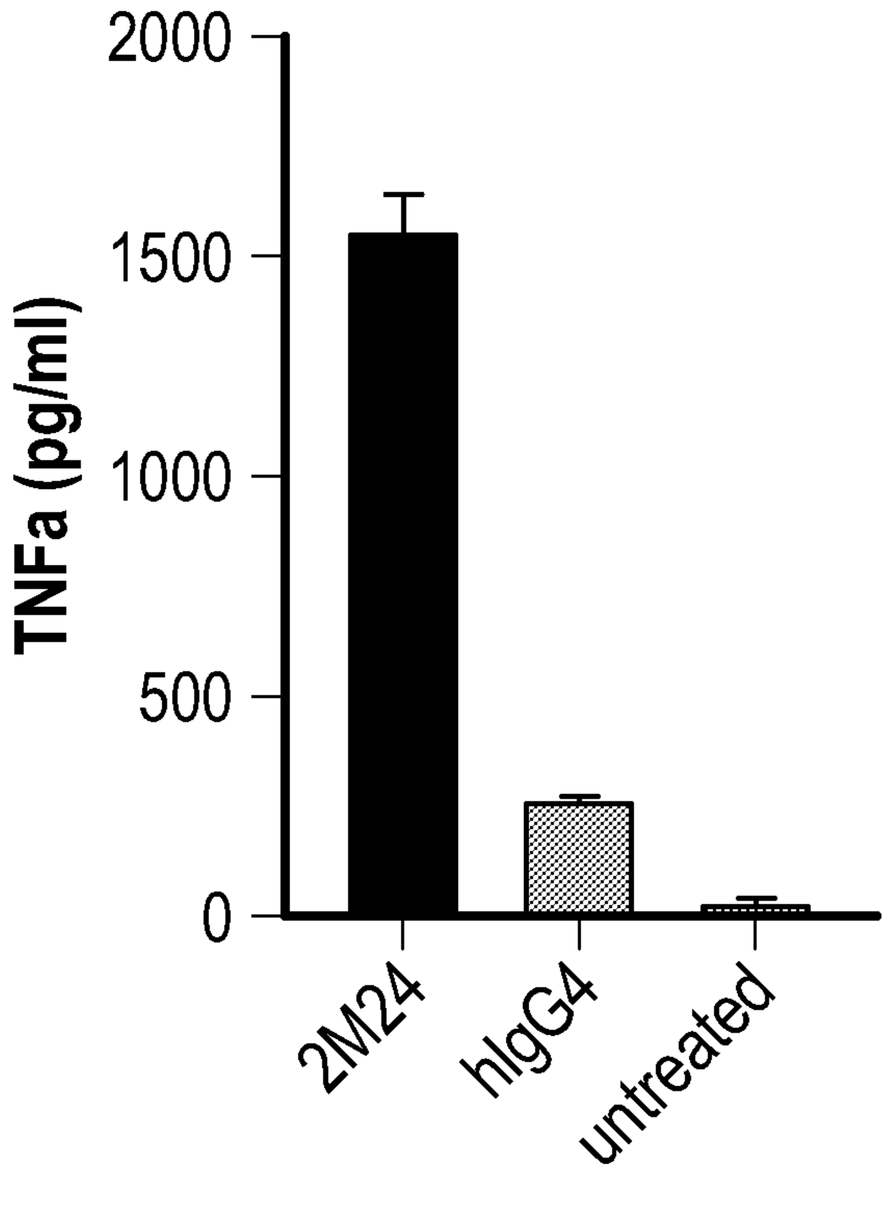


FIG. 41A

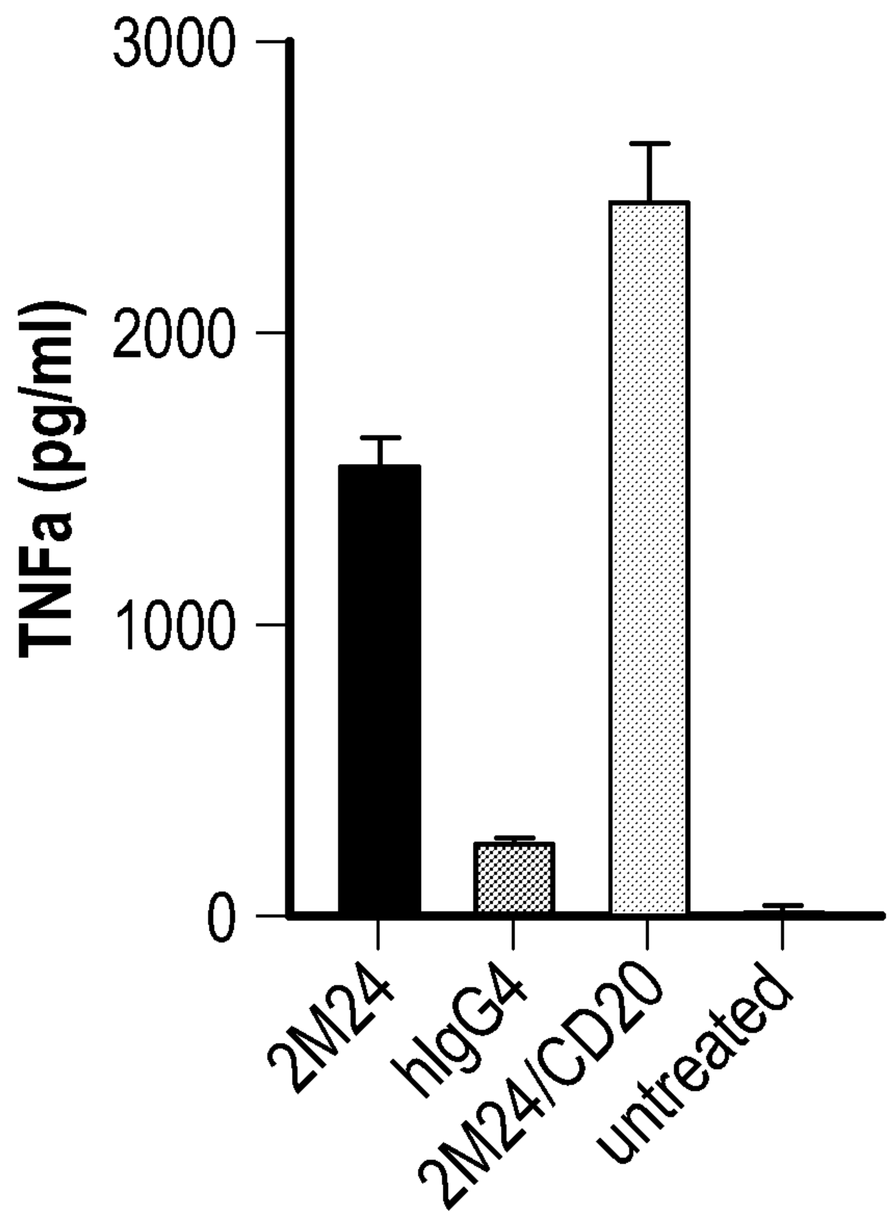


FIG. 41B

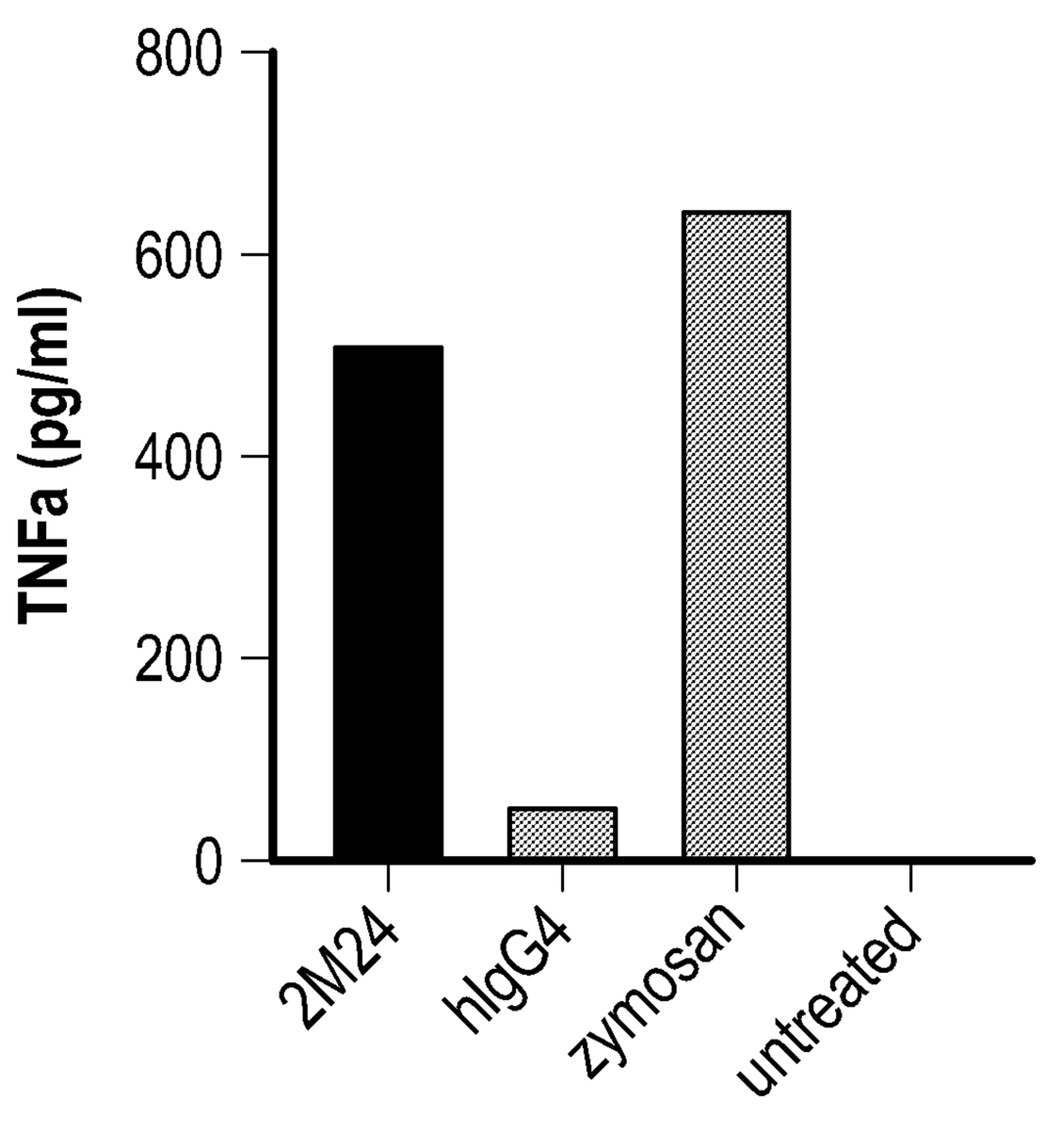


FIG. 41C

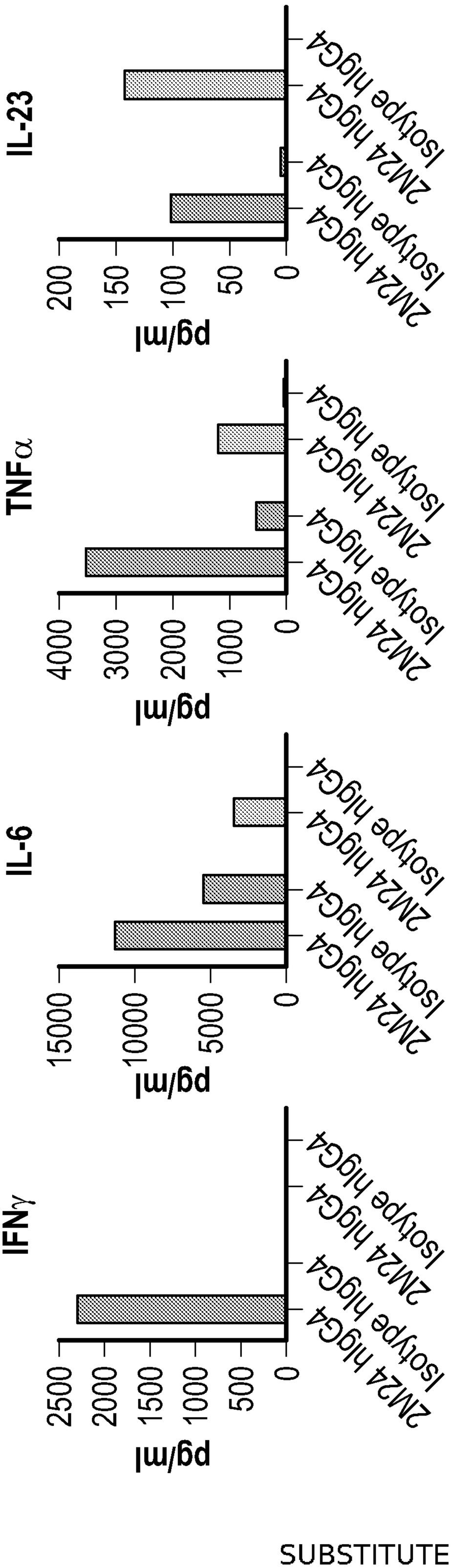

IL-23
pg/ml
200
150
100
50
0
2M24 hIgG4
Isotype hIgG4
2M24 hIgG4
Isotype hIgG4
TNFα
pg/ml
4000
3000
2000
1000
0
2M24 hIgG4
Isotype hIgG4
2M24 hIgG4
Isotype hIgG4
IL-6
pg/ml
15000
10000
5000
0
2M24 hIgG4
Isotype hIgG4
2M24 hIgG4
Isotype hIgG4
IFNγ
pg/ml
2500
2000
1500
1000
500
0
2M24 hIgG4
Isotype hIgG4
2M24 hIgG4
Isotype hIgG4
IL-13
pg/ml
15
10
5
0
2M24 hIgG4
Isotype hIgG4
2M24 hIgG4
Isotype hIgG4
IL-10
pg/ml
200
150
100
50
0
2M24 hIgG4
Isotype hIgG4
2M24 hIgG4
Isotype hIgG4
IL-12p70
pg/ml
0.15
0.10
0.05
0.00
2M24 hIgG4
Isotype hIgG4
2M24 hIgG4
Isotype hIgG4

FIG. 42

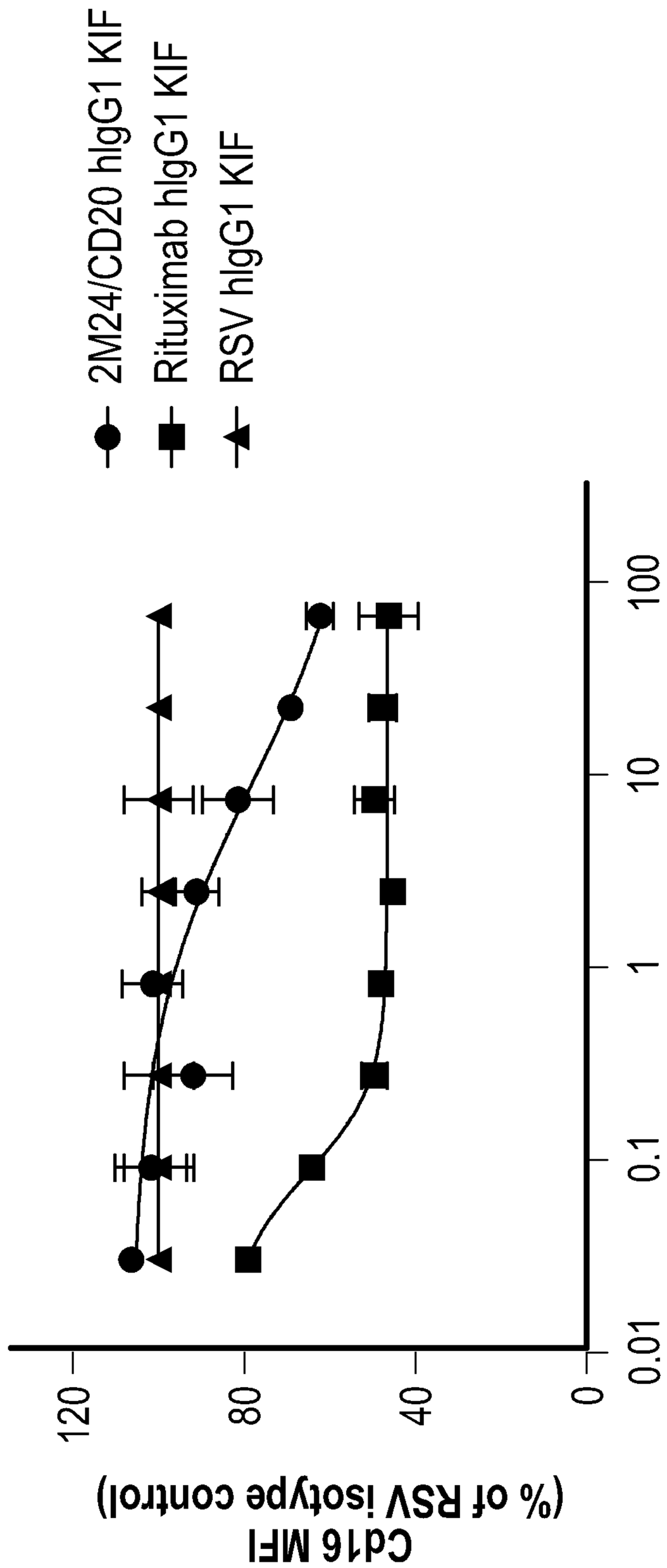

2M24/CD20 hIgG1 KIF
Rituximab hIgG1 KIF
RSV hIgG1 KIF
100
10
1
0.1
0.01
Antibody (nM)
120
80
40
0
CD16 MFI
(% of RSV isotype control)

FIG. 43

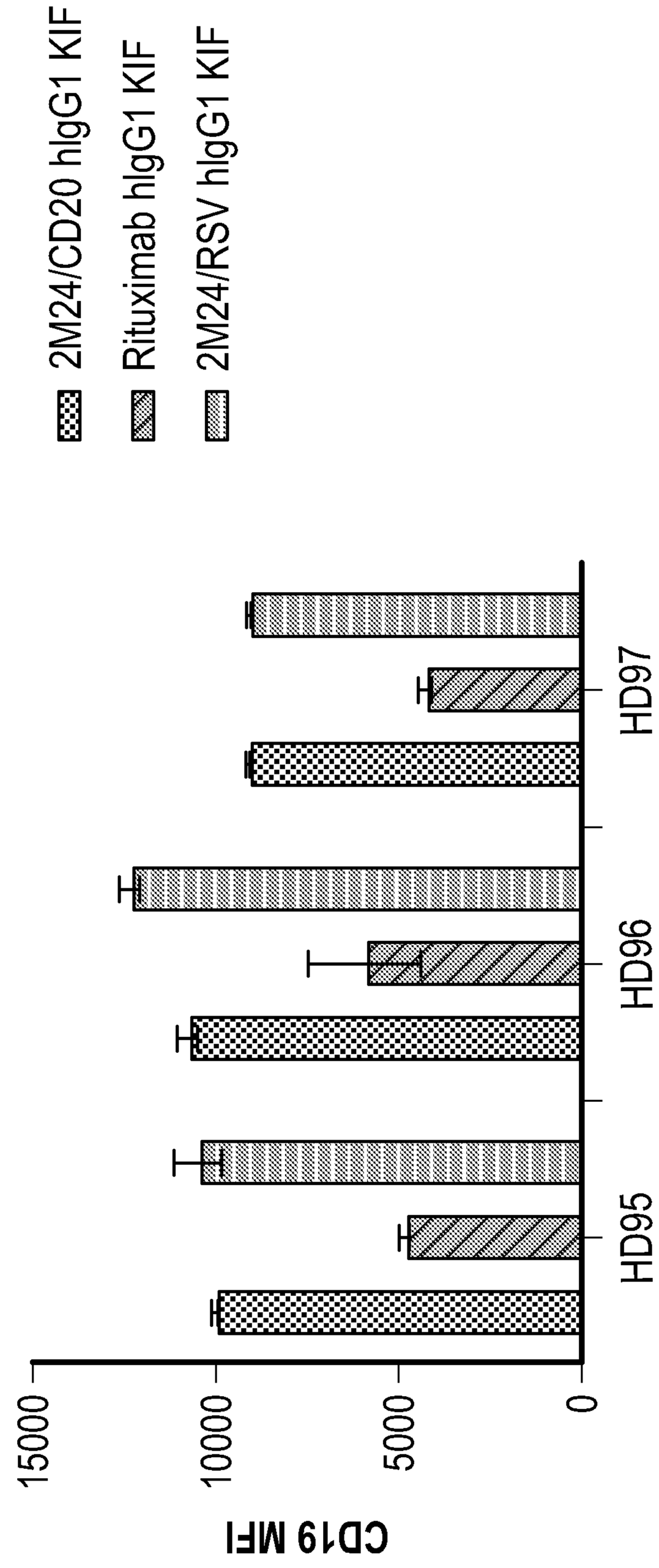

2M24/CD20 hIgG1 KIF
Rituximab hIgG1 KIF
2M24/RSV hIgG1 KIF
HD97
HD96
HD95
15000
10000
5000
0
CD19 MFI

FIG. 44

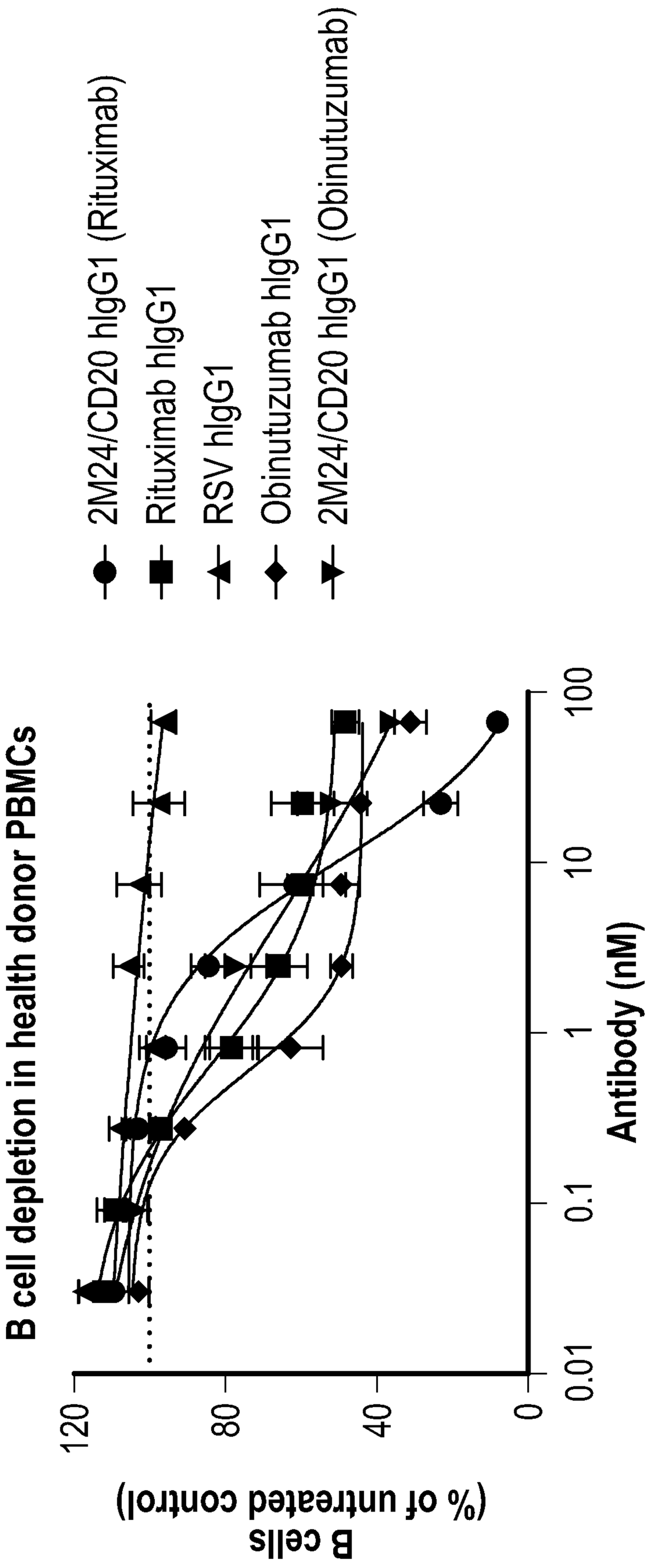

2M24/CD20 hIgG1 (Rituximab)
Rituximab hIgG1
RSV hIgG1
Obinutuzumab hIgG1
2M24/CD20 hIgG1 (Obinutuzumab)
B cell depletion in health donor PBMCs
B cells
(% of untreated control)
120
80
40
0
0.01
0.1
1
10
100
Antibody (nM)

FIG. 45

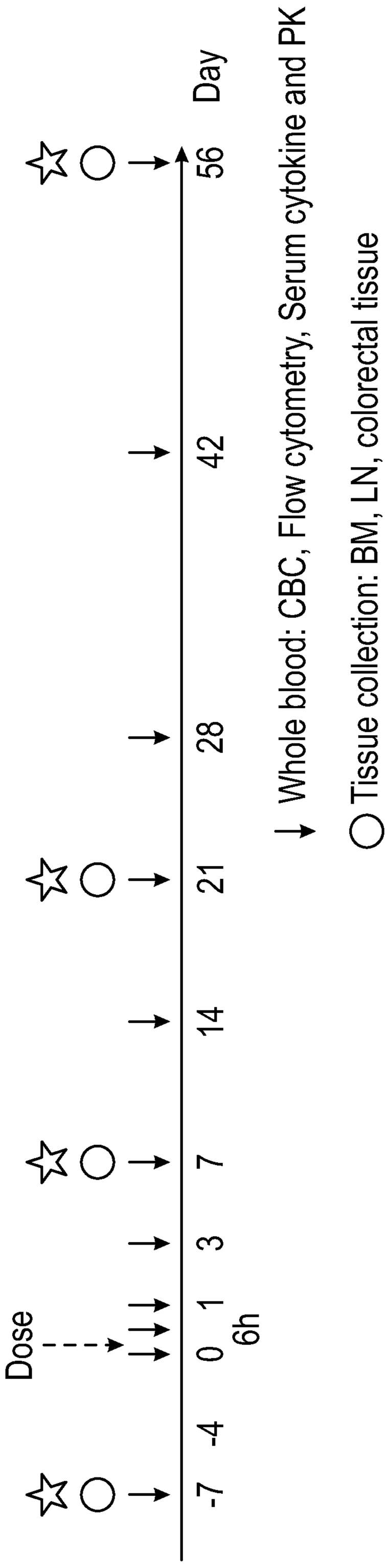
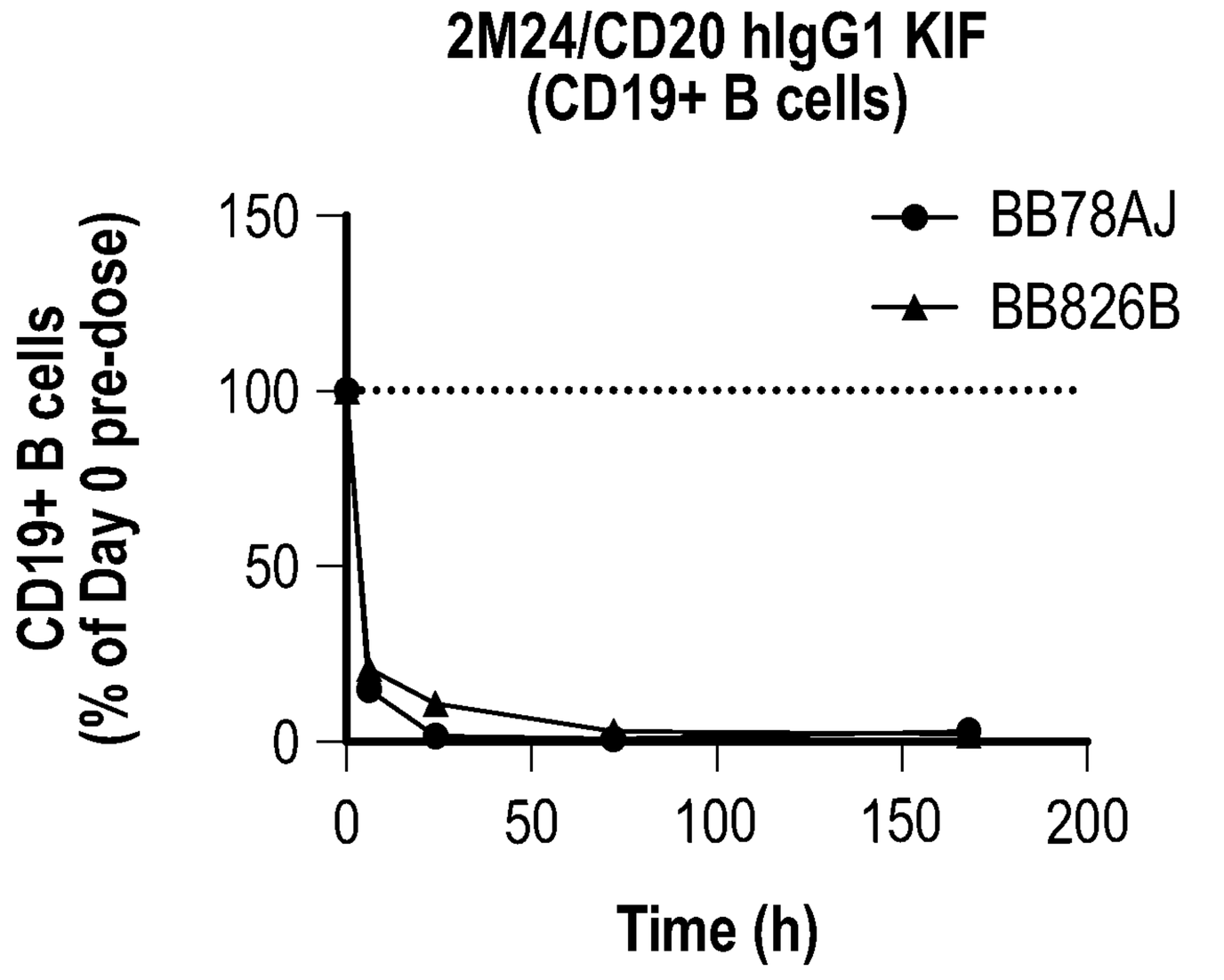

Day
56
42
28
21
14
7
3
1
0
-4
-7
Dose
6h
→ Whole blood: CBC, Flow cytometry, Serum cytokine and PK
○ Tissue collection: BM, LN, colorectal tissue
☆ Whole blood: Chemistry, Coagulation

FIG. 46


2M24/CD20 hIgG1 KIF
(CD19+ B cells)
CD19+ B cells
(% of Day 0 pre-dose)
150
100
50
0
0
50
100
150
200
Time (h)
BB78AJ
BB826B

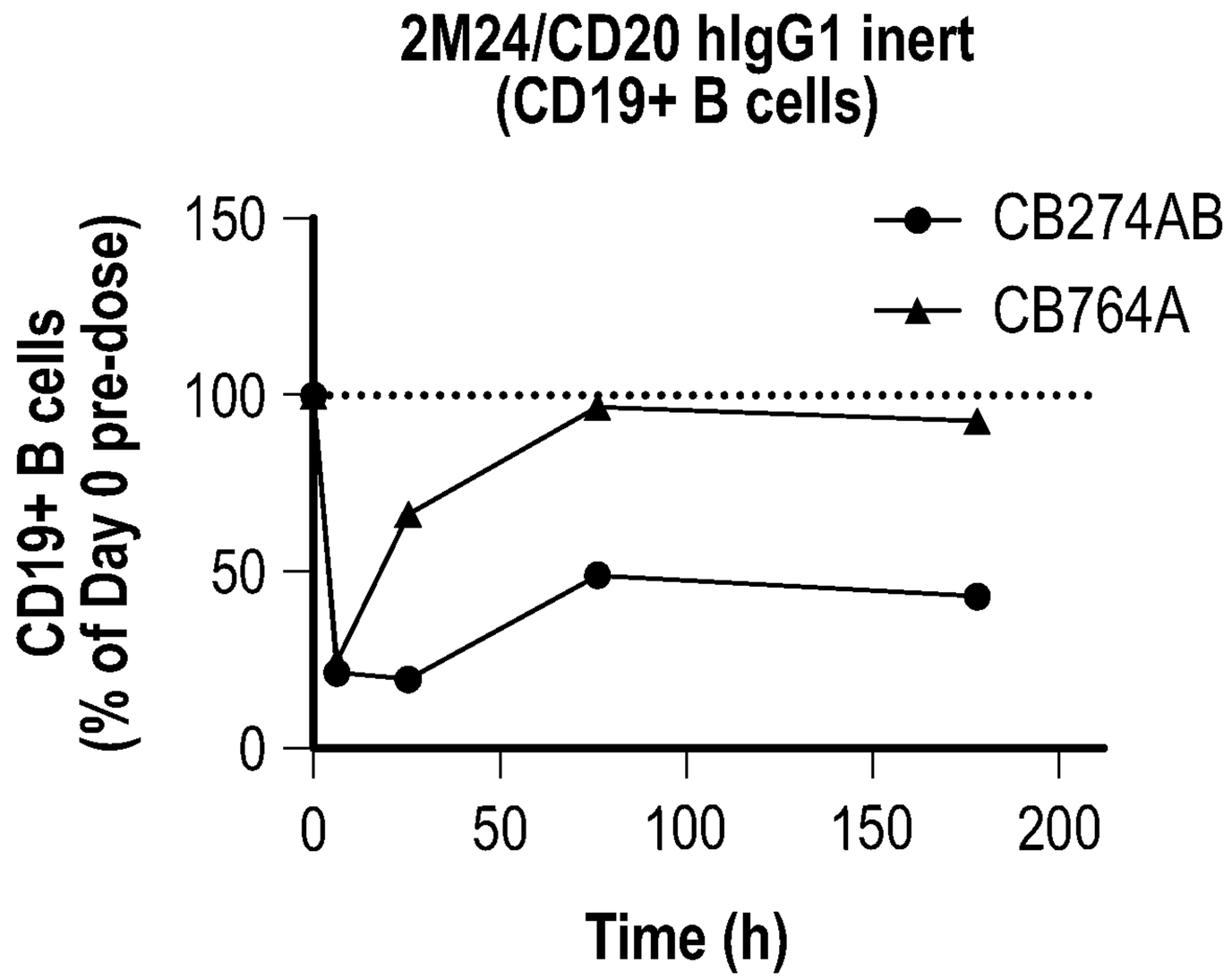

2M24/CD20 hIgG1 inert
(CD19+ B cells)
CD19+ B cells
(% of Day 0 pre-dose)
150
100
50
0
0
50
100
150
200
Time (h)
CB274AB
CB764A

FIG. 47

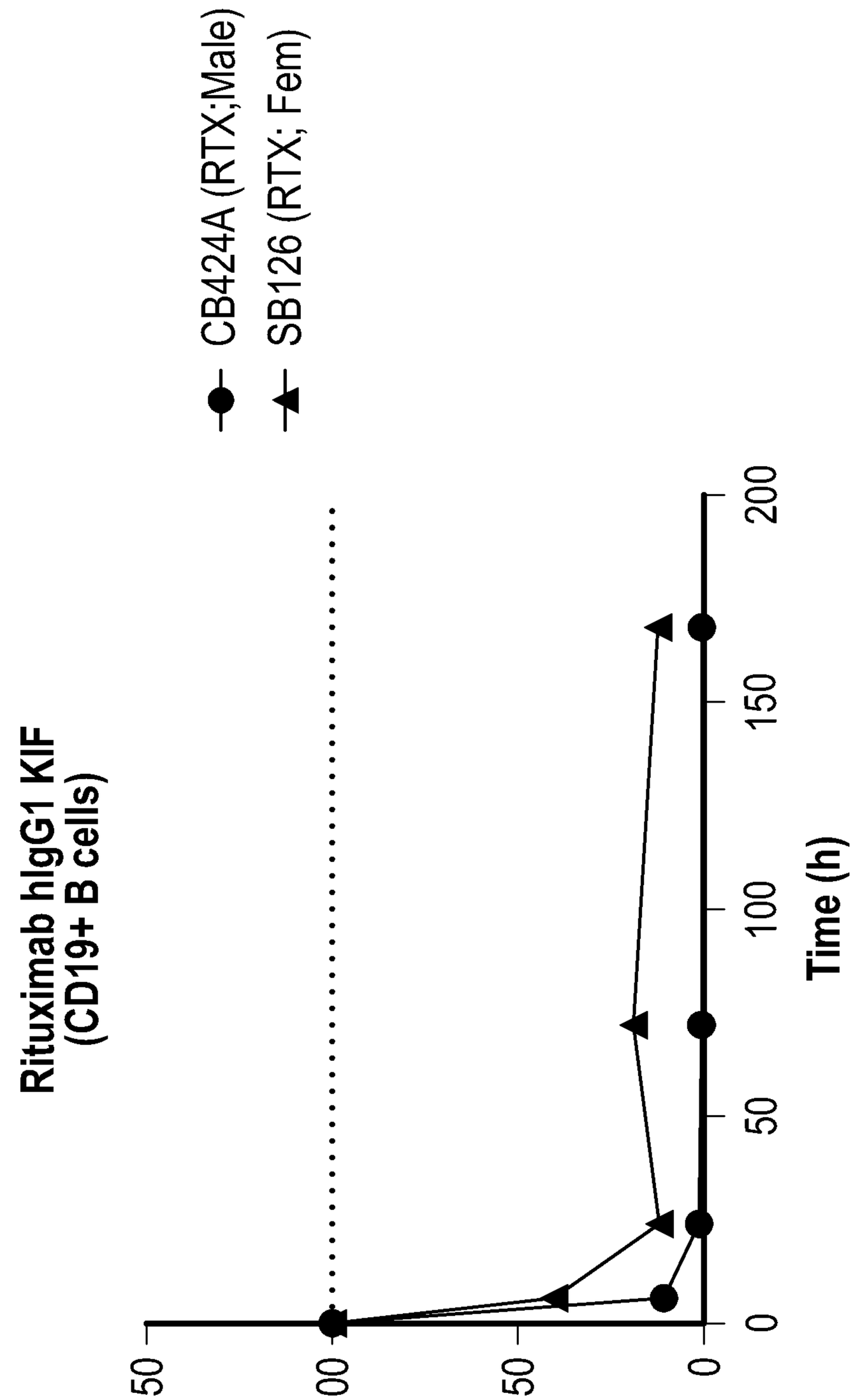

Rituximab hIgG1 KIF
(CD19+ B cells)
CB424A (RTX;Male)
SB126 (RTX; Female)
CD19+ B cells
(% of Day -7pre-dose)
150
100
50
0
Time (h)
0
50
100
150
200

FIG. 48

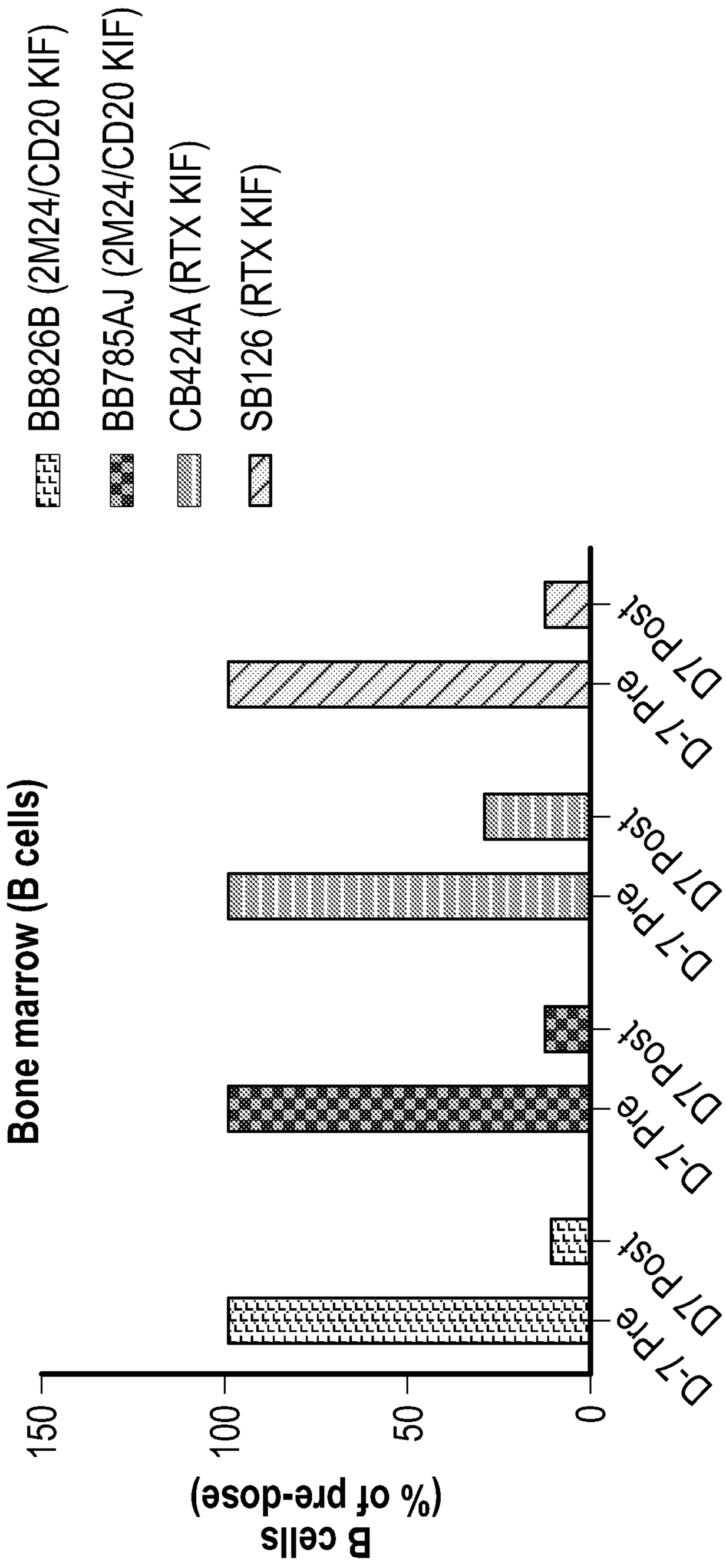

BB826B (2M24/CD20 KIF)
BB785AJ (2M24/CD20 KIF)
CB424A (RTX KIF)
SB126 (RTX KIF)
Bone marrow (B cells)
D-7 Pre
D7 Post
D-7 Pre
D7 Post
D-7 Pre
D7 Post
D-7 Pre
D7 Post
150
100
50
0
B cells
(% of pre-dose)

FIG. 49A

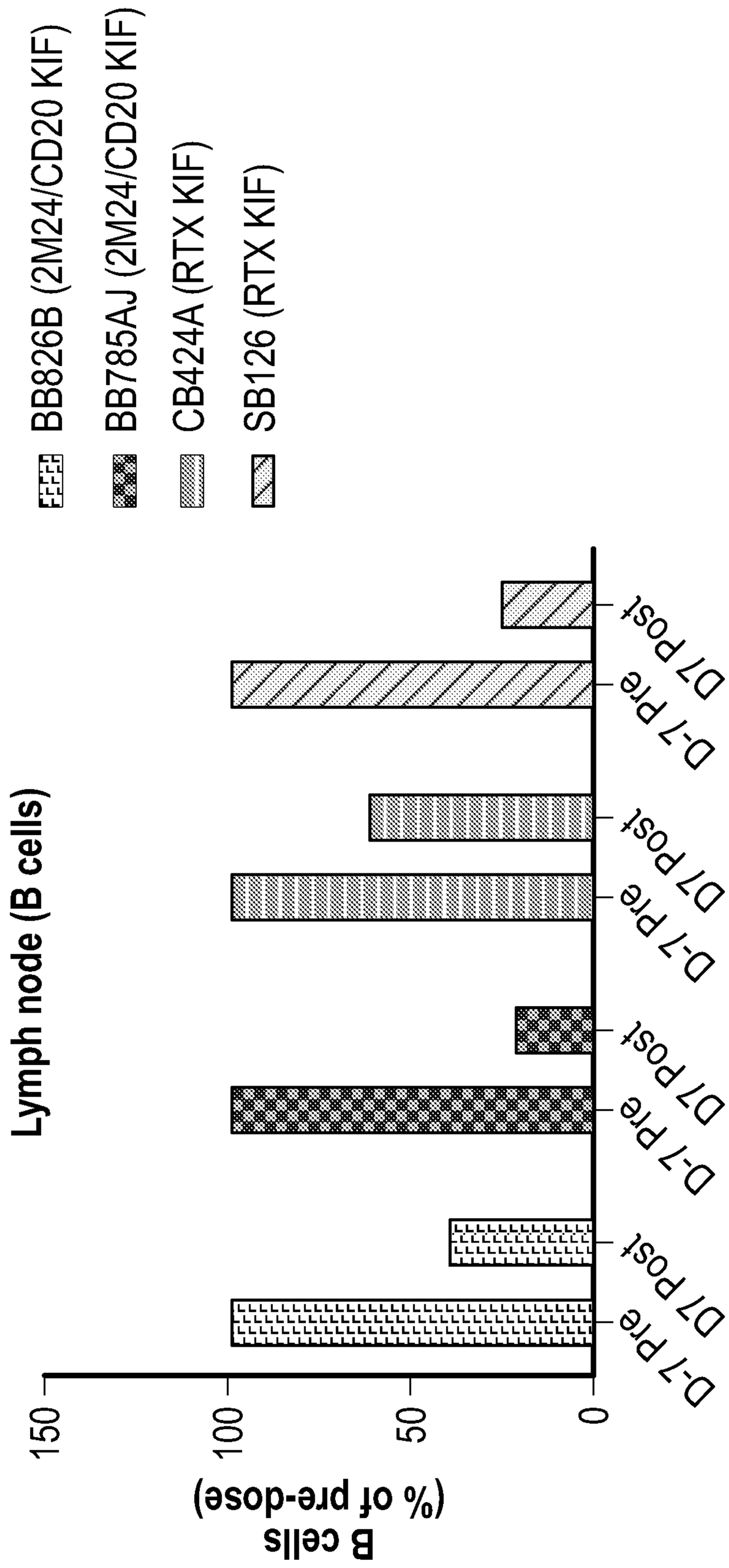

BB826B (2M24/CD20 KIF)
BB785AJ (2M24/CD20 KIF)
CB424A (RTX KIF)
SB126 (RTX KIF)
Lymph node (B cells)
D-7 Pre
D7 Post
D-7 Pre
D7 Post
D-7 Pre
D7 Post
D-7 Pre
D7 Post
150
100
50
0
B cells
(% of pre-dose)

FIG. 49B

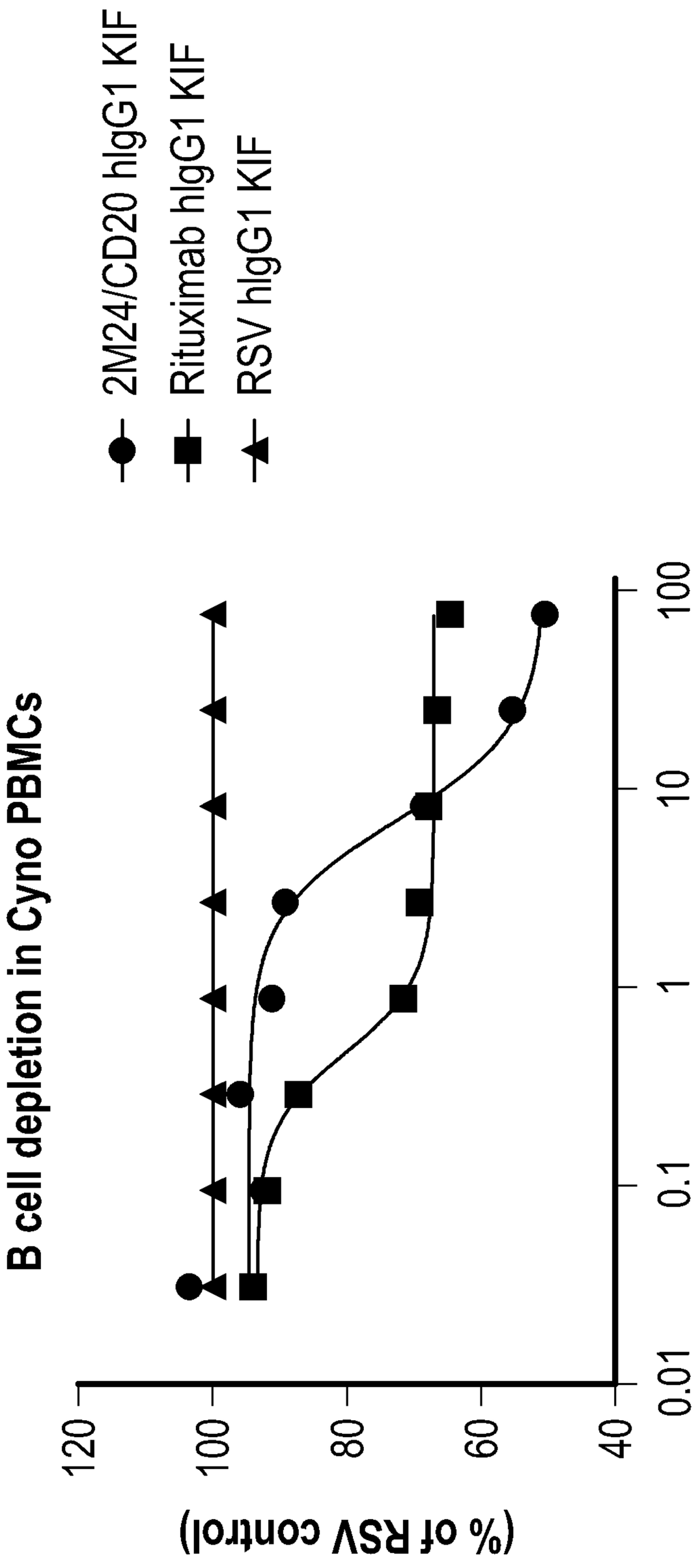

2M24/CD20 hIgG1 KIF
Rituximab hIgG1 KIF
RSV hIgG1 KIF
B cell depletion in Cyno PBMCs
(% of RSV control)
120
100
80
60
40
0.01
0.1
1
10
100
Antibody (nM)

FIG. 50

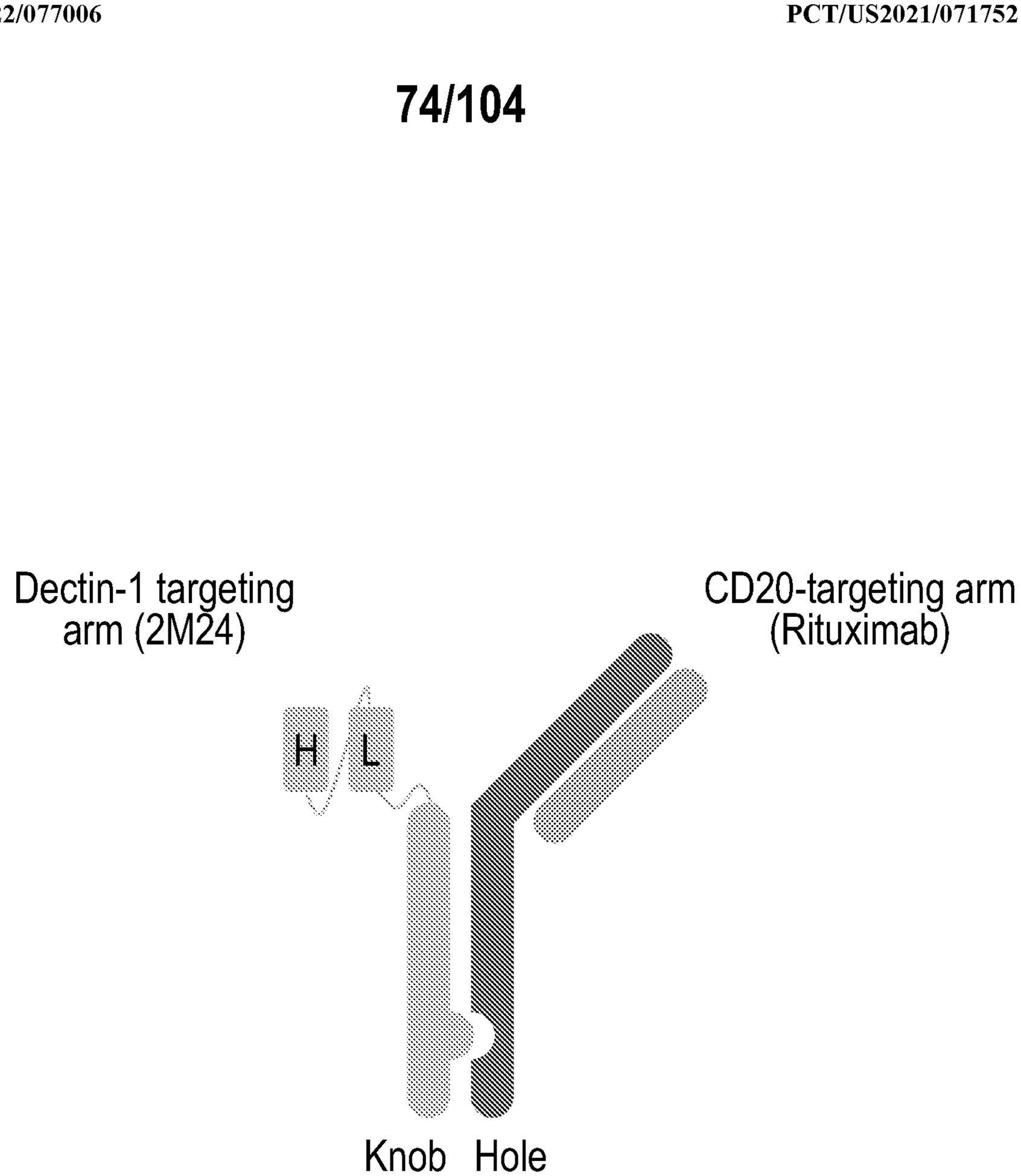

Dectin-1 targeting arm (2M24)
CD20-targeting arm (Rituximab)
H
L
Knob
Hole
hIgG1

FIG. 51

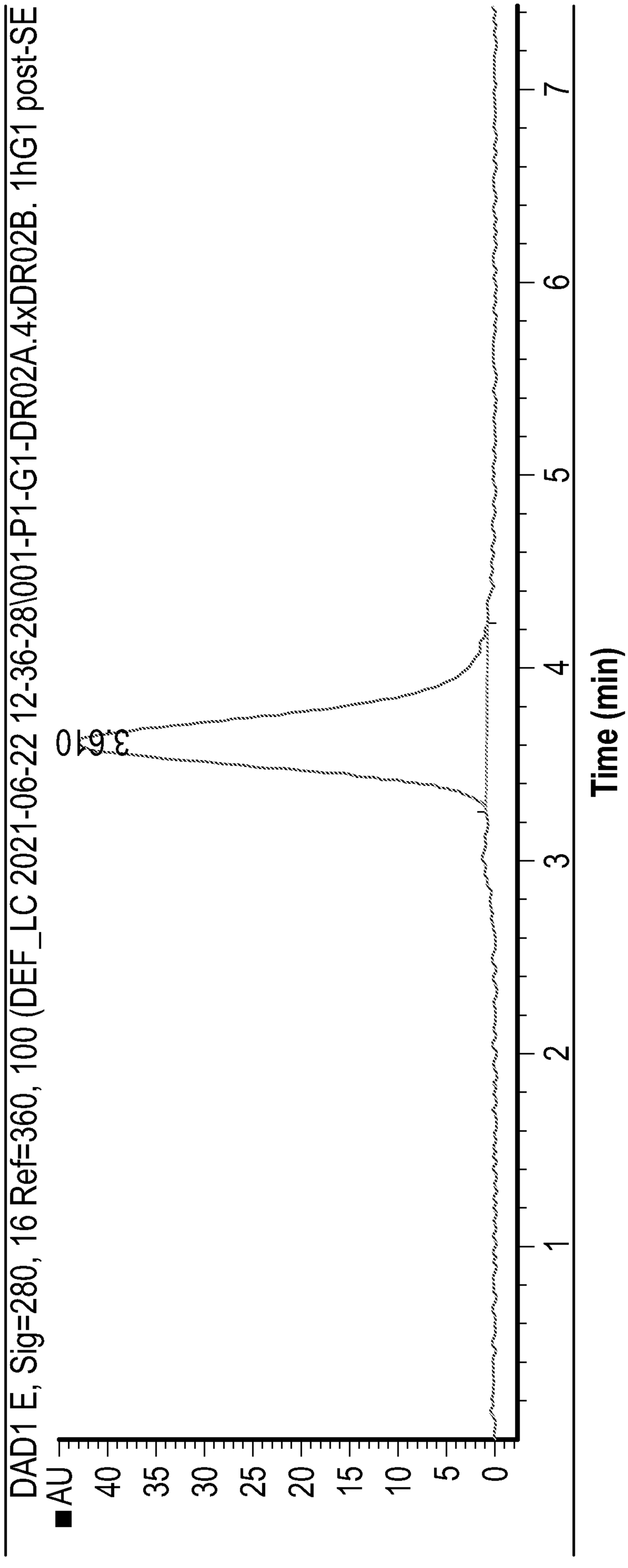

DAD1 E, Sig=280, 16 Ref=360, 100 (DEF_LC 2021-06-22 12-36-28\001-P1-G1-DR02A.4xDR02B. 1hG1 post-SE
mAU
40
35
30
25
20
15
10
5
0
3.610
1
2
3
4
5
6
7
Time (min)

FIG. 52A

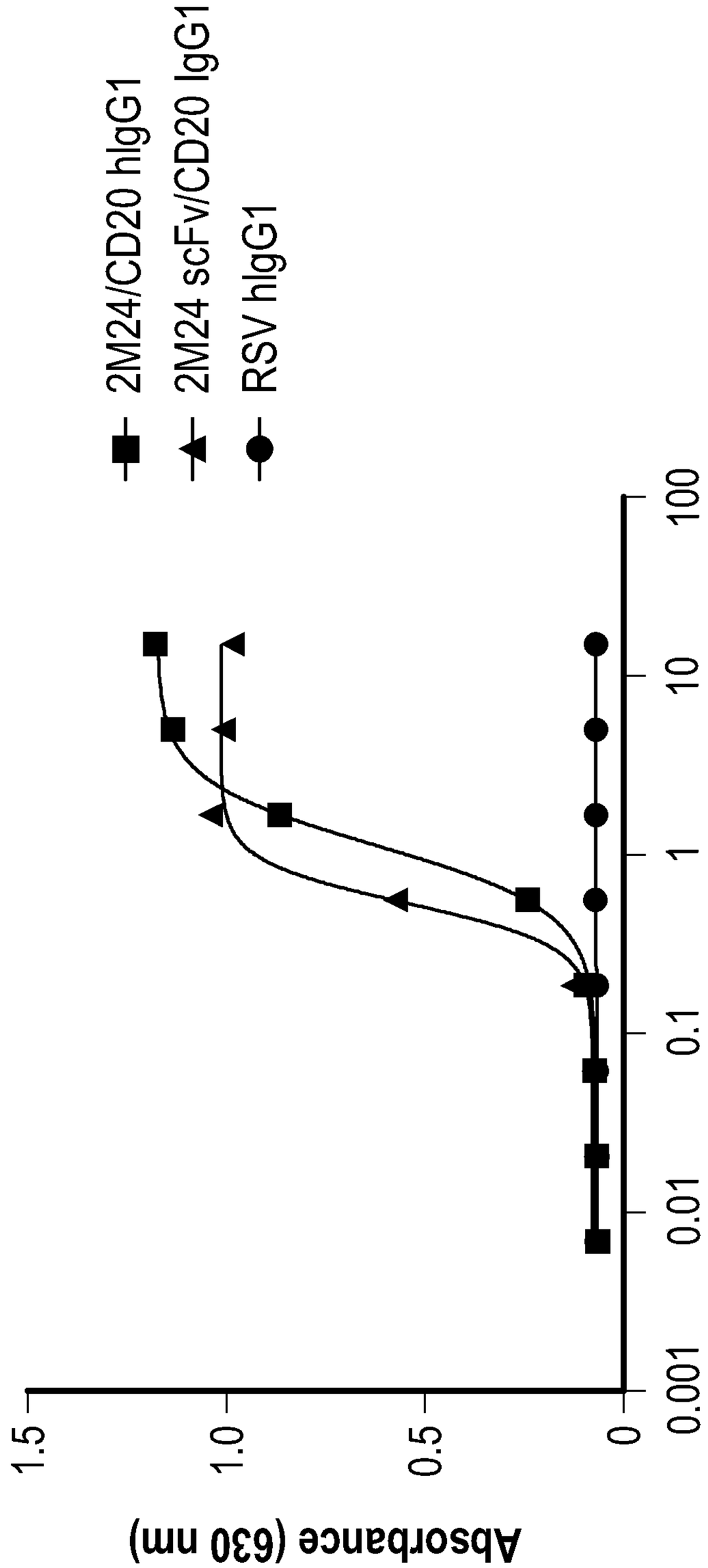

2M24/CD20 hIgG1
2M24 scFv/CD20
RSV hIgG1
100
10
1
0.1
0.01
0.001
Antibody (ug/mL)
1.5
1.0
0.5
0
Absorbance (630 nm)

FIG. 52B

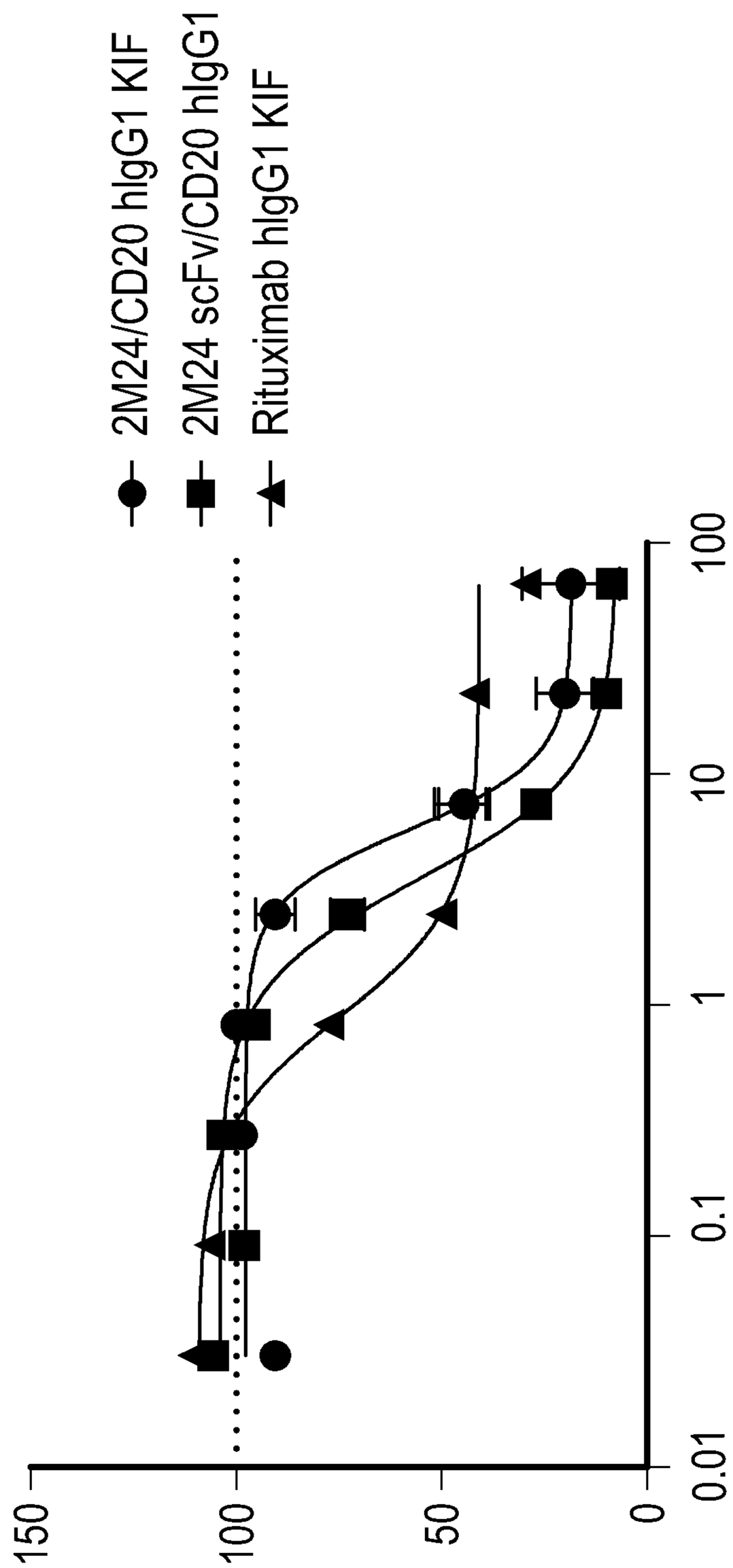

2M24/CD20 hIgG1 KIF
2M24 scFv/CD20 hIgG1 KIF
Rituximab hIgG1
100
10
1
0.1
0.01
Antibody (nM)
150
100
50
0
B cells (% of control)

FIG. 52C

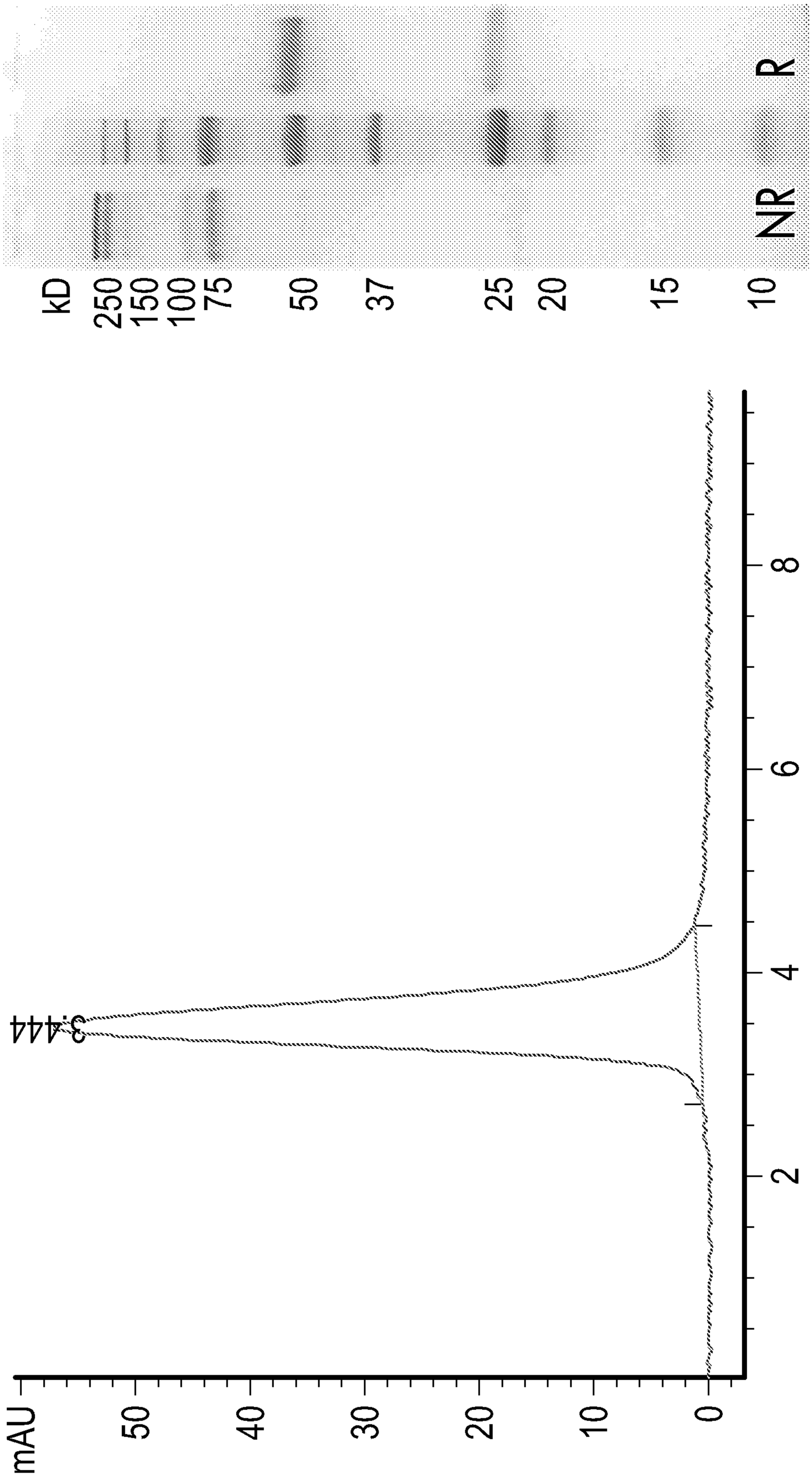

R
NR
kD
250
150
100
75
50
37
25
20
15
10
8
6
4
2
3.444
mAU
50
40
30
20
10
0

FIG. 53A

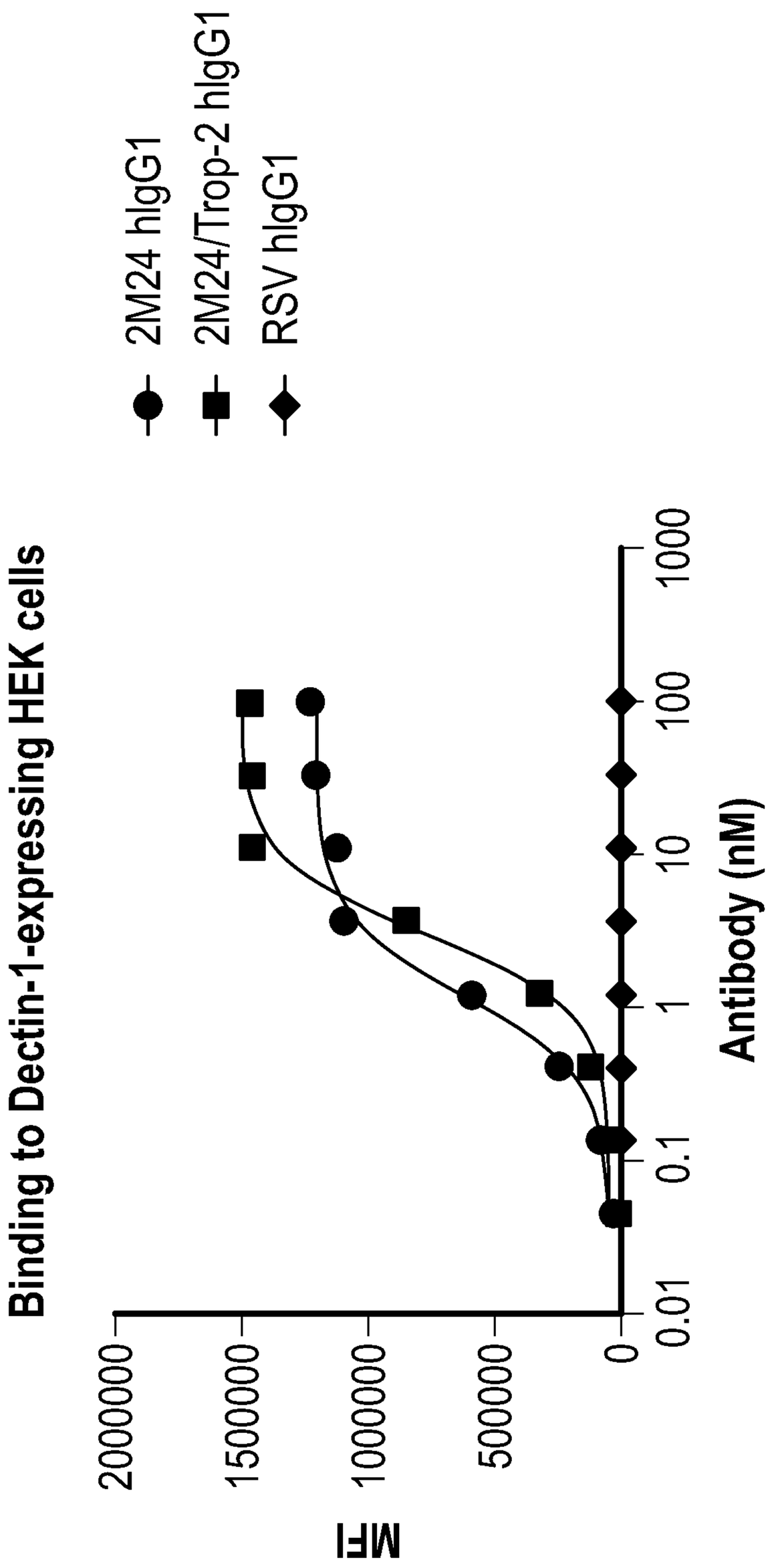

Binding to Dectin-1-expressing HEK cells
MFI
200000
150000
100000
50000
0
0
0
0
0
0.01
0.1
1
10
100
1000
Antibody (nM)
2M24 hIgG1
2M24/Trop-2
RSV hIgG1

FIG. 53B

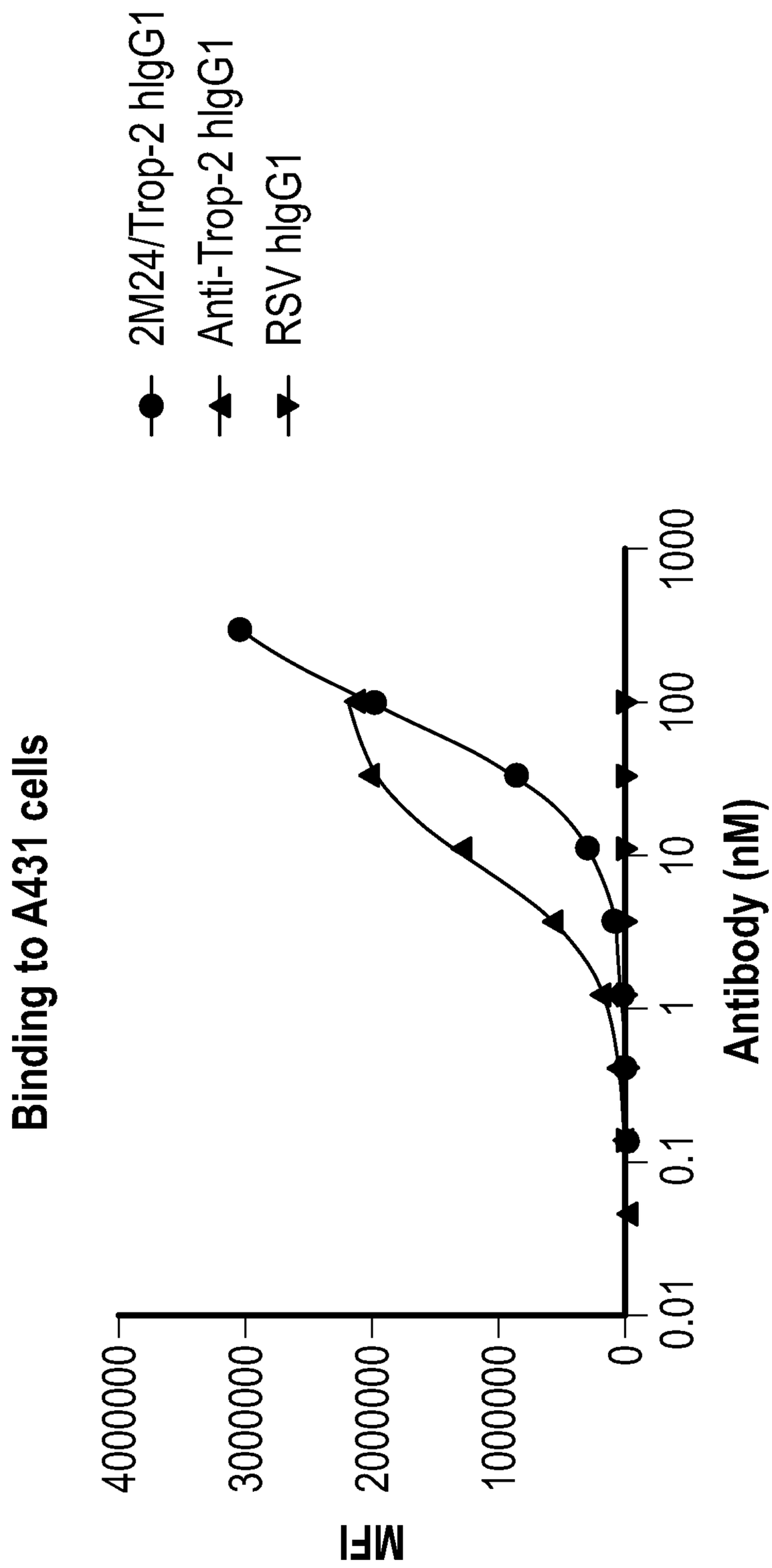

2M24/Trop-2 hIgG1
Anti-Trop-2 hIgG1
RSV hIgG1
MFI
400000
300000
200000
100000
0
0
0
0
0
Binding to A431 cells
0.01
0.1
1
10
100
1000
Antibody (nM)

FIG. 53C

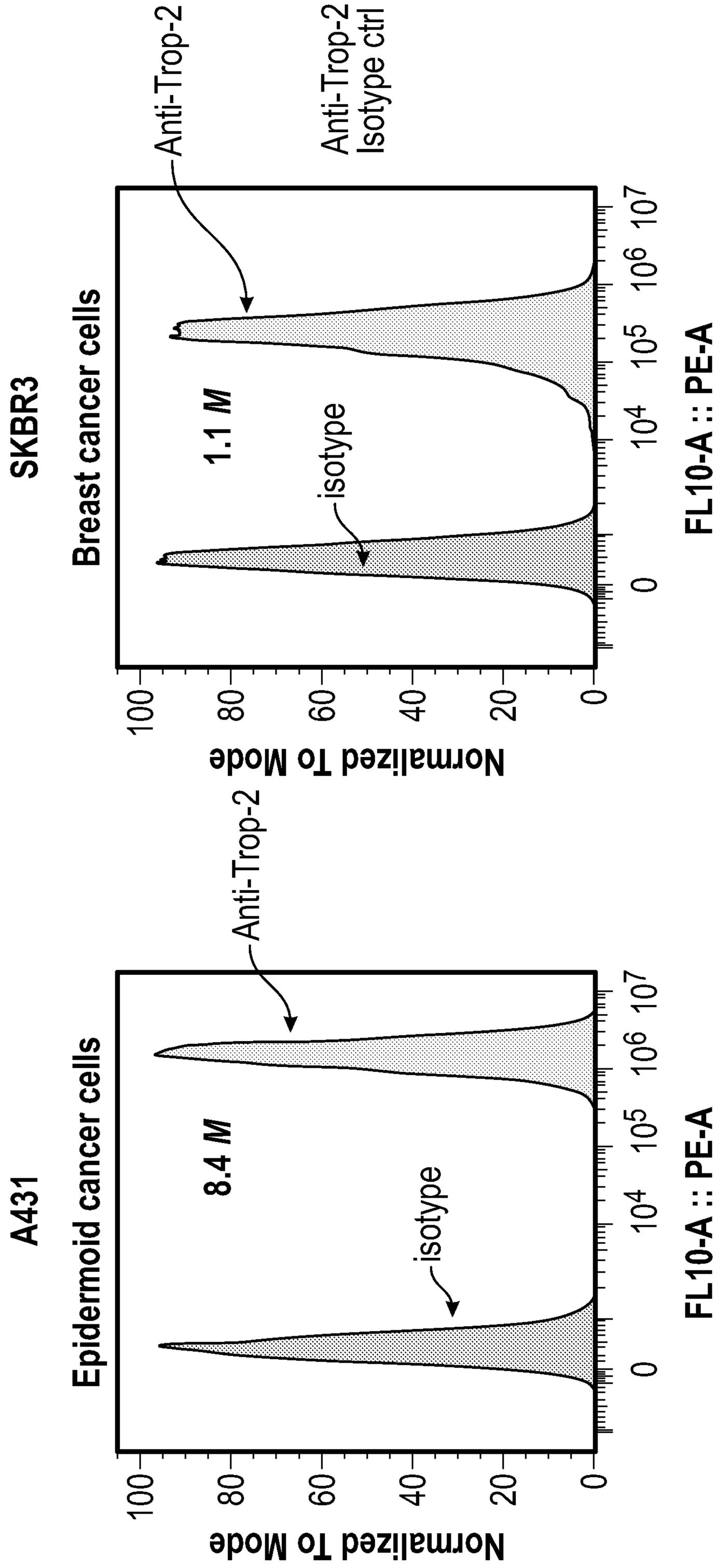

Anti-Trop-2
Anti-Trop-2
Isotype ctrl
SKBR3
Breast cancer cells
1.1 M
isotype
Normalized To Mode
FL10-A :: PE-A
A431
Epidermoid cancer cells
8.4 M
Anti-Trop-2
isotype
Normalized To Mode
FL10-A :: PE-A

FIG. 54

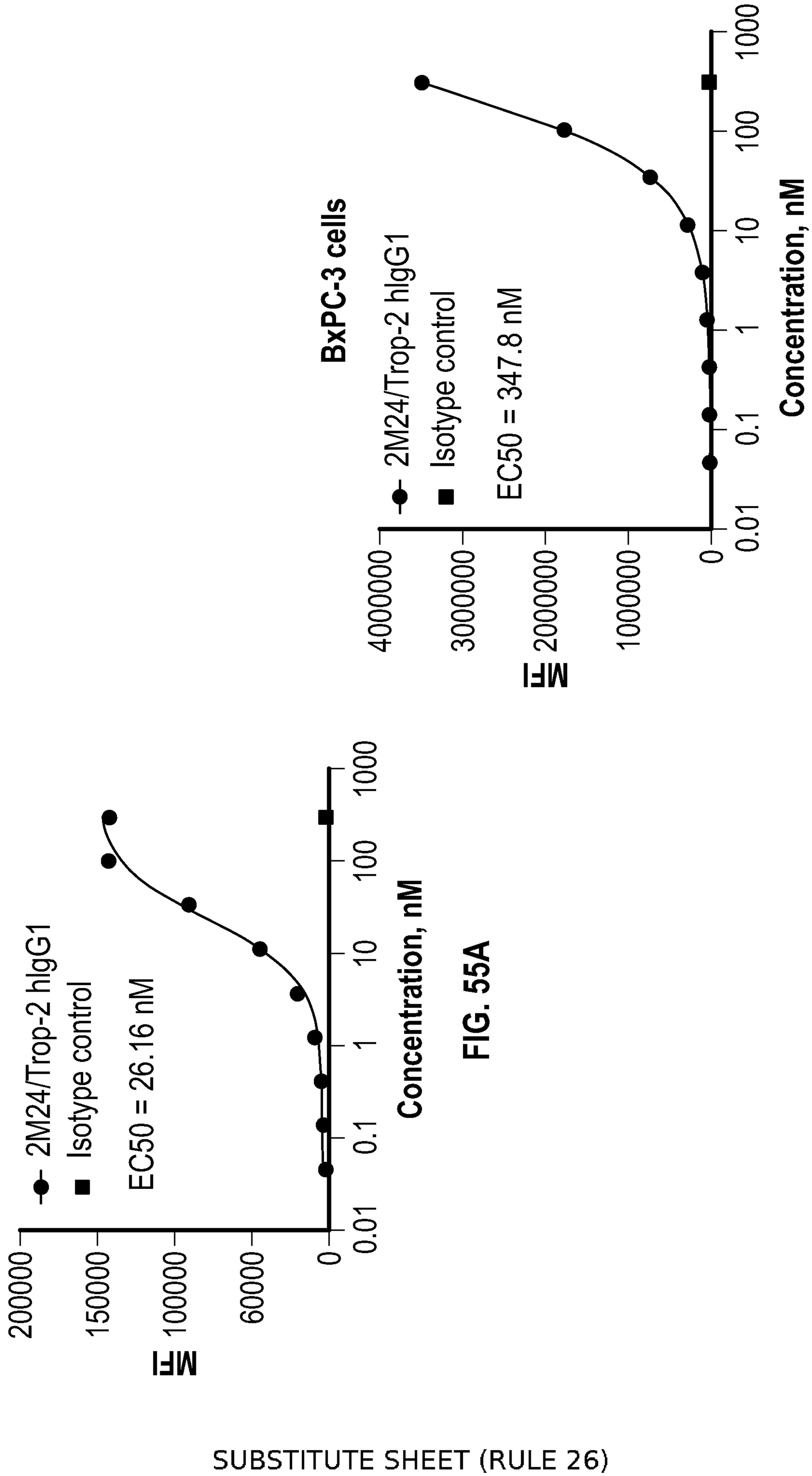


FIG. 55B

FIG. 55A

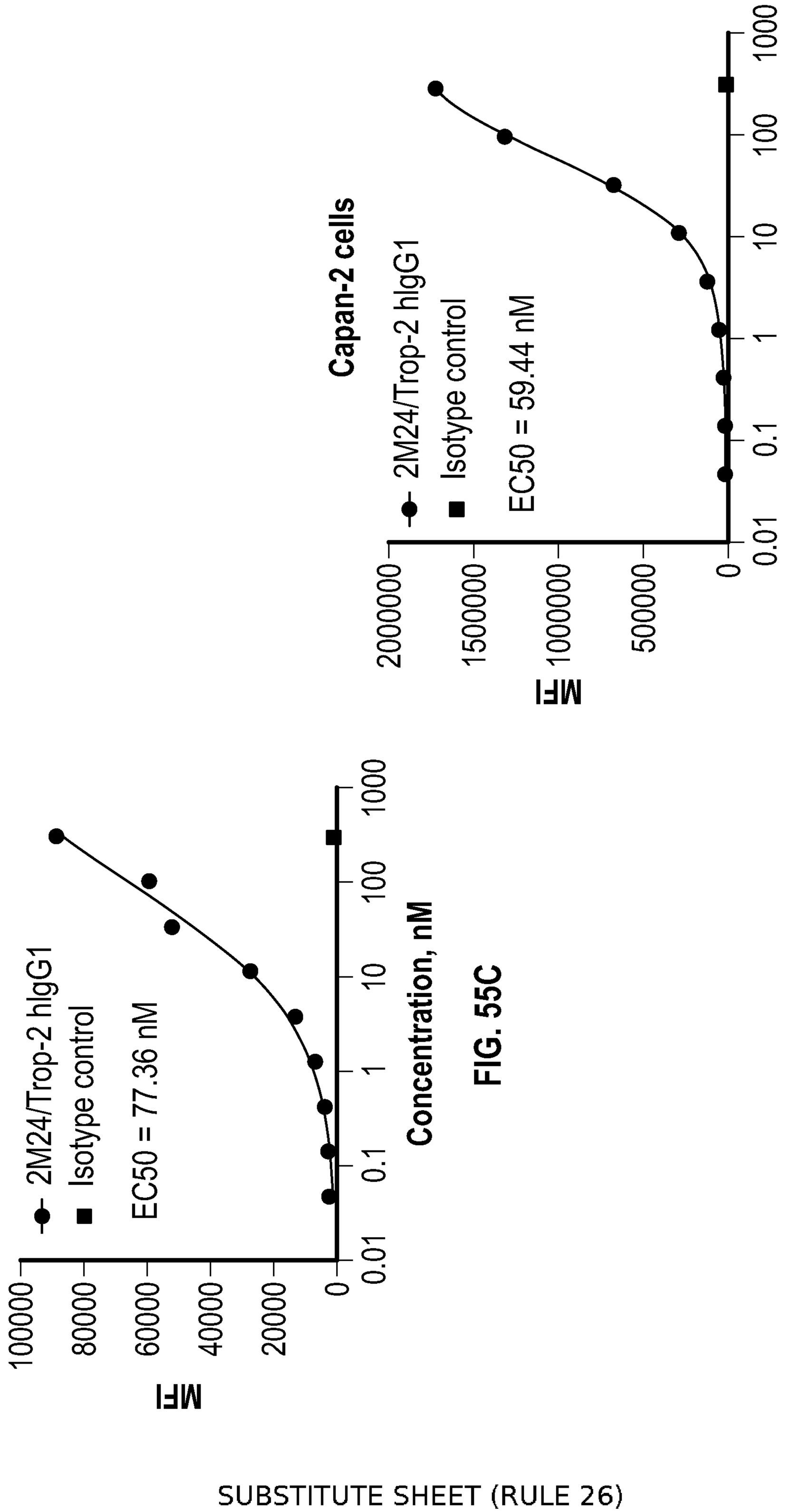


FIG. 55D

FIG. 55C

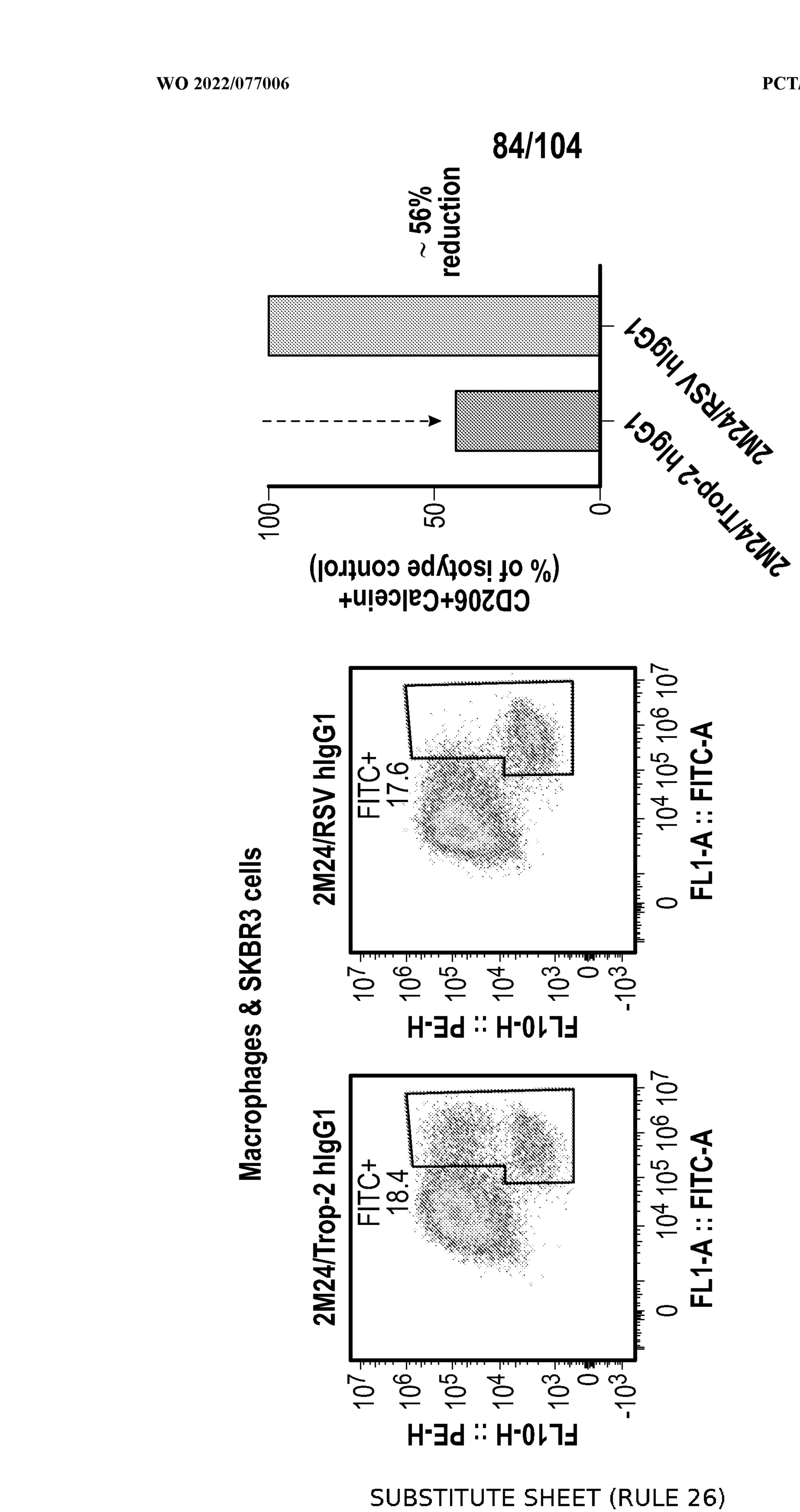
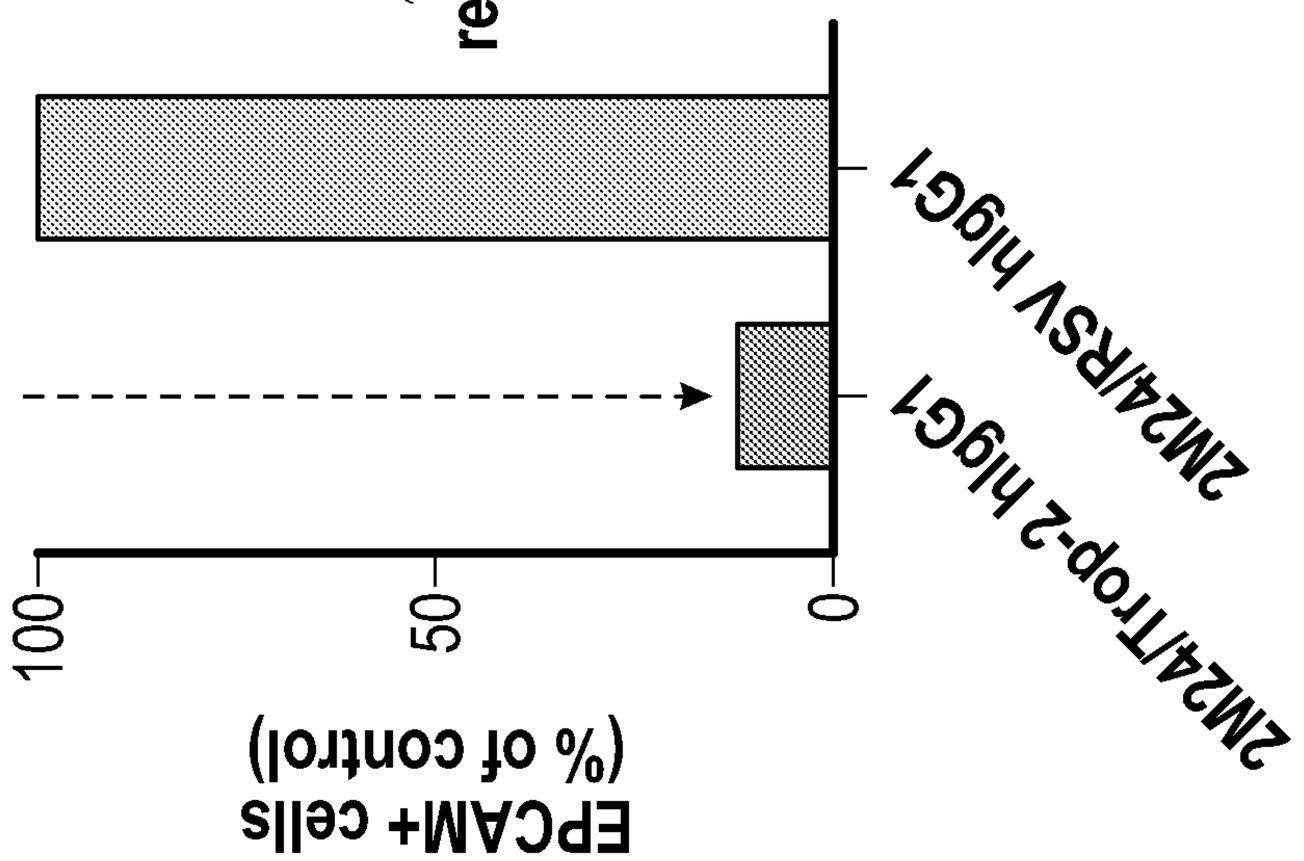

~ 56% reduction
2M24/Trop-2 hIgG1
2M24/RSV hIgG1
100
50
0
CD206+Calcein+
(% of isotype control)
Macrophages & SKBR3 cells
2M24/RSV hIgG1
FITC+
17.6
2M24/Trop-2 hIgG1
FITC+
18.4
FL10-H :: PE-H
FL1-A :: FITC-A
-10^3
0
10^3
10^4
10^5
10^6
10^7

FIG. 56A


~ 87% reduction
2M24/RSV hIgG1
2M24/Trop-2 hIgG1
EPCAM+ cells (% of control)
100
50
0

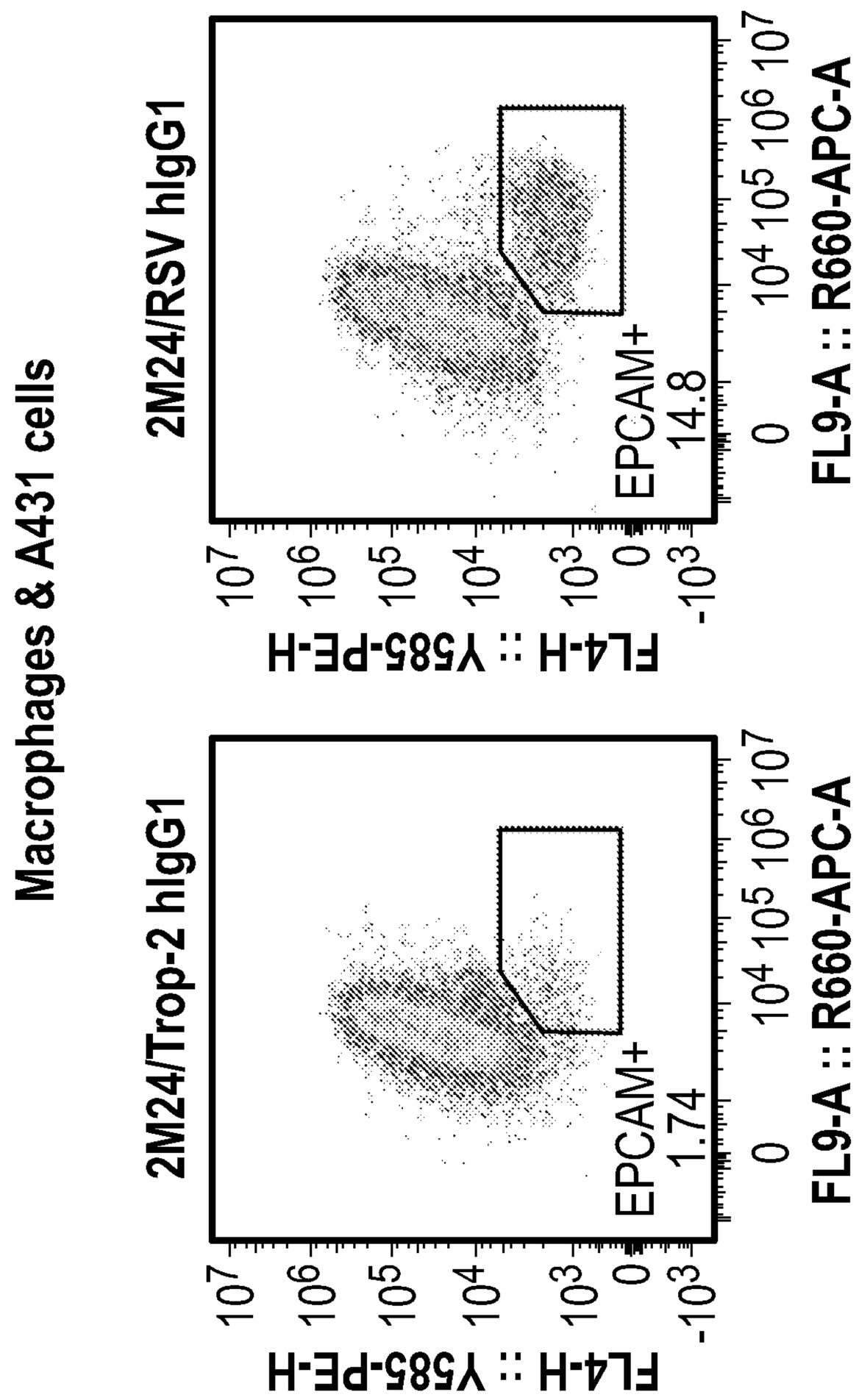

Macrophages & A431 cells
2M24/Trop-2 hIgG1
2M24/RSV hIgG1
FL4-H :: Y585-PE-H
FL9-A :: R660-APC-A
EPCAM+ 1.74
EPCAM+ 14.8

FIG. 56B

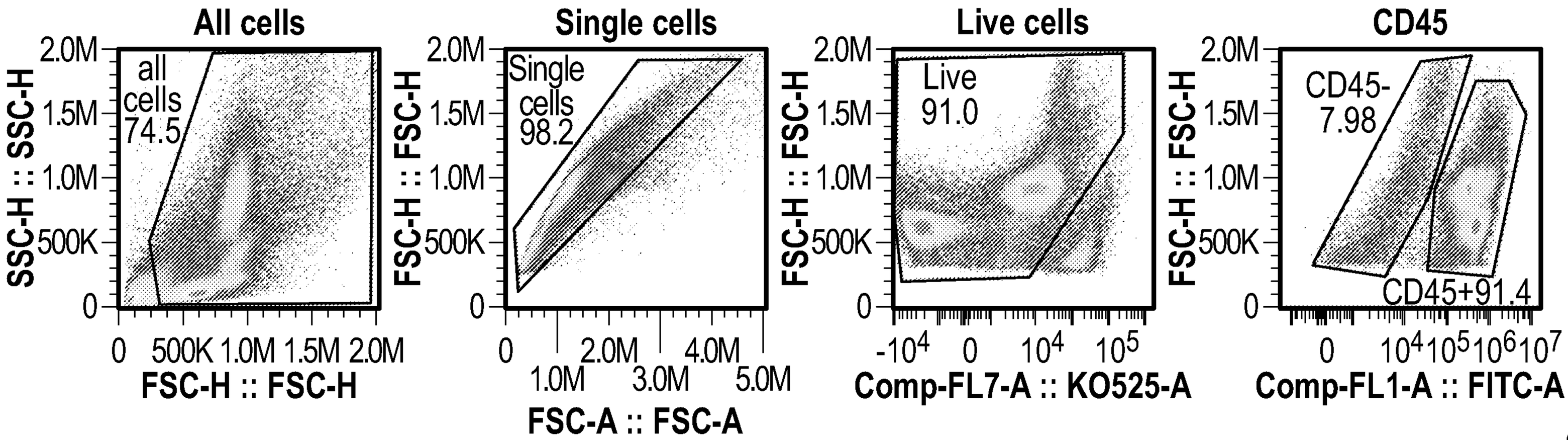

All cells
all cells 74.5
SSC-H :: SSC-H
FSC-H :: FSC-H
Single cells
Single cells 98.2
FSC-H :: FSC-H
FSC-A :: FSC-A
Live cells
Live 91.0
FSC-H :: FSC-H
Comp-FL7-A :: KO525-A
CD45
CD45- 7.98
CD45+91.4
FSC-H :: FSC-H
Comp-FL1-A :: FITC-A
CD45- or CD45+
CD45- 7.98
CD45+91.4
FSC-H :: FSC-H
Comp-FL1-A :: FITC-A
CD45- Trop-2+ /EPCAM+
Trop-2+ /EPCAM+ 67.5
Comp-FL10-A :: PE-A
Comp-FL3-A :: APC-A
CD45+ CD11b+
CD11b+ 87.5
Comp-FL8-H :: Violet 610-H
Comp-FL2-A :: PerCP-A
CD45+ CD11b+CD163+
CD163+ 14.3
Comp-FL8-H :: Violet 610-H
Comp-FL13-A :: PC7-A

FIG. 57A

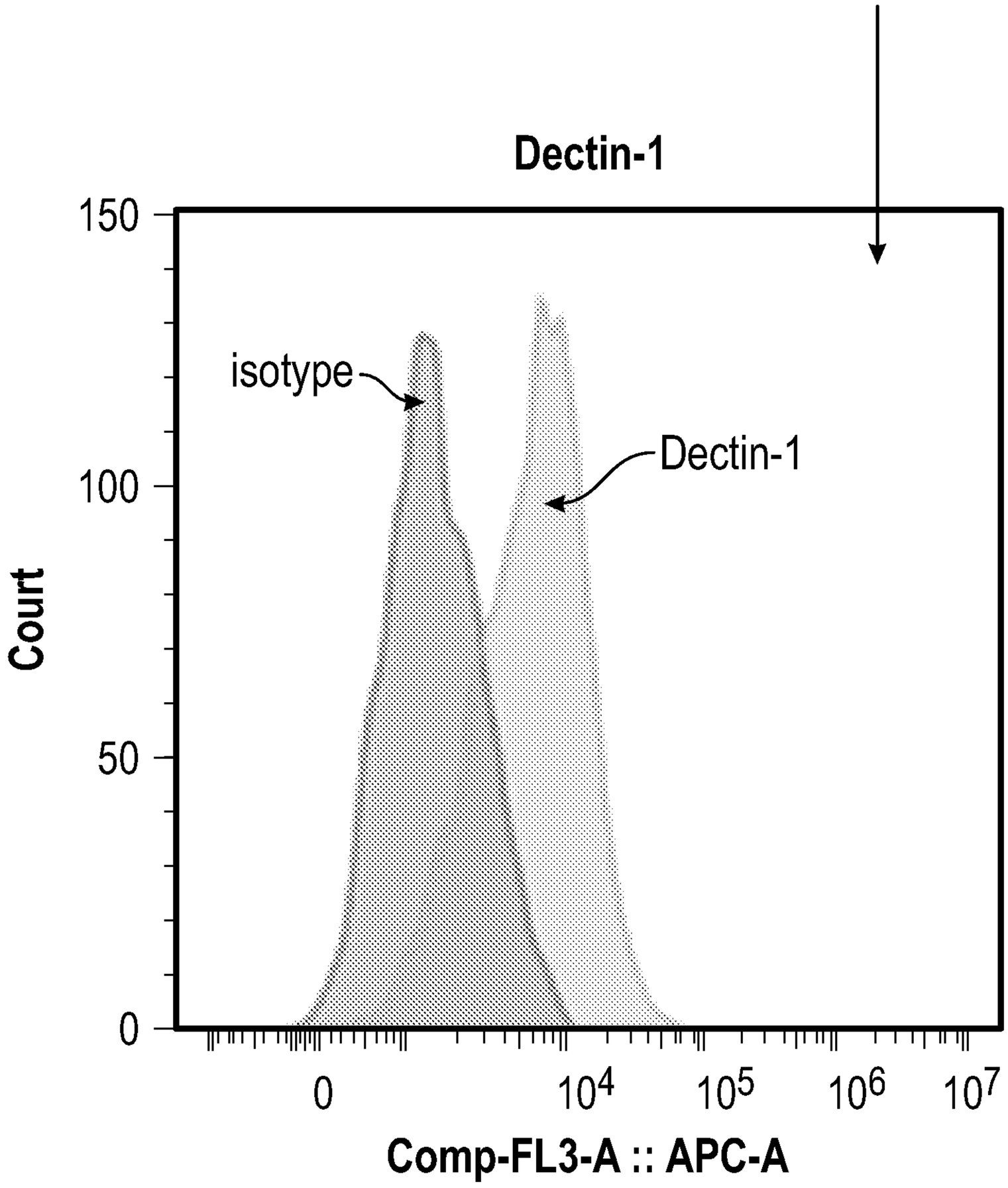

Dectin-1
150
100
50
0
Count
isotype
Dectin-1
0
10^4
10^5
10^6
10^7
Comp-FL3-A :: APC-A

FIG. 57B

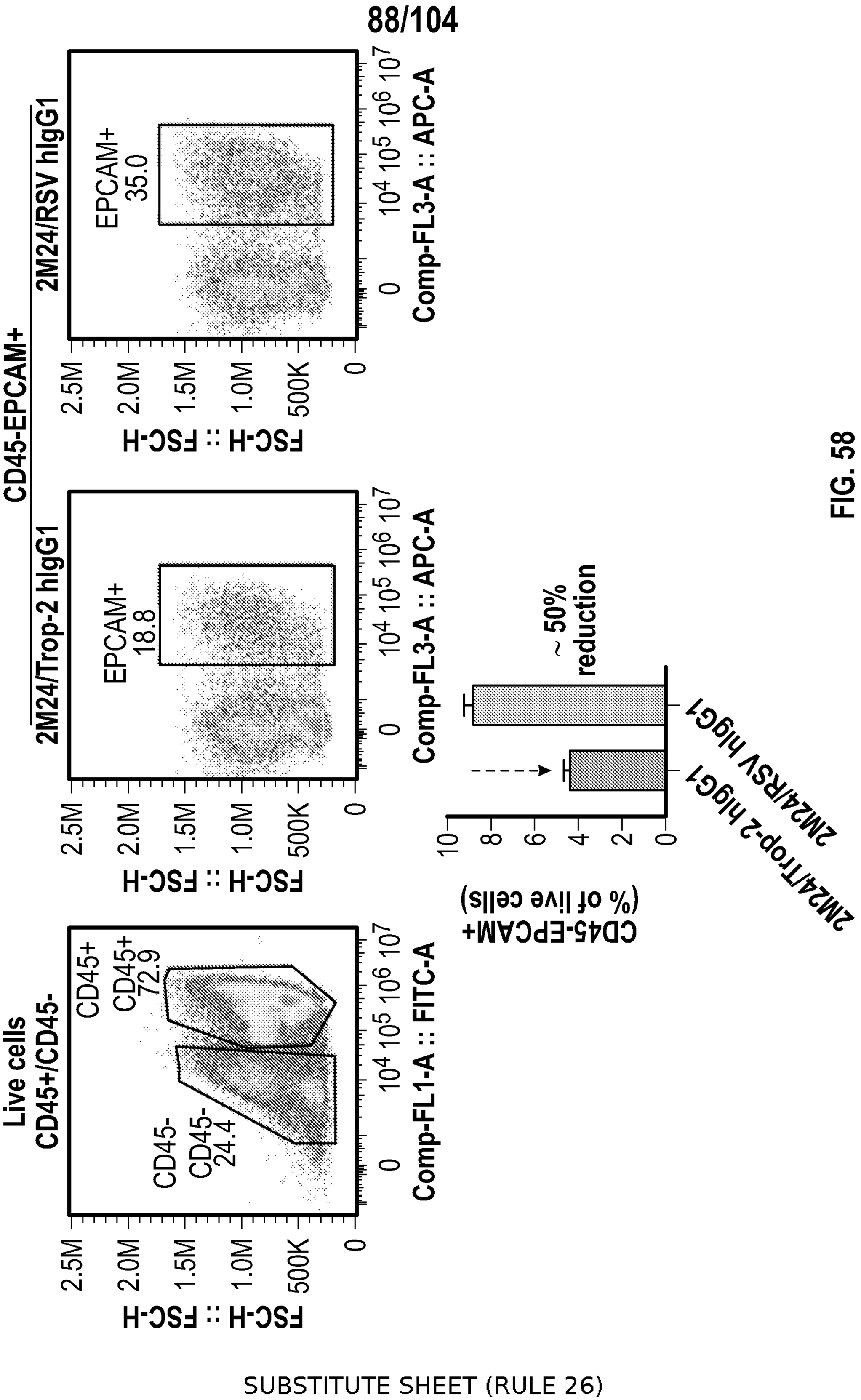

CD45-EPCAM+
2M24/Trop-2 hIgG1
EPCAM+
35.0
FSC-H :: FSC-H
2.5M
2.0M
1.5M
1.0M
500K
0
10^4 10^5 10^6 10^7
Comp-FL3-A :: APC-A
2M24/Trop-2 hIgG1
EPCAM+
18.8
FSC-H :: FSC-H
Live cells
CD45+/CD45-
CD45+
72.9
CD45-
24.4
Comp-FL1-A :: FITC-A
CD45-EPCAM+
(% of live cells)
~ 50%
reduction
2M24/Trop-2 hIgG1
2M24/RSV hIgG1

FIG. 58

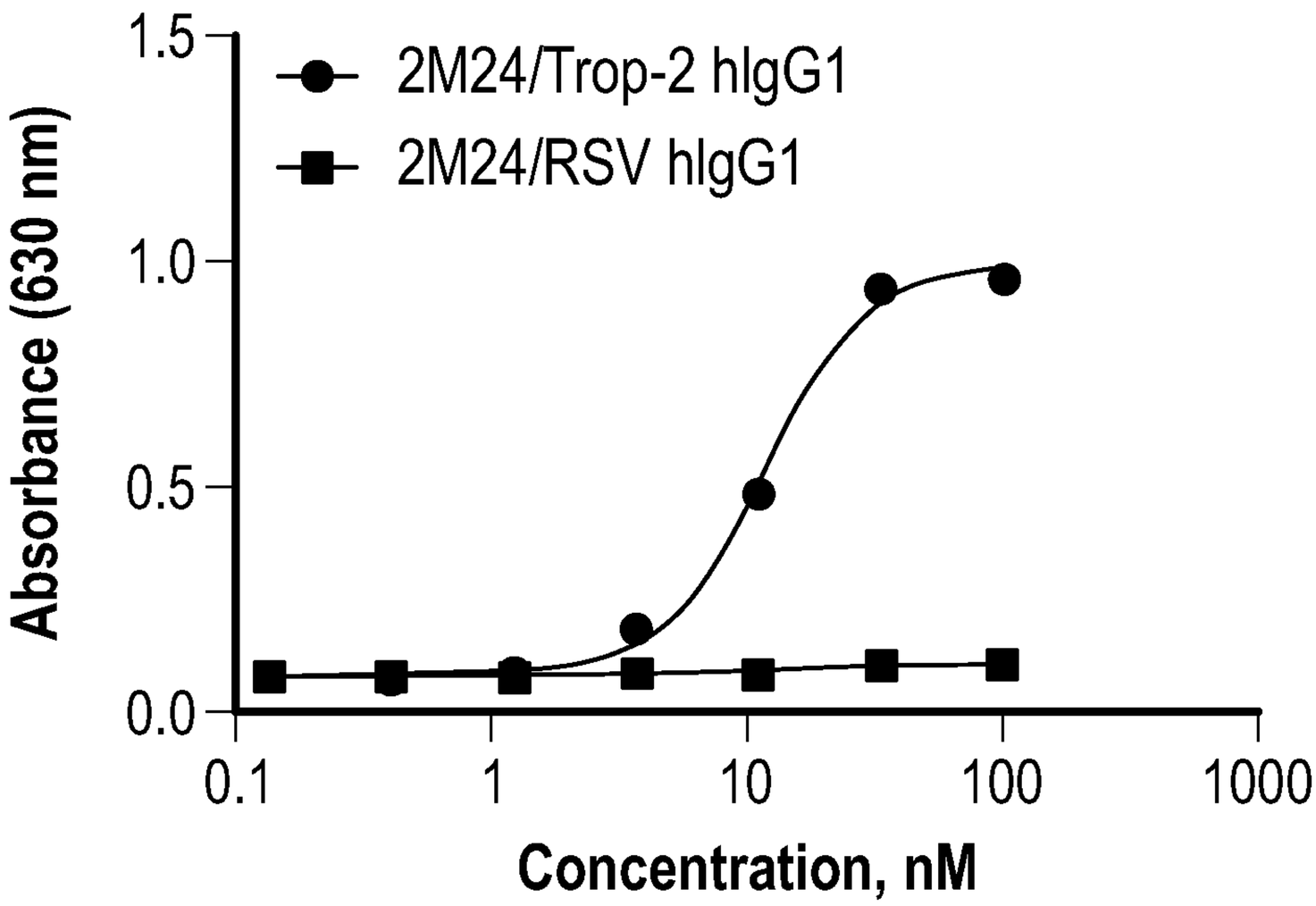

1.5
1.0
0.5
0.0
Absorbance (630 nm)
2M24/Trop-2 hIgG1
2M24/RSV hIgG1
0.1
1
10
100
1000
Concentration, nM

FIG. 59A

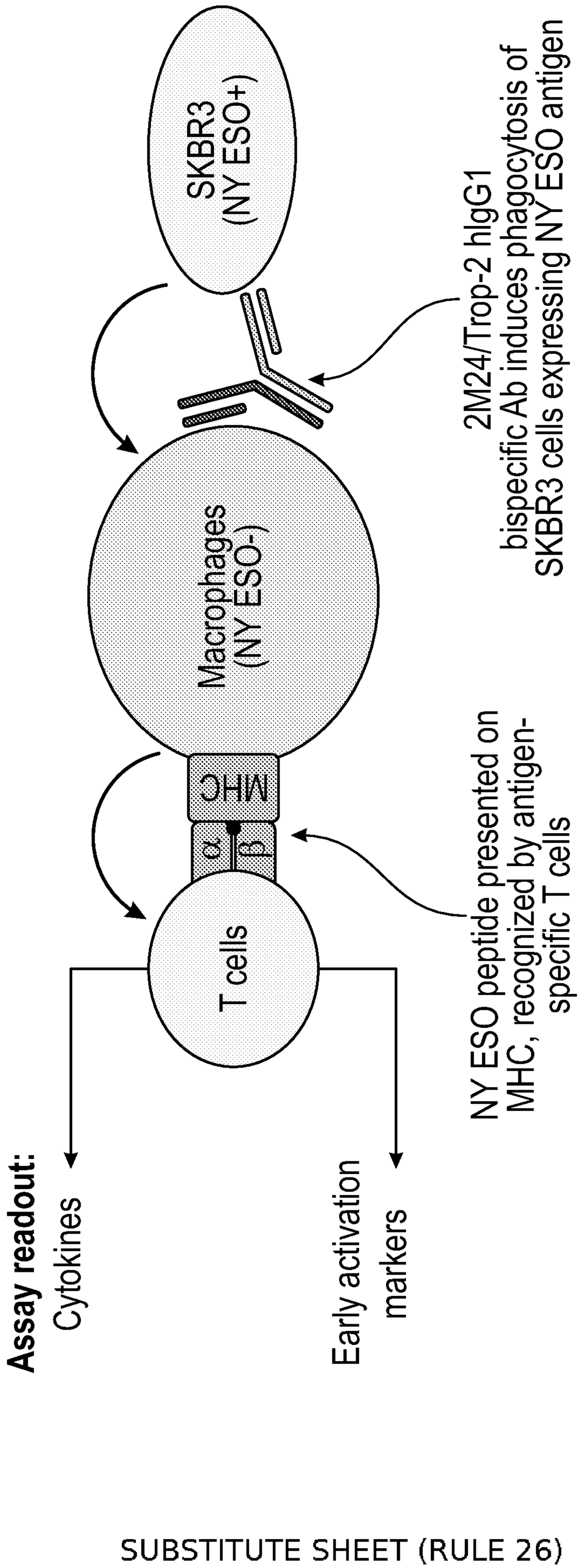

SKBR3
(NY ESO+)
2M24/Trop-2 hIgG1
bispecific Ab induces phagocytosis of
SKBR3 cells expressing NY ESO antigen
Macrophages
(NY ESO-)
MHC
α
β
T cells
NY ESO peptide presented on
MHC, recognized by antigen-
specific T cells
Assay readout:
Cytokines
Early activation
markers

FIG. 59B

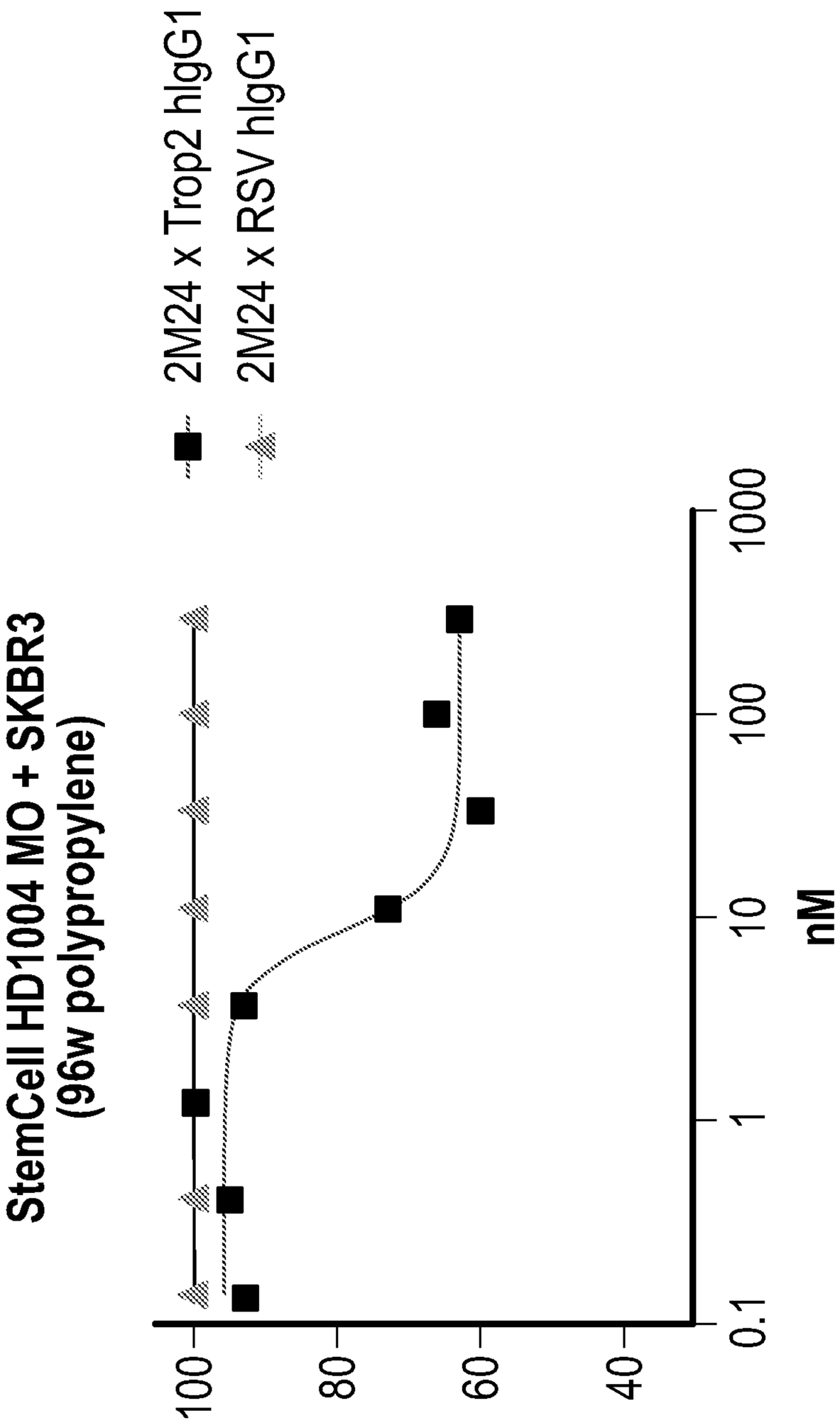

2M24 x Trop2 hIgG1
2M24 x RSV hIgG1
StemCell HD1004 MO + SKBR3
(96w polypropylene)
% SKBR3 cells remainning
over isotype
100
80
60
40
0.1
1
10
100
1000
nM

FIG. 59C

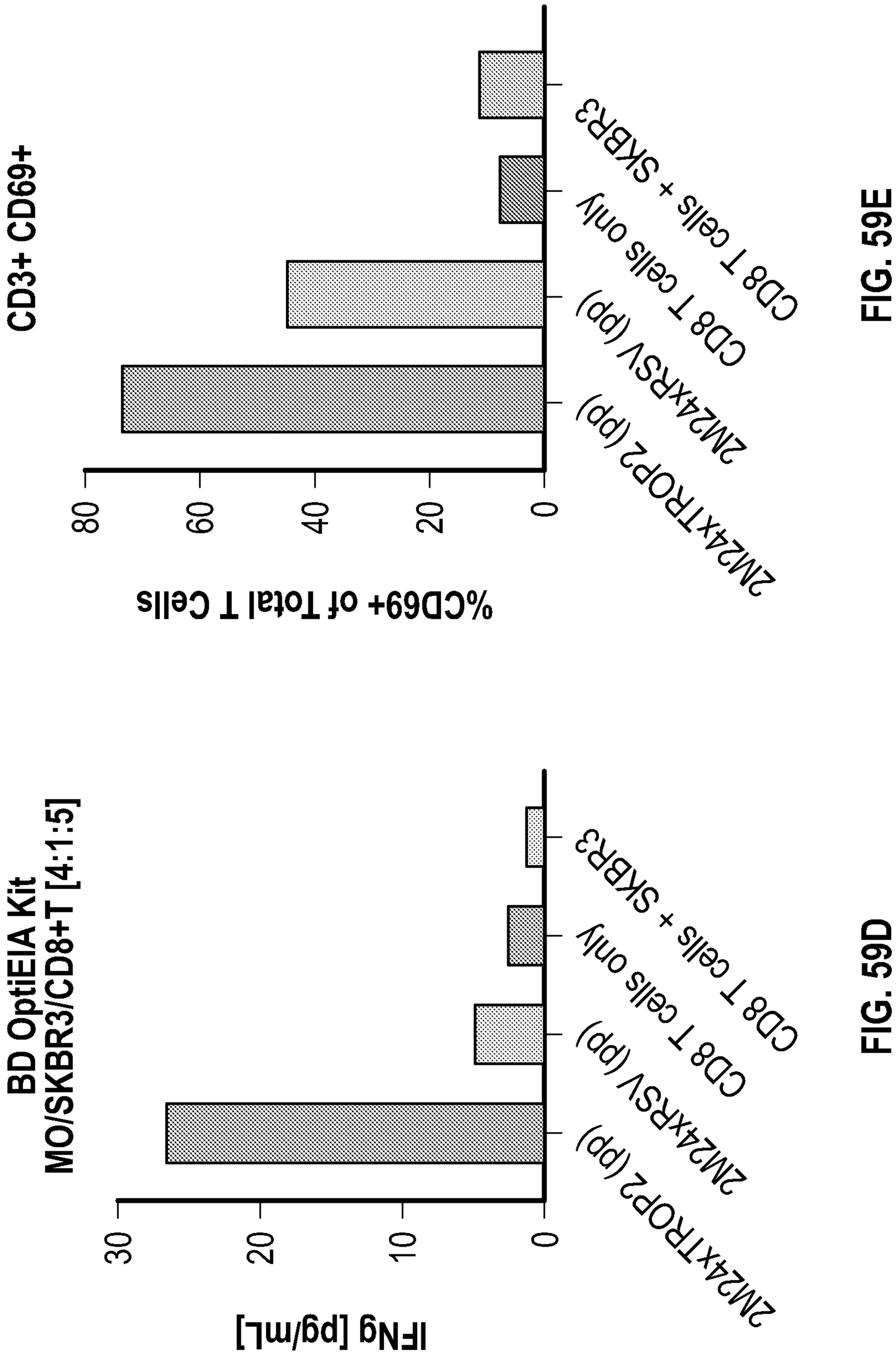


FIG. 59E

FIG. 59D

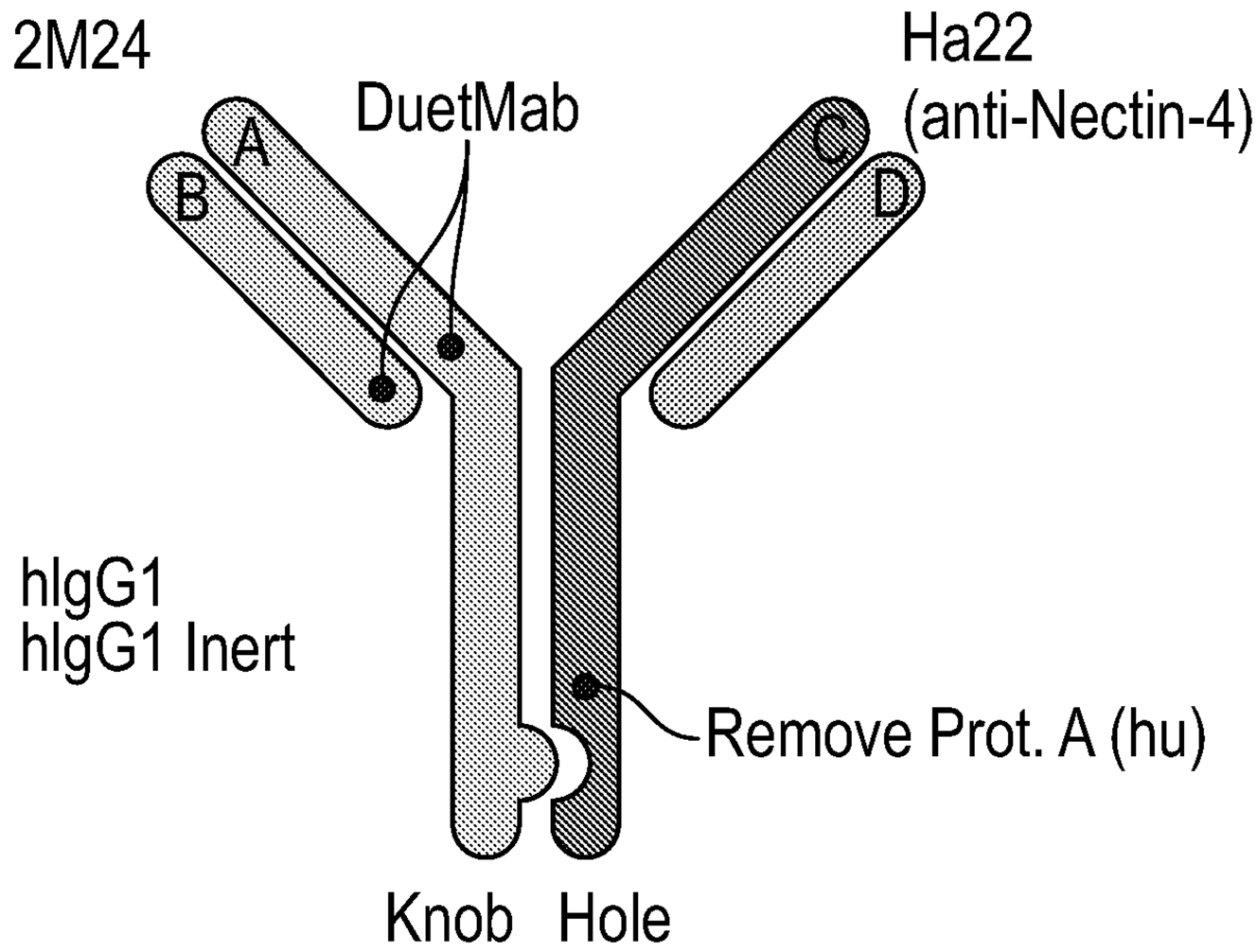

2M24
DuetMab
A
B
Ha22
(anti-Nectin-4)
C
D
hIgG1
hIgG1 Inert
Remove Prot. A (hu)
Knob
Hole

FIG. 60A

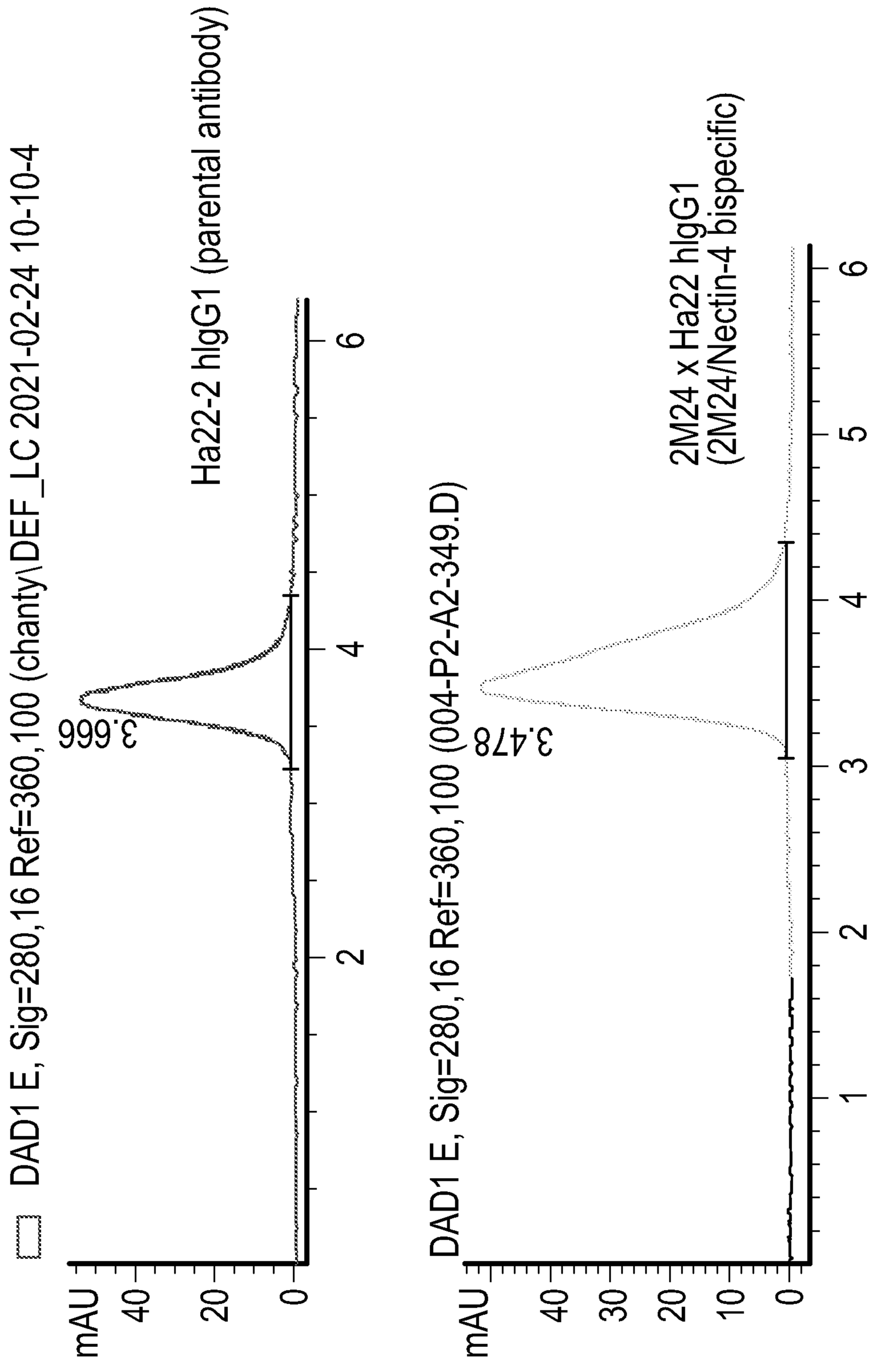

Ha22-2 hIgG1 (parental antibody)
DAD1 E, Sig=280,16 Ref=360,100 (chanty\DEF_LC 2021-02-24 10-10-49.D)
3.666
mAU
40
20
0
2
4
6
2M24 x Ha22 hIgG1
(2M24/Nectin-4 bispecific)
DAD1 E, Sig=280,16 Ref=360,100 (004-P2-A2-349.D)
3.478
mAU
40
30
20
10
0
1
2
3
4
5
6

FIG. 60B

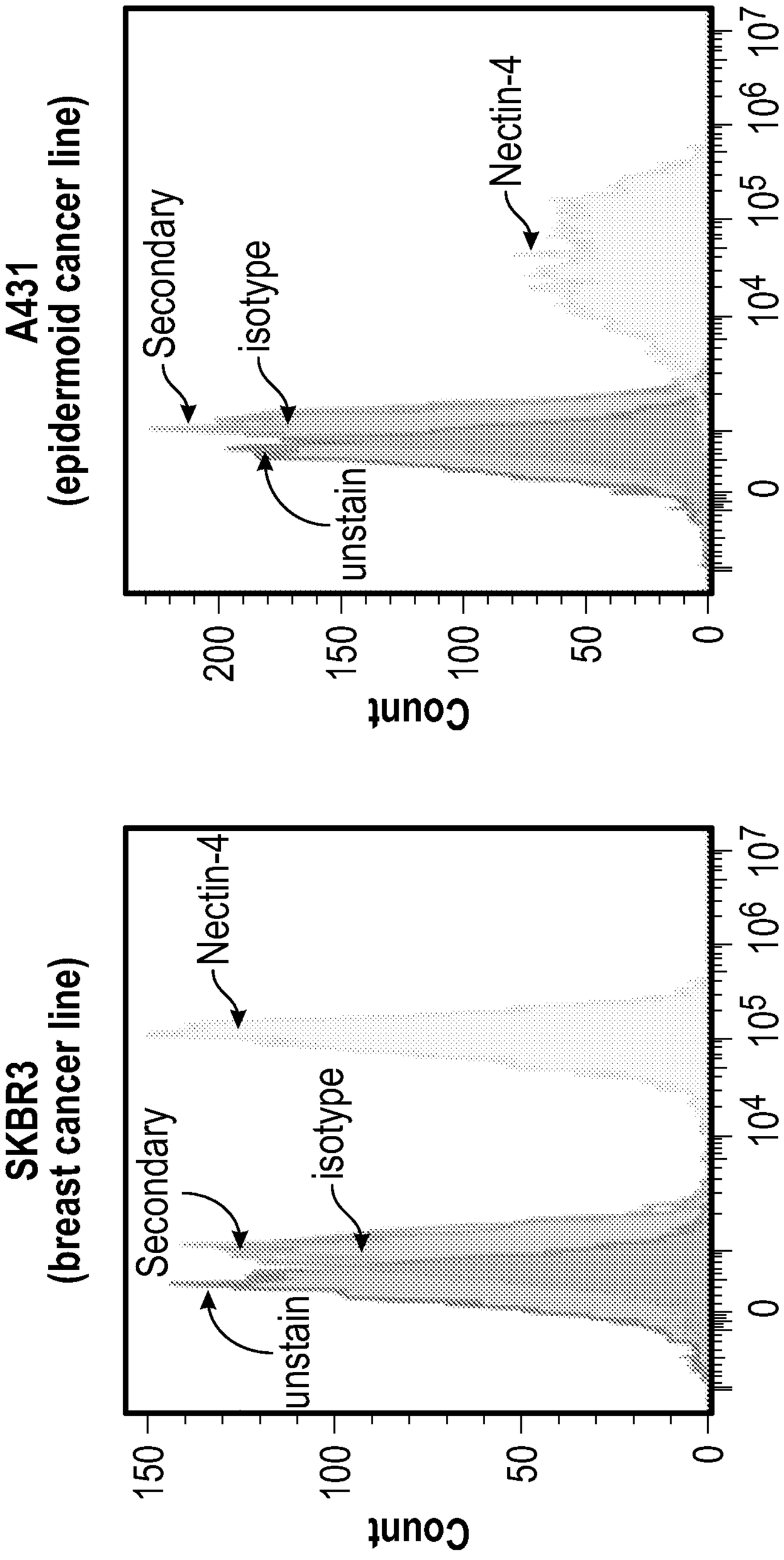

A431
(epidermoid cancer line)
Secondary
isotype
unstain
Nectin-4
Count
0
50
100
150
200
0
10^4
10^5
10^6
10^7
FL3-A :: APC-A
SKBR3
(breast cancer line)
Secondary
isotype
unstain
Nectin-4
Count
0
50
100
150
0
10^4
10^5
10^6
10^7
FL3-A :: APC-A

FIG. 61A

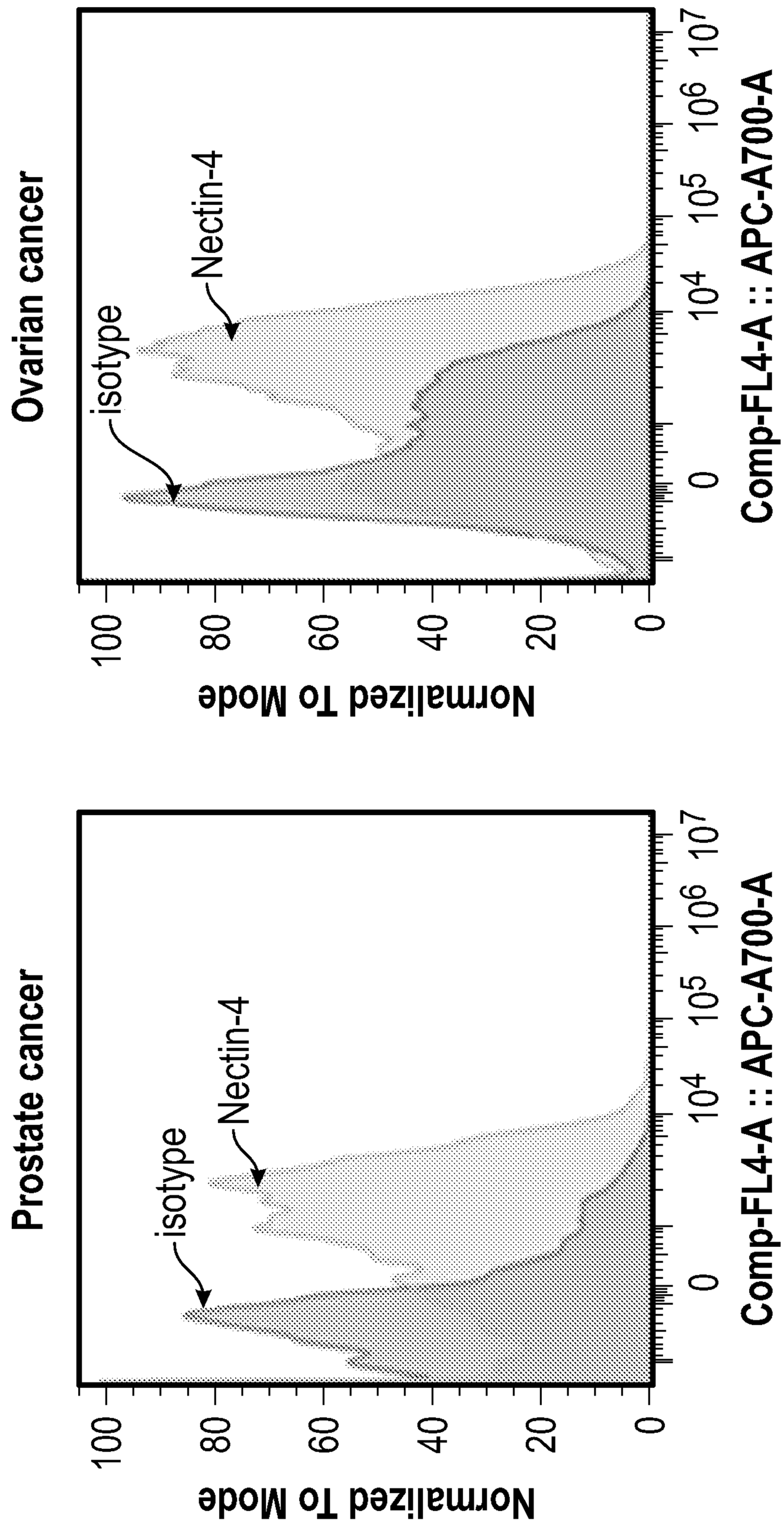
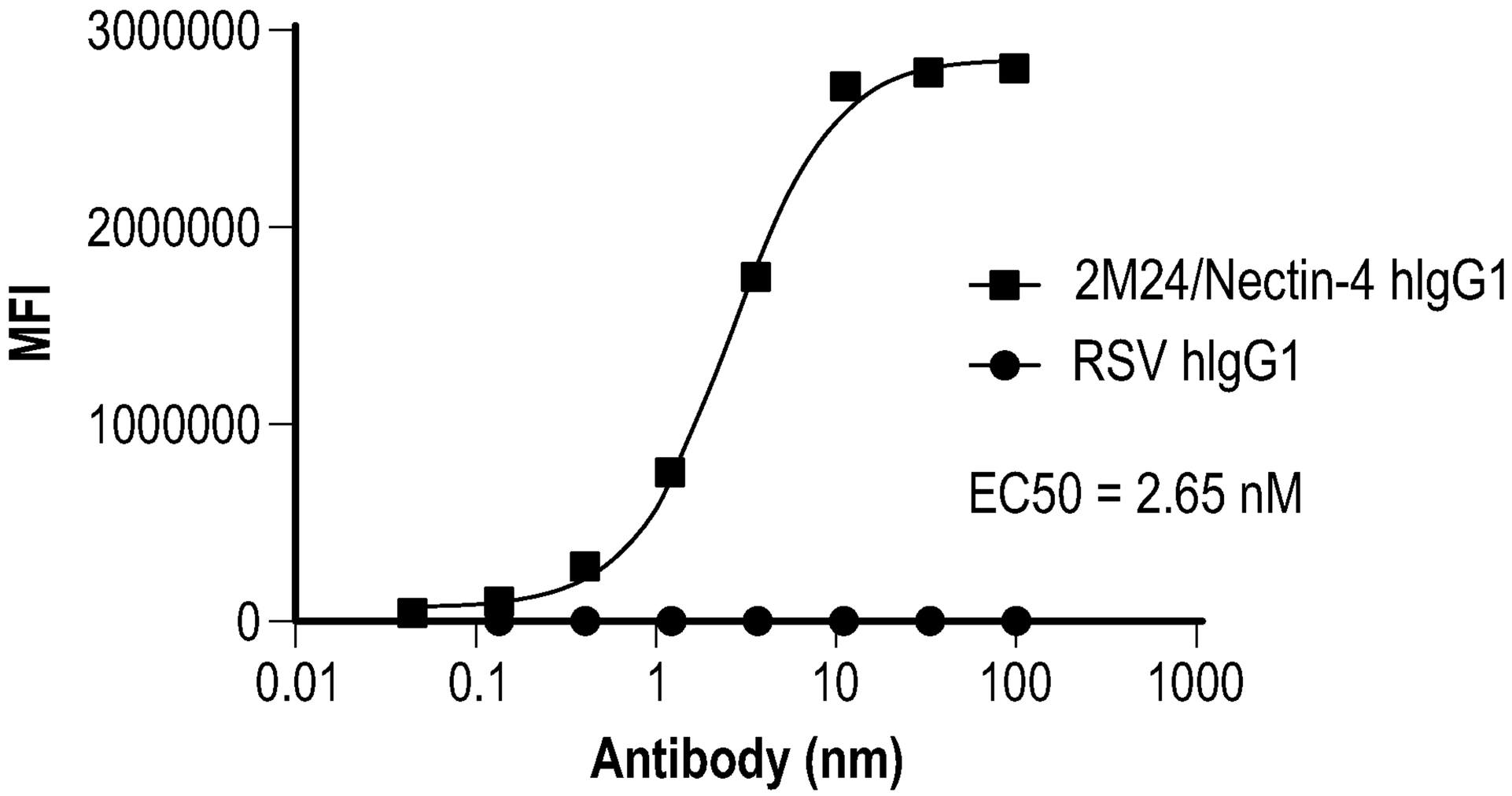

Ovarian cancer
isotype
Nectin-4
Normalized To Mode
100
80
60
40
20
0
0
10^4
10^5
10^6
10^7
Comp-FL4-A :: APC-A700-A
Prostate cancer
isotype
Nectin-4
Normalized To Mode
100
80
60
40
20
0
0
10^4
10^5
10^6
10^7
Comp-FL4-A :: APC-A700-A

FIG. 61B


3000000
2000000
1000000
0
MFI
0.01
0.1
1
10
100
1000
Antibody (nm)
2M24/Nectin-4 hIgG1
RSV hIgG1
EC50 = 2.65 nM

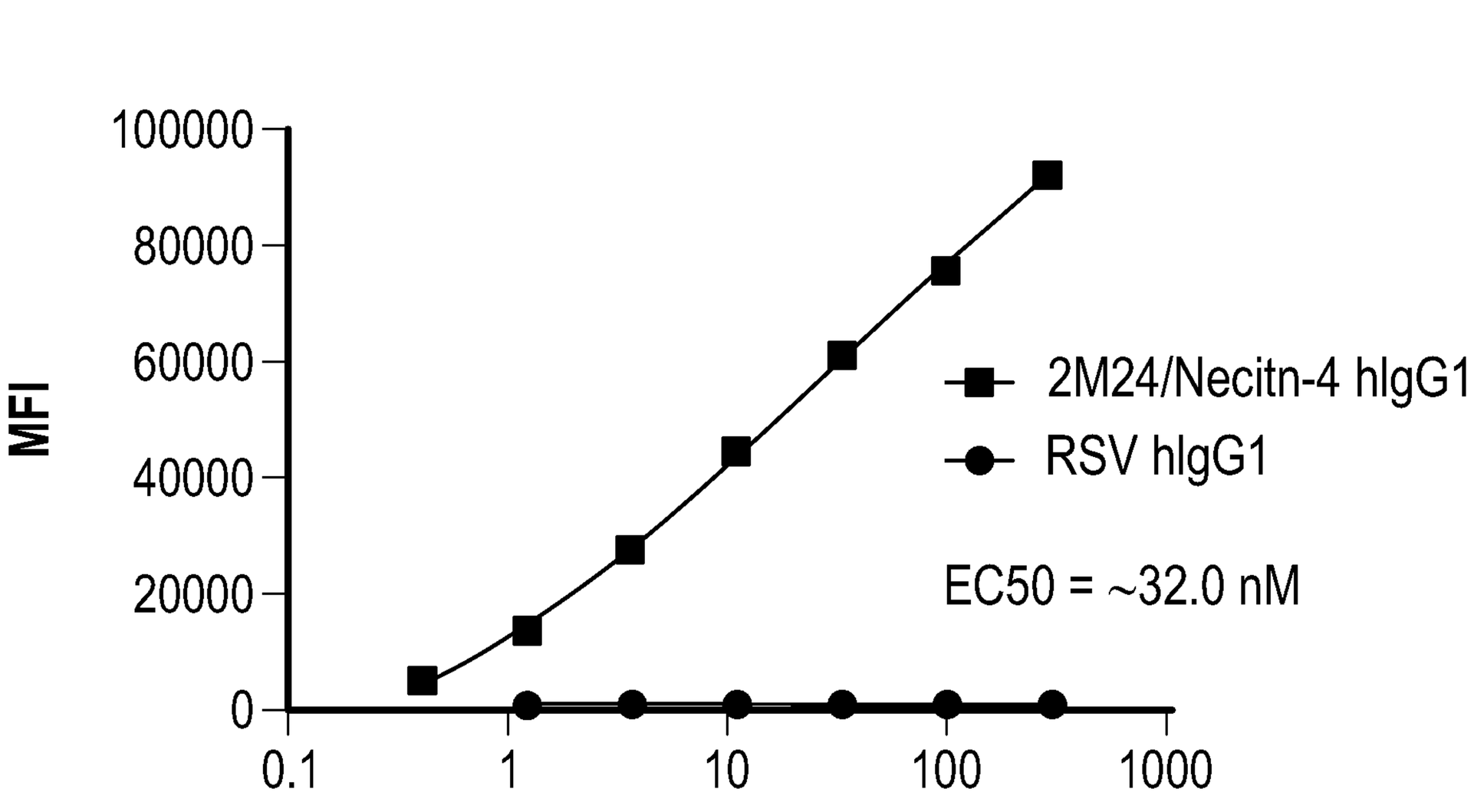

100000
80000
60000
40000
20000
0
MFI
0.1
1
10
100
1000
Antibody (nm)
2M24/Necitn-4 hIgG1
RSV hIgG1
EC50 = ~32.0 nM

FIG. 62

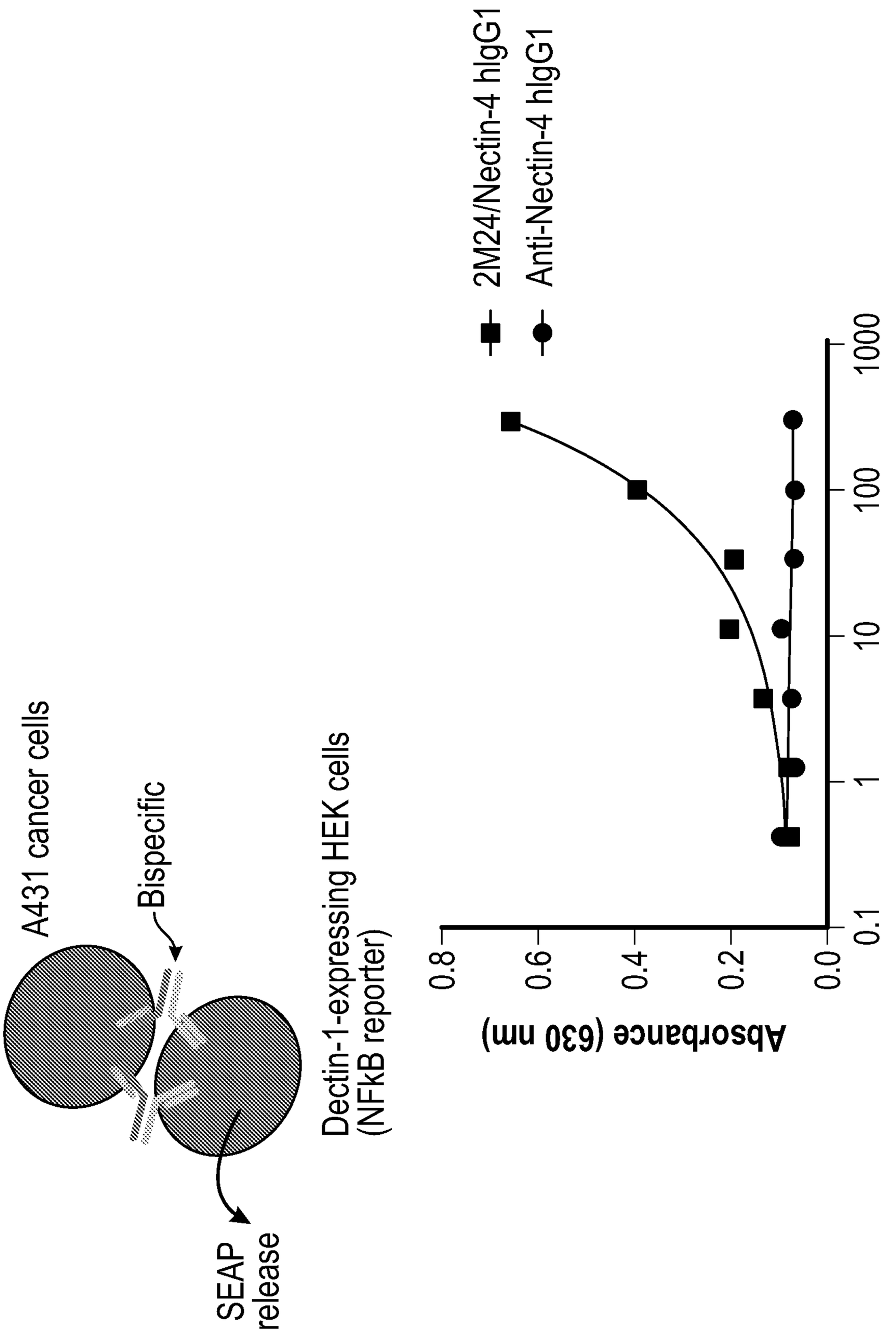

A431 cancer cells
Bispecific
SEAP release
Dectin-1-expressing HEK cells (NFkB reporter)
2M24/Nectin-4 hIgG1
Anti-Nectin-4 hIgG1
Absorbance (630 nm)
0.0
0.2
0.4
0.6
0.8
0.1
1
10
100
1000
Antibody (nM)

FIG. 63

SUBSTITUTE SHEET (RULE 26)

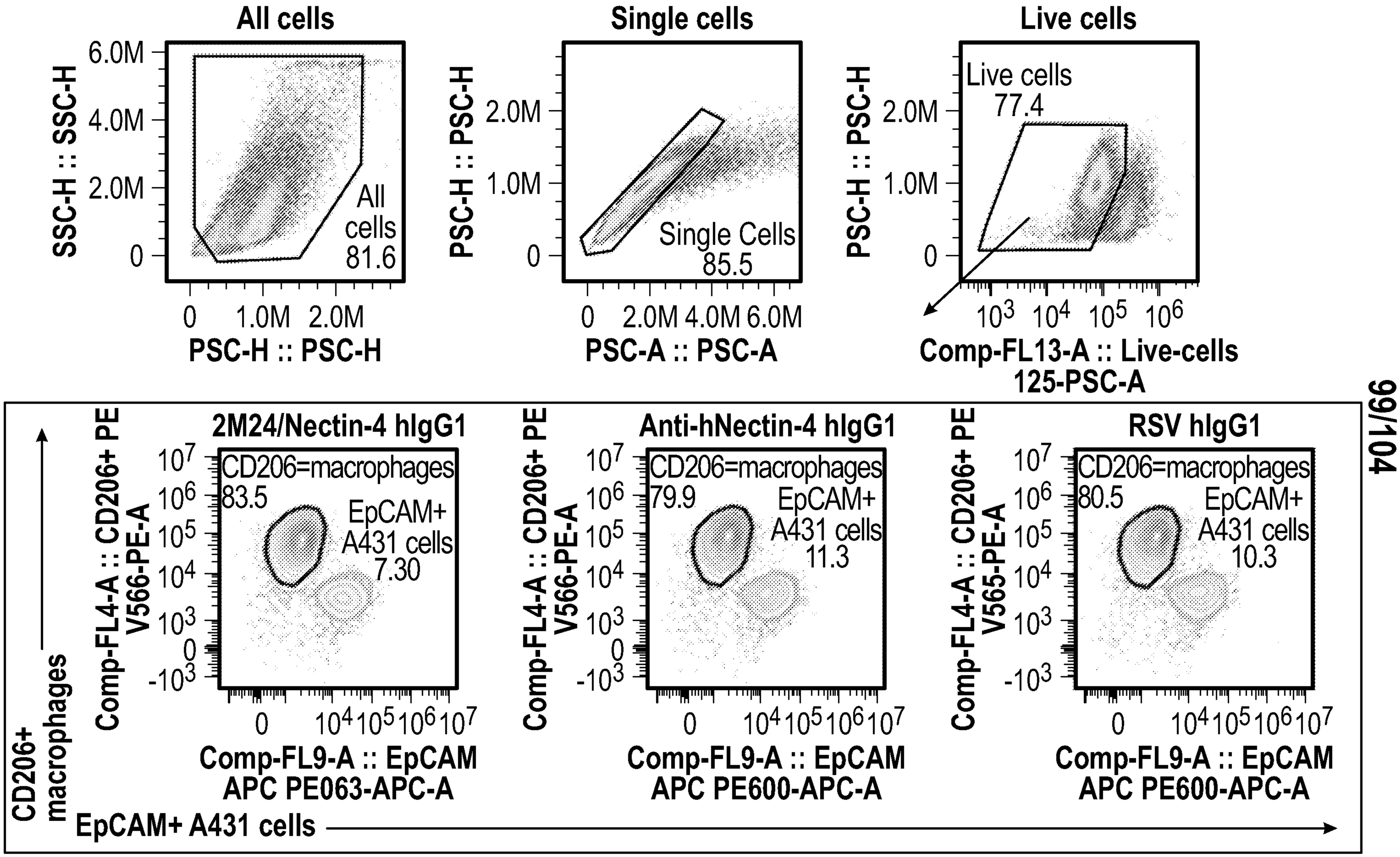


FIG. 64A

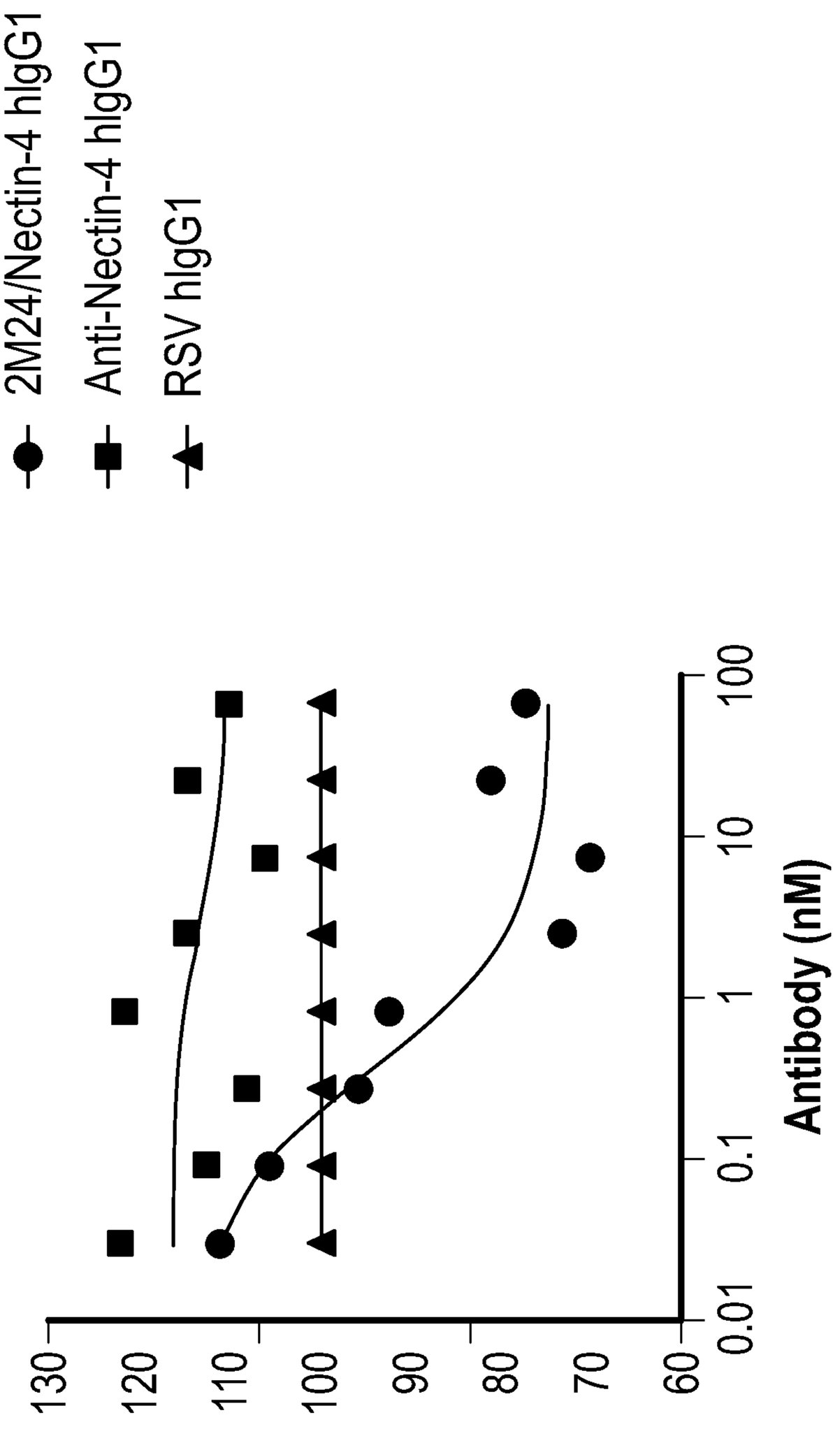

2M24/Nectin-4 hIgG1
Anti-Nectin-4 hIgG1
RSV hIgG1
Percent of RSV isotype control
130
120
110
100
90
80
70
60
0.01
0.1
1
10
100
Antibody (nM)

FIG. 64B

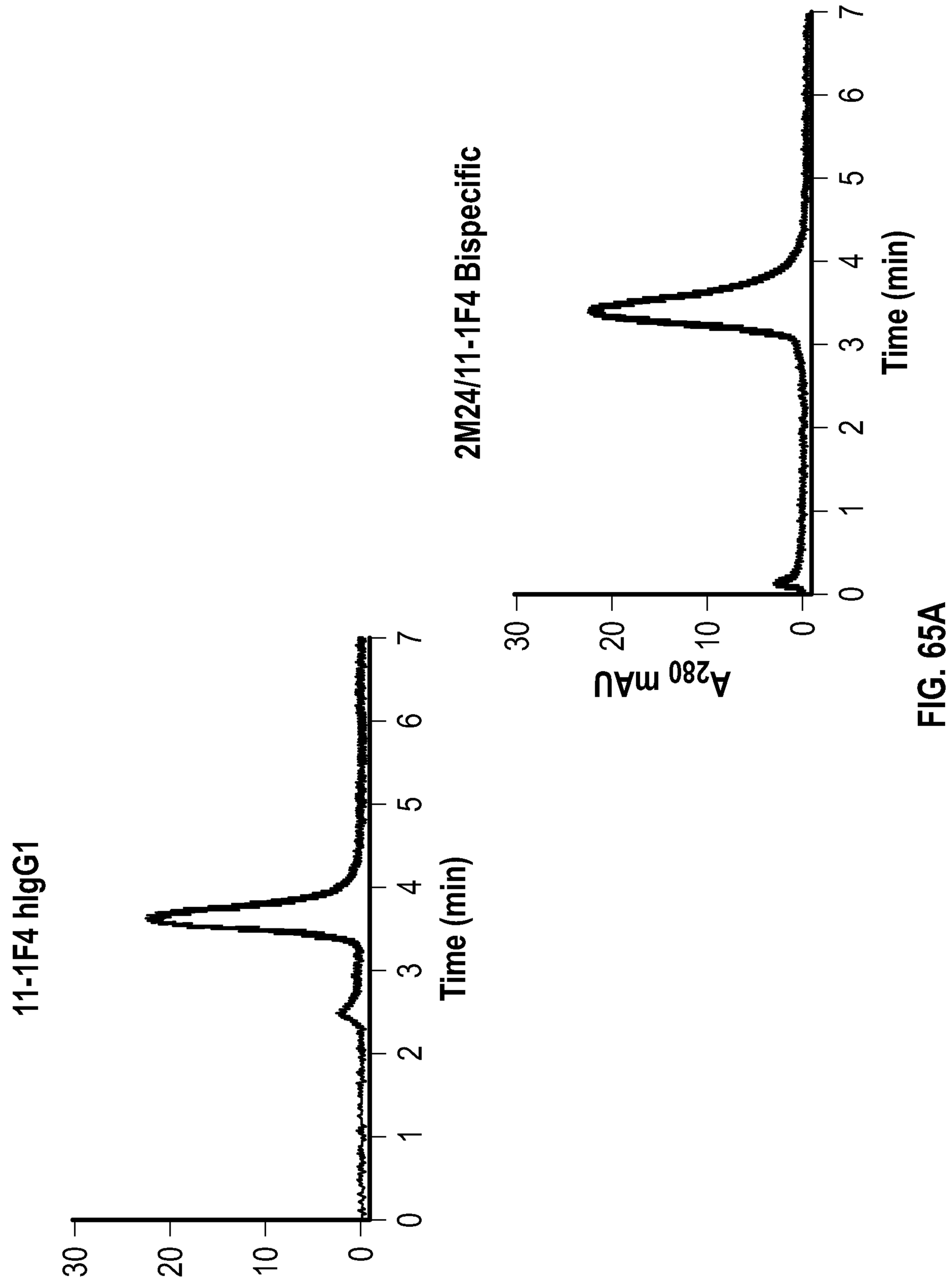

2M24/11-1F4 Bispecific
11-1F4 hIgG1
Time (min)
A_{280} mAU
0
1
2
3
4
5
6
7
0
10
20
30

FIG. 65A

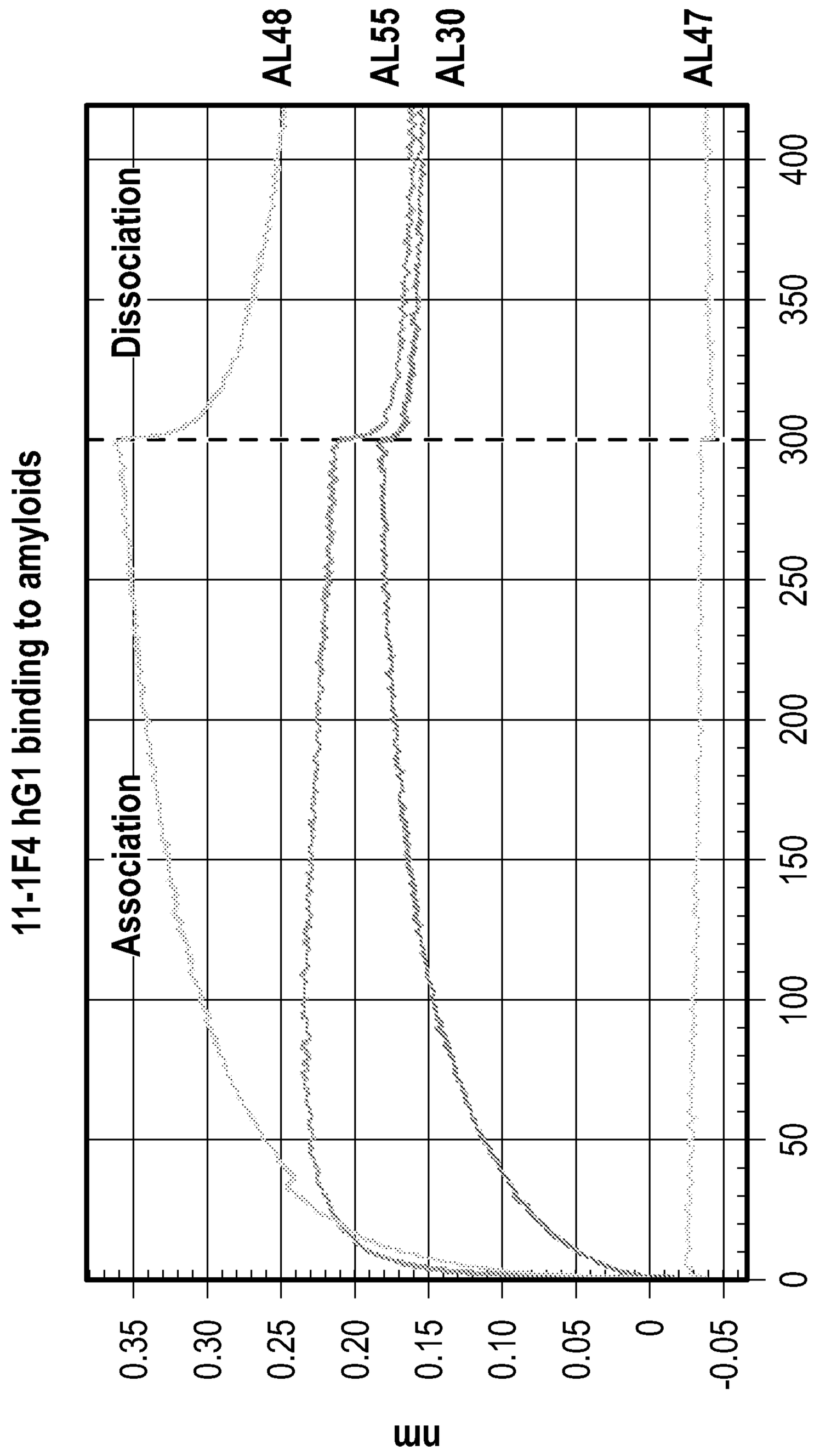

AL48
AL55
AL30
AL47
Dissociation
Association
11-1F4 hG1 binding to amyloids
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
-0.05
nm
0
50
100
150
200
250
300
350
400
Time (s)

FIG. 65B

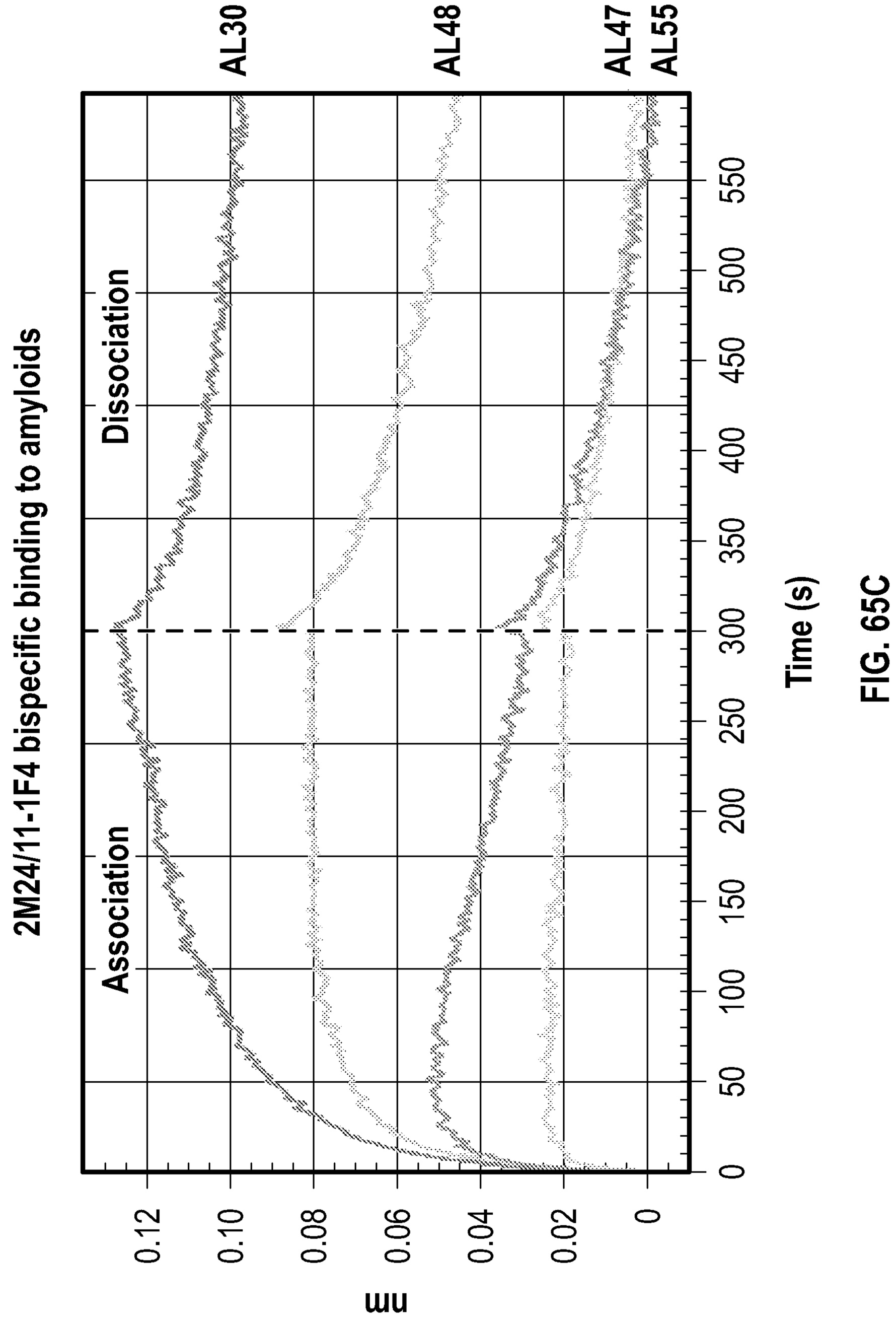

AL30
AL48
AL47
AL55
2M24/11-1F4 bispecific binding to amyloids
Dissociation
Association
0.12
0.10
0.08
0.06
0.04
0.02
0
nm
0
50
100
150
200
250
300
350
400
450
500
550
Time (s)

FIG. 65C

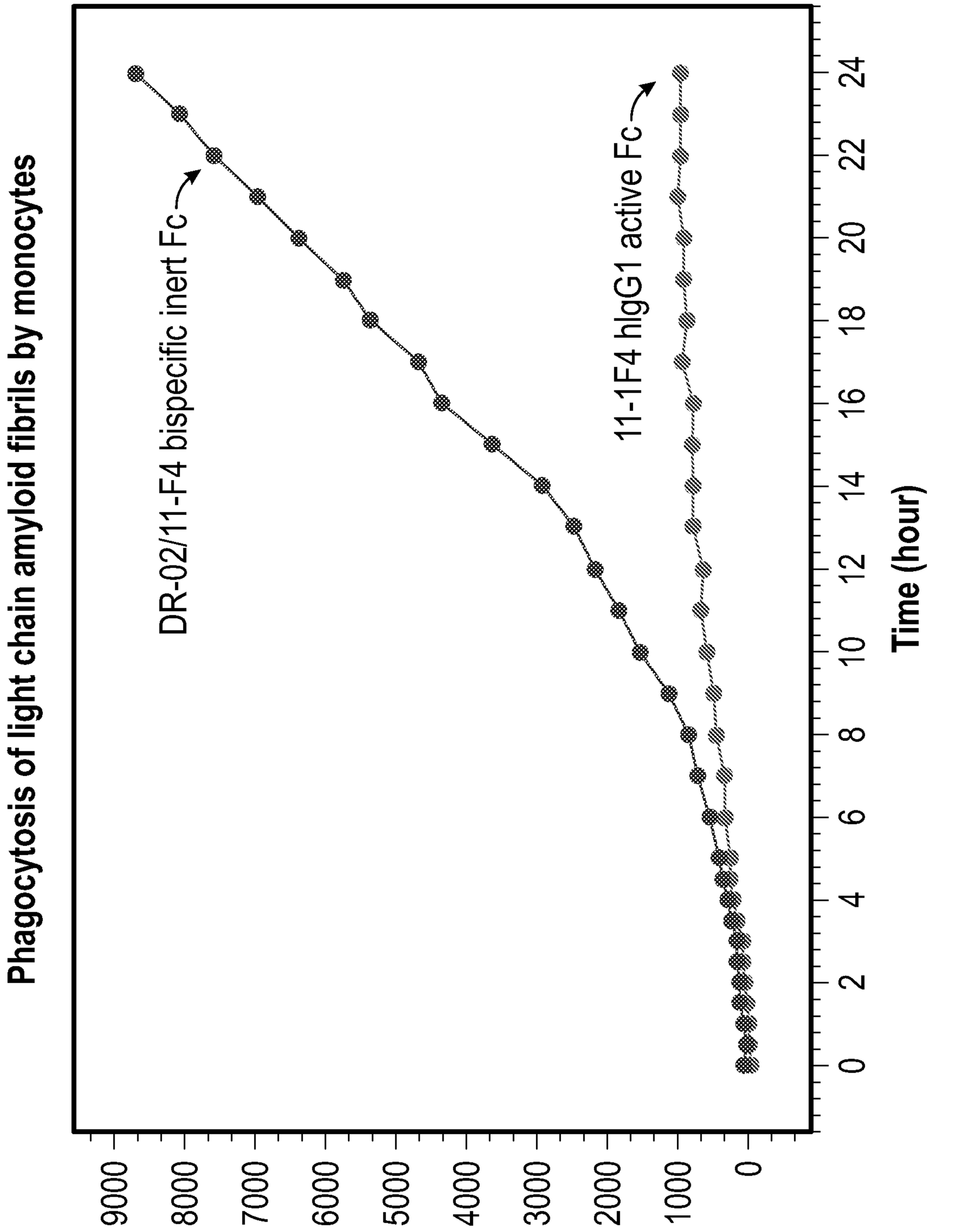

Phagocytosis of light chain amyloid fibrils by monocytes
pHrodo-red intensity
(RCU x um2 /image)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hour)
DR-02/11-F4 bispecific inert Fc
11-1F4 hIgG1 active Fc

FIG. 66

SEQUENCE LISTING

<110> Dren Bio, Inc.

<120> ANTI-DECTIN-1 ANTIBODIES AND METHODS OF USE THEREOF

<130> 18654-20004.40

<140> Not Yet Assigned
<141> Concurrently Herewith

<150> US 63/174,439
<151> 2021-04-13

<150> US 63/088,895
<151> 2020-10-07

<160> 92

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 1
Gly Tyr Thr Phe Thr Asp Tyr Tyr
 1   5

<210> 2
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 2
Ile Asn Pro Asn Ser Gly Asp Thr
 1   5

<210> 3
<211> 11

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 3
Ala Arg Asn Ser Gly Ser Tyr Ser Phe Gly Tyr
 1   5   10

<210> 4
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 4
Gln Gly Ile Ser Ser Trp
 1   5

<210> 5
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 5
Gly Ala Ser
 1

<210> 6
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 6
Gln Gln Ala Tyr Ser Phe Pro Phe Thr
 1   5

<210> 7
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 7
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Ile Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65   70   75   80
Leu Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Phe Tyr Cys
                85   90   95
Ala Arg Asn Ser Gly Ser Tyr Ser Phe Gly Tyr Trp Gly Gln Gly Thr
            100   105   110
Leu Val Thr Val Ser Ser
        115

<210> 8
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 8
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Phe Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Ser Phe Pro Phe
                85   90   95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Glu
            100   105

<210> 9
<211> 247
<212> PRT
<213> Homo sapiens

<400> 9
Met Glu Tyr His Pro Asp Leu Glu Asn Leu Asp Glu Asp Gly Tyr Thr
 1   5   10   15
Gln Leu His Phe Asp Ser Gln Ser Asn Thr Arg Ile Ala Val Val Ser
            20   25   30
Glu Lys Gly Ser Cys Ala Ala Ser Pro Pro Trp Arg Leu Ile Ala Val
        35   40   45
Ile Leu Gly Ile Leu Cys Leu Val Ile Leu Val Ile Ala Val Val Leu
    50   55   60
Gly Thr Met Ala Ile Trp Arg Ser Asn Ser Gly Ser Asn Thr Leu Glu
65   70   75   80
Asn Gly Tyr Phe Leu Ser Arg Asn Lys Glu Asn His Ser Gln Pro Thr
                85   90   95
Gln Ser Ser Leu Glu Asp Ser Val Thr Pro Thr Lys Ala Val Lys Thr
            100   105   110
Thr Gly Val Leu Ser Ser Pro Cys Pro Pro Asn Trp Ile Ile Tyr Glu
        115   120   125
Lys Ser Cys Tyr Leu Phe Ser Met Ser Leu Asn Ser Trp Asp Gly Ser
    130   135   140
Lys Arg Gln Cys Trp Gln Leu Gly Ser Asn Leu Leu Lys Ile Asp Ser
145   150   155   160
Ser Asn Glu Leu Gly Phe Ile Val Lys Gln Val Ser Ser Gln Pro Asp
                165   170   175
Asn Ser Phe Trp Ile Gly Leu Ser Arg Pro Gln Thr Glu Val Pro Trp
            180   185   190
Leu Trp Glu Asp Gly Ser Thr Phe Ser Ser Asn Leu Phe Gln Ile Arg
        195   200   205
Thr Thr Ala Thr Gln Glu Asn Pro Ser Pro Asn Cys Val Trp Ile His
    210   215   220
Val Ser Val Ile Tyr Asp Gln Leu Cys Ser Val Pro Ser Tyr Ser Ile
225   230   235   240
Cys Glu Lys Lys Phe Ser Met
                245

<210> 10
<211> 201
<212> PRT
<213> Homo sapiens

<400> 10
Met Glu Tyr His Pro Asp Leu Glu Asn Leu Asp Glu Asp Gly Tyr Thr
 1   5   10   15

```
Gln Leu His Phe Asp Ser Gln Ser Asn Thr Arg Ile Ala Val Val Ser
            20                  25                  30
Glu Lys Gly Ser Cys Ala Ala Ser Pro Pro Trp Arg Leu Ile Ala Val
        35                  40                  45
Ile Leu Gly Ile Leu Cys Leu Val Ile Leu Val Ile Ala Val Val Leu
    50                  55                  60
Gly Thr Met Gly Val Leu Ser Ser Pro Cys Pro Pro Asn Trp Ile Ile
65                  70                  75                  80
Tyr Glu Lys Ser Cys Tyr Leu Phe Ser Met Ser Leu Asn Ser Trp Asp
                85                  90                  95
Gly Ser Lys Arg Gln Cys Trp Gln Leu Gly Ser Asn Leu Leu Lys Ile
            100                 105                 110
Asp Ser Ser Asn Glu Leu Gly Phe Ile Val Lys Gln Val Ser Ser Gln
        115                 120                 125
Pro Asp Asn Ser Phe Trp Ile Gly Leu Ser Arg Pro Gln Thr Glu Val
    130                 135                 140
Pro Trp Leu Trp Glu Asp Gly Ser Thr Phe Ser Ser Asn Leu Phe Gln
145                 150                 155                 160
Ile Arg Thr Thr Ala Thr Gln Glu Asn Pro Ser Pro Asn Cys Val Trp
                165                 170                 175
Ile His Val Ser Val Ile Tyr Asp Gln Leu Cys Ser Val Pro Ser Tyr
            180                 185                 190
Ser Ile Cys Glu Lys Lys Phe Ser Met
        195                 200
```

<210> 11
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 11

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Ile Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Phe Tyr Cys
                85                  90                  95
Ala Arg Asn Ser Gly Ser Tyr Ser Phe Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
```

```
        115                 120                 125
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
    130                 135                 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190
Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205
Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
    210                 215                 220
Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
225                 230                 235                 240
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                245                 250                 255
Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
            260                 265                 270
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        275                 280                 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320
Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            340                 345                 350
Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400
Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
                405                 410                 415
Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            420                 425                 430
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440
```

<210> 12
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 12
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Phe Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Ser Phe Pro Phe
                85   90   95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Glu Arg Thr Val Ala Ala
            100   105   110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115   120   125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130   135   140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145   150   155   160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165   170   175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180   185   190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195   200   205
Phe Asn Arg Gly Glu Cys
    210

<210> 13
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 13
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
 1   5   10

<210> 14
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 14
Glu Phe Ala Ser Ala Glu Ala Gly Ile Thr Gly Thr Trp Tyr Asn Gln
 1   5   10   15
His Gly Ser Thr Phe Thr Val Thr Ala Gly Ala Asp Gly Asn Leu Thr
            20   25   30
Gly Gln Tyr Glu Asn Arg Ala Gln Gly Thr Gly Cys Gln Asn Ser Pro
        35   40   45
Tyr Thr Leu Thr Gly Arg Tyr Asn Gly Thr Lys Leu Glu Trp Arg Val
    50   55   60
Glu Trp Asn Asn Ser Thr Glu Asn Cys His Ser Arg Thr Glu Trp Arg
65   70   75   80
Gly Gln Tyr Gln Gly Gly Ala Glu Ala Arg Ile Asn Thr Gln Trp Asn
                85   90   95
Leu Thr Tyr Glu Gly Gly Ser Gly Pro Ala Thr Glu Gln Gly Gln Asp
            100   105   110
Thr Phe Thr Lys Val Lys Pro Ser Ala Ala Ser Gly Ser
        115   120   125

<210> 15
<211> 582
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 15
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Ile Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65   70   75   80
Leu Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Phe Tyr Cys
                85   90   95
Ala Arg Asn Ser Gly Ser Tyr Ser Phe Gly Tyr Trp Gly Gln Gly Thr
            100   105   110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115   120   125
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
    130   135   140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn

```
145                 150                 155                 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190
Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205
Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys
    210                 215                 220
Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
225                 230                 235                 240
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                245                 250                 255
Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
            260                 265                 270
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        275                 280                 285
Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320
Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            340                 345                 350
Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400
Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
                405                 410                 415
Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            420                 425                 430
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly
        435                 440                 445
Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Phe Ala Ser Ala Glu Ala
    450                 455                 460
Gly Ile Thr Gly Thr Trp Tyr Asn Gln His Gly Ser Thr Phe Thr Val
465                 470                 475                 480
Thr Ala Gly Ala Asp Gly Asn Leu Thr Gly Gln Tyr Glu Asn Arg Ala
                485                 490                 495
Gln Gly Thr Gly Cys Gln Asn Ser Pro Tyr Thr Leu Thr Gly Arg Tyr
            500                 505                 510
Asn Gly Thr Lys Leu Glu Trp Arg Val Glu Trp Asn Asn Ser Thr Glu
        515                 520                 525
Asn Cys His Ser Arg Thr Glu Trp Arg Gly Gln Tyr Gln Gly Gly Ala
    530                 535                 540
Glu Ala Arg Ile Asn Thr Gln Trp Asn Leu Thr Tyr Glu Gly Gly Ser
```

```
545                 550                 555                 560
Gly Pro Ala Thr Glu Gln Gly Gln Asp Thr Phe Thr Lys Val Lys Pro
                565                 570                 575
Ser Ala Ala Ser Gly Ser
            580
```

<210> 16
<211> 353
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 16

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Ile Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Phe Tyr Cys
                85                  90                  95
Ala Arg Asn Ser Gly Ser Tyr Ser Phe Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
    130                 135                 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190
Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205
Asn Thr Lys Val Asp Lys Arg Val Gly Gly Gly Ser Gly Gly Gly Ser
    210                 215                 220
Gly Gly Gly Ser Glu Phe Ala Ser Ala Glu Ala Gly Ile Thr Gly Thr
225                 230                 235                 240
Trp Tyr Asn Gln His Gly Ser Thr Phe Thr Val Thr Ala Gly Ala Asp
                245                 250                 255
Gly Asn Leu Thr Gly Gln Tyr Glu Asn Arg Ala Gln Gly Thr Gly Cys
            260                 265                 270
```

```
Gln Asn Ser Pro Tyr Thr Leu Thr Gly Arg Tyr Asn Gly Thr Lys Leu
        275                 280                 285
Glu Trp Arg Val Glu Trp Asn Asn Ser Thr Glu Asn Cys His Ser Arg
    290                 295                 300
Thr Glu Trp Arg Gly Gln Tyr Gln Gly Gly Ala Glu Ala Arg Ile Asn
305                 310                 315                 320
Thr Gln Trp Asn Leu Thr Tyr Glu Gly Gly Ser Gly Pro Ala Thr Glu
                325                 330                 335
Gln Gly Gln Asp Thr Phe Thr Lys Val Lys Pro Ser Ala Ala Ser Gly
            340                 345                 350
Ser
```

<210> 17
<211> 365
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 17

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Ile Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Phe Tyr Cys
                85                  90                  95
Ala Arg Asn Ser Gly Ser Tyr Ser Phe Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125
Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
    130                 135                 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190
Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205
Asn Thr Lys Val Asp Lys Arg Val Gly Gly Gly Ser Gly Gly Gly Ser
```

```
    210                 215                 220
Gly Gly Gly Ser Glu Phe Ala Ser Ala Glu Ala Gly Ile Thr Gly Thr
225                 230                 235                 240
Trp Tyr Asn Gln His Gly Ser Thr Phe Thr Val Thr Ala Gly Ala Asp
                245                 250                 255
Gly Asn Leu Thr Gly Gln Tyr Glu Asn Arg Ala Gln Gly Thr Gly Cys
            260                 265                 270
Gln Asn Ser Pro Tyr Thr Leu Thr Gly Arg Tyr Asn Gly Thr Lys Leu
        275                 280                 285
Glu Trp Arg Val Glu Trp Asn Asn Ser Thr Glu Asn Cys His Ser Arg
    290                 295                 300
Thr Glu Trp Arg Gly Gln Tyr Gln Gly Gly Ala Glu Ala Arg Ile Asn
305                 310                 315                 320
Thr Gln Trp Asn Leu Thr Tyr Glu Gly Gly Ser Gly Pro Ala Thr Glu
                325                 330                 335
Gln Gly Gln Asp Thr Phe Thr Lys Val Lys Pro Ser Ala Ala Ser Gly
            340                 345                 350
Ser Ala Ala Ala Gly Ala Ser His His His His His His
        355                 360                 365


<210> 18
<211> 368
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 18
Gln Trp Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
 1               5                  10                  15
Ser Trp Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30
Thr Met His Trp Trp Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Ser
65                  70                  75                  80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Trp Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Arg Ala Val Leu Val Pro Tyr Ala Met Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
```

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Gly Gly Gly Ser Gly
    210                 215                 220
Gly Gly Ser Gly Gly Gly Ser Glu Phe Ala Ser Ala Glu Ala Gly Ile
225                 230                 235                 240
Thr Gly Thr Trp Tyr Asn Gln His Gly Ser Thr Phe Thr Val Thr Ala
                245                 250                 255
Gly Ala Asp Gly Asn Leu Thr Gly Gln Tyr Glu Asn Arg Ala Gln Gly
            260                 265                 270
Thr Gly Cys Gln Asn Ser Pro Tyr Thr Leu Thr Gly Arg Tyr Asn Gly
        275                 280                 285
Thr Lys Leu Glu Trp Arg Val Glu Trp Asn Asn Ser Thr Glu Asn Cys
    290                 295                 300
His Ser Arg Thr Glu Trp Arg Gly Gln Tyr Gln Gly Gly Ala Glu Ala
305                 310                 315                 320
Arg Ile Asn Thr Gln Trp Asn Leu Thr Tyr Glu Gly Gly Ser Gly Pro
                325                 330                 335
Ala Thr Glu Gln Gly Gln Asp Thr Phe Thr Lys Val Lys Pro Ser Ala
            340                 345                 350
Ala Ser Gly Ser Ala Ala Ala Gly Ala Ser His His His His His His
        355                 360                 365
```

<210> 19
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 19

```
Gln Ile Val Leu Thr Gln Ser Pro Ala Val Met Ser Ala Ser Pro Gly
 1               5                  10                  15
Glu Lys Trp Thr Ile Thr Cys Thr Ala Ser Ser Ser Leu Ser Tyr Met
            20                  25                  30
His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Leu Trp Leu Tyr
        35                  40                  45
Ser Thr Ser Ile Leu Ala Ser Gly Val Pro Thr Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Ser Pro Phe Thr
                85                  90                  95
Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
```

```
            100                 105                 110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205
Asn Arg Gly Glu Cys
    210


<210> 20
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 20
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
        35                  40                  45
Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
            100                 105                 110
Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
```

```
Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Ala Ala Ala Gly Ala
    210                 215                 220
Ser His His His His His His Gly Ser Gly Leu Asn Asp Ile Phe Glu
225                 230                 235                 240
Ala Gln Lys Ile Glu Trp His Glu
                245
```

<210> 21
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 21

```
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
 1               5                  10                  15
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30
His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205
Asn Arg Gly Glu Cys
    210
```

<210> 22

<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 22
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20   25   30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115   120   125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130   135   140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145   150   155   160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165   170   175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180   185   190
Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195   200   205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Ala Ala Ala Gly Ala Ser
    210   215   220
His His His His His His Gly Ser Gly Leu Asn Asp Ile Phe Glu Ala
225   230   235   240
Gln Lys Ile Glu Trp His Glu
                245

<210> 23
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 23
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115   120   125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130   135   140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145   150   155   160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165   170   175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180   185   190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195   200   205
Phe Asn Arg Gly Glu Cys
    210

<210> 24
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 24
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30
Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
        35   40   45
Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80

```
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
            100                 105                 110
Ala Gly Thr Thr Val Thr Val Ser Ala
        115                 120
```

<210> 25
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 25

```
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
 1               5                  10                  15
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30
His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 26
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 26

```
Gly Gly Gly Gly Ser
 1               5
```

<210> 27
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 27
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 1   5   10   15

<210> 28
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 28
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 1   5   10   15
Gly Gly Gly Ser
            20

<210> 29
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 29
Glu Pro Lys Arg Ser Asp Lys Thr His Thr Cys Pro Pro Cys
 1   5   10

<210> 30
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 30
Ser Ala Thr His Thr Cys Pro Pro Cys
 1   5

<210> 31
<211> 476
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 31
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Ile Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65   70   75   80
Leu Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Phe Tyr Cys
                85   90   95
Ala Arg Asn Ser Gly Ser Tyr Ser Phe Gly Tyr Trp Gly Gln Gly Thr
            100   105   110
Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115   120   125
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln
    130   135   140
Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
145   150   155   160
Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln
                165   170   175
Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Phe Gly Ala Ser Ser Leu
            180   185   190
Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195   200   205
Phe Thr Leu Thr Val Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
    210   215   220
Tyr Cys Gln Gln Ala Tyr Ser Phe Pro Phe Thr Phe Gly Pro Gly Thr
225   230   235   240
Lys Val Asp Ile Glu Glu Pro Lys Arg Ser Asp Lys Thr His Thr Cys
                245   250   255
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            260   265   270
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        275   280   285
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
    290   295   300
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305   310   315   320
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu

```
                325                 330                 335
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            340                 345                 350
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        355                 360                 365
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    370                 375                 380
Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys
385                 390                 395                 400
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                405                 410                 415
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            420                 425                 430
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        435                 440                 445
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
    450                 455                 460
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475


<210> 32
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 32
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
        35                  40                  45
Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
            100                 105                 110
Ala Gly Thr Thr Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
```

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365
Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
                405                 410                 415
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430
His Glu Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
Pro Gly
    450
```

<210> 33
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 33
```
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
```

```
 1               5                  10                  15
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30
His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45
Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205
Asn Arg Gly Glu Cys
    210
```

<210> 34
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 34

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 35
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 35
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
            20                  25                  30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 36
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 36
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
 1               5                  10                  15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30
Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45
Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
    50                  55                  60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ala Asn Gln Val
65                  70                  75                  80
```

```
Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95
Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala
            100                 105                 110
Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 37
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 37

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Lys Cys Gln Leu Ser Val Gly Tyr Met
            20                  25                  30
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35                  40                  45
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ala Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65                  70                  75                  80
Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 38
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 38

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Val Tyr
            20                  25                  30
Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Asp Ile Asn Asn Glu Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Ala Gly Tyr Ser Asn His Val Pro Ile Phe Asp Ser Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 39
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 39

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Lys Ser Gly Ser Val Thr Ser Asp
            20                  25                  30
Asn Phe Pro Thr Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Leu
        35                  40                  45
Leu Ile Tyr Asn Thr Asn Thr Arg His Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ala Glu Tyr Phe Cys Ala Leu Phe Ile Ser Asn
                85                  90                  95
Pro Ser Val Glu Phe Gly Gly Gly Thr Gln Leu Thr Val Leu
            100                 105                 110
```

<210> 40
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 40

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Ser
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ala Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110
Val Thr Val Ser Ser
        115
```

<210> 41
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 41
```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Gly Trp
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Pro
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 42
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 42
```
Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30
```

```
Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45
Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe
    50                  55                  60
Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95
Ala Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
            100                 105                 110
Gln Gly Ser Leu Val Thr Val Ser Ser
        115                 120


<210> 43
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 43
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala
            20                  25                  30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu
                85                  90                  95
Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 44
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 44
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
 1               5                  10                  15
```

```
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Ser Tyr
            20                  25                  30
Gly Val Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45
Gly Val Ile Trp Gly Asp Gly Ser Thr Asn Tyr Lys Pro Asn Leu Met
    50                  55                  60
Ser Arg Leu Ser Ile Ser Lys Asp Ile Ser Lys Ser Gln Val Leu Phe
65                  70                  75                  80
Lys Leu Asn Ser Leu Gln Thr Asp Asp Thr Ala Thr Tyr Tyr Cys Val
                85                  90                  95
Thr Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
            100                 105                 110


<210> 45
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 45
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1               5                  10                  15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Arg
            20                  25                  30
Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
Ser Arg Val Glu Ala Glu Asp Leu Gly Leu Tyr Phe Cys Phe Gln Thr
                85                  90                  95
Thr Tyr Val Pro Asn Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> 46
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 46
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
```

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Tyr Ser
            20                  25                  30
Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Arg Ile Phe Pro Gly Asp Gly Asp Thr Asp Tyr Asn Gly Lys Phe
    50                  55                  60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asn Val Phe Asp Gly Tyr Trp Leu Val Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 47
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 47

```
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
 1               5                  10                  15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
            20                  25                  30
Asn Gly Ile Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45
Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Val Ser Gly Val Pro
    50                  55                  60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Asn
                85                  90                  95
Leu Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 48
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 48

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Val Ile Trp Phe Asp Gly Thr Lys Lys Tyr Tyr Thr Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Thr Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Arg Gly Ile Gly Ala Arg Arg Gly Pro Tyr Tyr Met Asp
            100                 105                 110
Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 49
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 49

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 50
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 50
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Ser Phe
            20   25   30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Gly Asp Thr Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65   70   75   80
Leu Gln Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Gly Gly Tyr Tyr Tyr Gly Arg Ser Tyr Tyr Thr Met Asp
            100   105   110
Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 51
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 51
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1   5   10   15
Ala Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
            20   25   30
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
65   70   75   80
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Phe Gln Gly
                85   90   95
Ser His Val Pro Pro Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
            100   105   110

<210> 52
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 52
Glu Val Gln Leu Val Glu Ser Gly Gly Arg Leu Val Gln Pro Lys Gly
 1   5   10   15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20   25   30
Ala Met Tyr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Ile Tyr Tyr Ala Asp
    50   55   60
Ser Val Lys Asp Arg Phe Thr Ile Phe Arg Asp Asp Ser Gln Ser Met
65   70   75   80
Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85   90   95
Tyr Cys Val Arg Pro Tyr Ser Asp Ser Phe Ala Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ala
        115

<210> 53
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 53
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1   5   10   15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20   25   30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Lys Ile
65   70   75   80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85   90   95
Thr His Val Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105   110

<210> 54
<211> 119
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 54
Glu Val Gln Leu Val Glu Ser Gly Gly Arg Leu Val Gln Pro Lys Gly
 1   5   10   15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20   25   30
Ala Met Tyr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Ile Tyr Tyr Ala Asp
    50   55   60
Ser Val Lys Asp Arg Phe Thr Ile Phe Arg Asp Asp Ser Gln Ser Met
65   70   75   80
Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85   90   95
Tyr Cys Val Arg Pro Tyr Ser Asp Ser Phe Ala Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ala
        115

<210> 55
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 55
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1   5   10   15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Leu Ser Leu Val His Ser
            20   25   30
Thr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Lys Ile
65   70   75   80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85   90   95
Thr His Val Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105   110

<210> 56

<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 56
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
 1   5   10   15
Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20   25   30
Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35   40   45
Gly Trp Ile Asn Thr Lys Thr Gly Glu Pro Thr Tyr Ala Glu Glu Phe
    50   55   60
Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65   70   75   80
Leu Gln Ile Asn Asn Leu Lys Lys Glu Asp Thr Ala Thr Tyr Phe Cys
                85   90   95
Gly Arg Gly Gly Tyr Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly
            100   105   110
Ala Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 57
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 57
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
 1   5   10   15
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Val Leu Ile
        35   40   45
Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Arg Val Gln Ala
65   70   75   80
Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu
                85   90   95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100   105

<210> 58
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 58
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Thr
 1   5   10   15
Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ile Tyr
            20   25   30
Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
        35   40   45
Gly Asn Ile Phe Pro Gly Ser Ala Tyr Ile Asn Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Thr Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85   90   95
Ala Arg Glu Gly Ser Asn Ser Gly Tyr Trp Gly Gln Gly Thr Thr Leu
            100   105   110
Thr Val Ser Ser
        115

<210> 59
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 59
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Val Ser Ala Gly
 1   5   10   15
Glu Lys Val Thr Met Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20   25   30
Gly Asn Gln Gln Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35   40   45
Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu Ser Gly Val
    50   55   60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65   70   75   80
Ile Asn Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Ser
                85   90   95
Asp His Ile Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile

100 105 110
Lys

<210> 60
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 60
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1 5 10 15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ser Gly Gly Ser Thr Asp Tyr Asn Ala Ala Phe Ile
50 55 60
Ser Arg Leu Ser Ile Ser Lys Asp Thr Ser Lys Ser Gln Val Phe Phe
65 70 75 80
Lys Met Asn Ser Leu Gln Ala Asp Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95
Arg Glu Leu Ile His Ala Met Asp Asn Trp Gly Gln Gly Thr Ser Val
100 105 110
Thr Val Ser Ser
115

<210> 61
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 61
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
1 5 10 15
Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Gln Gly Asn Ser Pro Gln Leu Leu Val
35 40 45
Phe Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser

65 70 75 80
Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Thr
85 90 95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 62
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 62
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1 5 10 15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30
Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45
Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50 55 60
Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80
Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95
Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ala
115

<210> 63
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 63
Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
20 25 30
Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45
Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly

```
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65                  70                  75                  80
Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
                85                  90                  95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 64
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 64

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30
Asp Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35                  40                  45
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asp Tyr Asn Pro Ser
    50                  55                  60
Leu Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80
Ser Leu Lys Val Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95
Cys Ala Arg Val Ser Ile Phe Gly Val Gly Thr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 65
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 65

```
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
```

```
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Gly Ser Thr Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Ala Glu Ile Lys
            100                 105
```

<210> 66
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 66

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30
Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
Gly Val Ile Trp Thr Gly Gly Ser Thr Asp Tyr Asn Ser Ala Leu Met
    50                  55                  60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Arg Asp Gly Asp Tyr Asp Arg Tyr Thr Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 67
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 67

```
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1               5                  10                  15
Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
```

```
            20                  25                  30
Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45
Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
    50                  55                  60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80
Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95
Glu Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> 68
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 68
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60
Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Ile Gly Asp Ser Ser Pro Ser Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser
        115


<210> 69
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 69
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
```

```
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30
Val Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Tyr Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asp Tyr Thr Ser Pro Trp
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 70
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 70

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
Gly Tyr Val Tyr Tyr Ser Gly Thr Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
Ser Ile Ala Val Thr Gly Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser
        115
```

<210> 71
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 71
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1   5   10   15
Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Asn Asn Asn
            20   25   30
Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65   70   75   80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Arg Ser Pro
                85   90   95
Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 72
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 72
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
            20   25   30
Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35   40   45
Gly Leu Ile Thr Pro Tyr Asn Gly Ala Ser Ser Tyr Asn Gln Lys Phe
    50   55   60
Arg Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Asp Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85   90   95
Ala Arg Gly Gly Tyr Asp Gly Arg Gly Phe Asp Tyr Trp Gly Ser Gly
            100   105   110
Thr Pro Val Thr Val Ser Ser
        115

<210> 73
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 73
Asp Ile Glu Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1   5   10   15
Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20   25   30
His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
        35   40   45
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Gly Arg Phe Ser Gly Ser
    50   55   60
Gly Ser Gly Asn Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu Ala Glu
65   70   75   80
Asp Asp Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Lys His Pro Leu Thr
                85   90   95
Phe Gly Ser Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 74
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 74
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ile Thr Asp Ser
            20   25   30
Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Ser Leu Glu Trp Ile
        35   40   45
Gly Tyr Ile Tyr Pro Tyr Asn Gly Gly Thr Asp Tyr Asn Gln Lys Phe
    50   55   60
Lys Asn Arg Ala Thr Leu Thr Val Asp Asn Pro Thr Asn Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Phe Tyr Tyr Cys
                85   90   95
Val Asn Gly Asn Pro Trp Leu Ala Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110
Thr Val Ser Ser
        115

<210> 75
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 75
Asp Ile Gln Leu Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Leu Asp Asn Tyr
            20   25   30
Gly Ile Arg Phe Leu Thr Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro
        35   40   45
Lys Leu Leu Met Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
    50   55   60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
65   70   75   80
Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Lys
                85   90   95
Glu Val Pro Trp Ser Phe Gly Gln Gly Thr Lys Val Glu Val Lys
            100   105   110

<210> 76
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 76
Glu Val Gln Leu Val Glu Ser Gly Gly Arg Leu Val Gln Pro Lys Gly
 1   5   10   15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Asn Thr Tyr
            20   25   30
Ala Leu Tyr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50   55   60
Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Ser Met
65   70   75   80
Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85   90   95
Tyr Cys Val Arg Ala Arg Phe Tyr Tyr Ser Asp Tyr Gly Tyr Ala Met
            100   105   110
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115   120   125

<210> 77
<211> 112

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 77
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly
 1   5   10   15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
            20   25   30
Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
        35   40   45
Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro
    50   55   60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile
65   70   75   80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
                85   90   95
Leu Glu Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100   105   110

<210> 78
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 78
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85   90   95
Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
            100   105   110
Leu Val Thr Val Ser Ser
        115

<210> 79
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 79
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Ser
            20   25   30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45
Ile Tyr Gly Ala Phe Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65   70   75   80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
                85   90   95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 80
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 80
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30
Trp Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Gly Met Ile Asp Pro Ser Asn Ser Asp Thr Arg Phe Asn Pro Asn Phe
    50   55   60
Lys Asp Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Thr Tyr Arg Ser Tyr Val Thr Pro Leu Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 81
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 81
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr
            20   25   30
Ser Ser Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
        35   40   45
Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50   55   60
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65   70   75   80
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                85   90   95
Tyr Tyr Ala Tyr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100   105   110
Lys

<210> 82
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 82
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ile Glu Asp Tyr
            20   25   30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Thr Phe
    50   55   60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

```
Ala Arg His Asp Ala His Tyr Gly Thr Trp Phe Ala Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 83
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 83
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1               5                  10                  15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Ile Arg Asn
            20                  25                  30
Asp Gly Asn Thr Tyr Leu Glu Trp Tyr Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45
Pro Arg Arg Leu Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95
Ser His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210> 84
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 84
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ala Phe Thr Ala Tyr
            20                  25                  30
Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ser Phe Asp Pro Tyr Asp Gly Gly Ser Ser Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val
65                  70                  75                  80
```

```
Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Trp Tyr Tyr Phe Asp Tyr Trp Gly His Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser
        115
```

<210> 85
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 85

```
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
 1               5                  10                  15
Glu Pro Ala Ser Ile Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Pro Arg Phe Ser Gly
    50                  55                  60
Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Asn Asn Ile Glu Ser
65                  70                  75                  80
Glu Asp Ala Ala Tyr Tyr Phe Cys Gln Gln His Asp Glu Ser Pro Tyr
                85                  90                  95
Thr Phe Gly Glu Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 86
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 86

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ala Thr Tyr
            20                  25                  30
Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Tyr Ile Tyr Pro Gly Asp Gly Asn Ala Asn Tyr Asn Gln Gln Phe
    50                  55                  60
```

```
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Asp Phe Asp Tyr Asp Gly Gly Tyr Tyr Phe Asp Ser Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 87
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 87

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
His Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His His Tyr Gly Ala Pro Leu
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 88
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 88

```
Asp Tyr Tyr Ile
 1
```

<210> 89
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 89
Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe Gln
 1   5   10   15
Gly

<210> 90
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 90
Asn Ser Gly Ser Tyr Ser Phe Gly Tyr
 1   5

<210> 91
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 91
Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
 1   5   10

<210> 92
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 92
Gly Ala Ser Ser Leu Gln Ser
 1   5