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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2017 (21.12.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/218714 A1

(51) International Patent Classification:
A01K 67/027 (2006.01) *C12N 15/85* (2006.01)
C12N 15/12 (2006.01)

(21) International Application Number:
PCT/US2017/037566

(22) International Filing Date:
14 June 2017 (14.06.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/350,048 14 June 2016 (14.06.2016) US

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

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

Published:
— *with international search report (Art. 21(3))*

WO 2017/218714 A1

(54) Title: GENETICALLY MODIFIED CELLS, TISSUES, AND ORGANS FOR TREATING DISEASE

(57) Abstract: Genetically modified cells, tissues, and organs for treating or preventing diseases are disclosed. Also disclosed are methods of making the genetically modified cells and non-human animals. The genetic modification may include a nucleic acid that is transcribed as a human leukocyte antigen G (HLA-G) mRNA comprising a deletion in the 3 ' untranslated region, or a nucleic acid comprising a CD47 gene that is codon-optimized for expression in pig cells.

GENETICALLY MODIFIED CELLS, TISSUES, AND ORGANS FOR TREATING DISEASE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/350,048, filed June 14, 2016, which application is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] There is a shortage of organs, tissues or cells available for transplantation in recipients such as humans. Xenotransplantation or allotransplantation of organs, tissues, or cells into humans has the potential to fulfill this need and help hundreds of thousands of people every year. Non-human animals can be chosen as organ donors based on their anatomical and physiological similarities to humans. Additionally, xenotransplantation has implications not only in humans, but also in veterinary applications.

[0003] However, unmodified wild-type non-human animal tissues can be rejected by recipients, such as humans, by the immune system. Rejection is believed to be caused at least in part by antibodies binding to the tissues and cell-mediated immunity leading to graft loss. For example, pig grafts can be rejected by cellular mechanisms mediated by adaptive immune cells.

INCORPORATION BY REFERENCE

[0004] All publications, patents, and patent applications herein are incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. In the event of a conflict between a term herein and a term in an incorporated reference, the term herein controls.

SUMMARY

[0005] In a first aspect, disclosed herein are genetically modified non-human animals comprising an exogenous nucleic acid sequence at least 95% identical to SEQ ID NO: 359 or SEQ ID NO: 502.

[0006] In some embodiments of the first aspect, the exogenous nucleic acid is at least 96% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the exogenous nucleic acid is at least 97% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the

exogenous nucleic acid is at least 98% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the exogenous nucleic acid is at least 99% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the exogenous nucleic acid is 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.

[0007] In a second aspect, disclosed herein are genetically modified non-human animals comprising an exogenous nucleic acid that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region.

[0008] In some embodiments of the second aspect, the modified 3' untranslated region comprises one or more deletions. In some embodiments, the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA. In some embodiments, the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7. In some embodiments, the HLA-G is HLA-G1. In some embodiments, the HLA-G is HLA-G2.

[0009] In some embodiments of the first or second aspect, at least one cell of the genetically modified non-human animal expresses a HLA-G protein. In some embodiments, the HLA-G protein is HLA-G1.

[0010] Some embodiments of the first or second aspect further comprise a second exogenous nucleic acid that encodes for a β-2-microglobulin (B2M) protein. In some embodiments, the B2M protein is a human B2M protein.

[0011] In a third aspect, disclosed herein are genetically modified non-human animals comprising an exogenous nucleic acid sequence at least 75% identical to SEQ ID NO: 240.

[0012] In some embodiments of the third aspect, the exogenous nucleic acid sequence is at least 80% identical to SEQ ID NO: 240. In some embodiments, the exogenous nucleic acid sequence is at least 85% identical to SEQ ID NO: 240. In some embodiments, the exogenous nucleic acid sequence is at least 90% identical to SEQ ID NO: 240. In some embodiments, the exogenous nucleic acid sequence is at least 95% identical to SEQ ID NO: 240. In some embodiments, the exogenous nucleic acid sequence is identical to SEQ ID NO: 240.

[0013] In some embodiments of the third aspect, at least one cell of the genetically modified non-human animal expresses a human CD47 protein.

[0014] Some embodiments of the third aspect further comprise a second exogenous nucleic acid sequence that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region. In some embodiments, the modified 3' untranslated region comprises one or

more deletions. In some embodiments, the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA. In some embodiments, the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7. In some embodiments, the HLA-G is HLA-G1. In some embodiments, the HLA-G is HLA-G2.

[0015] In some embodiments of the third aspect, the second exogenous nucleic acid sequence is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.

[0016] In some embodiments of the first, second, or third aspects, the exogenous nucleic acid sequence is operatively linked to a constitutively active endogenous promoter.

[0017] In some embodiments of the first, second, or third aspects, the exogenous nucleic acid sequence is inserted in the genetically modified non-human animal's genome at a ROSA 26 gene site.

[0018] In some embodiments of the first, second, or third aspects, the exogenous nucleic acid sequence is inserted in the genetically modified non-human animal's genome at a site effective to reduce expression of a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a NOD-like receptor family CARD domain containing 5 (NLRC5), or a combination thereof in comparison to: an animal of the same species without the exogenous nucleic acid sequence or an animal of the same species with the exogenous nucleic acid inserted in a different site.

[0019] In some embodiments of the first, second, or third aspects, the exogenous nucleic acid sequence is inserted in the genetically modified non-human animal's genome at the site effective to reduce expression of the glycoprotein galactosyltransferase alpha 1,3 (GGTA1).

[0020] In some embodiments of the first, second, or third aspects, the genetically modified non-human animal further comprises a genomic disruption in one or more genes selected from the list consisting of: a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a NOD-like receptor family CARD domain containing 5 (NLRC5), and any combination thereof.

[0021] In some embodiments of the first, second, or third aspects, the genetically modified non-human animal further comprises a genomic disruption in one or more genes selected from the list consisting of: a component of an MHC I-specific enhanceosome, a transporter of an MHC I-binding peptide, a natural killer (NK) group 2D ligand, a CXC chemokine receptor (CXCR)3 ligand, MHC II transactivator (CIITA), C3, an endogenous gene not expressed in a human, and any combination thereof. Some embodiments comprise the genomic disruption of the component of a MHC I-specific enhanceosome, wherein the component of a MHC I-specific enhanceosome is NOD-like receptor family CARD domain containing 5 (NLRC5). Some embodiments comprise the genomic disruption of the transporter of a MHC I-binding peptide, wherein the transporter is transporter associated with antigen processing 1 (TAP1). Some embodiments comprise the genomic disruption of C3. Some embodiments comprise the genomic disruption of the NK group 2D ligand, wherein the NK group 2D ligand is MHC class I polypeptide-related sequence A (MICA) or MHC class I polypeptide-related sequence B (MICB). Some embodiments comprise the genomic disruption of the endogenous gene not expressed in a human, wherein the endogenous gene not expressed in a human is glycoprotein galactosyltransferase alpha 1,3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), or β1,4 N-acetylgalactosaminyltransferase (B4GALNT2). Some embodiments comprise the genomic disruption of the CXCR3 ligand, wherein the CXCR3 ligand is C-X-C motif chemokine 10 (CXCL10).

[0022] In some embodiments, the genomic disruption reduces expression of the disrupted gene in comparison to an animal of the same species without the genomic disruption.

[0023] In some embodiments, the the genomic disruption reduces protein expression from the disrupted gene in comparison to an animal of the same species without the genomic disruption.

[0024] Some embodiments of the first, second, or third aspect further comprise an additional exogenous nucleic acid sequence encoding an infected cell protein 47 (ICP47).

[0025] In some embodiments of the first, second, or third aspect, the genetically modified non-human animal is a member of the Laurasiatheria superorder.

[0026] In some embodiments of the first, second, or third aspect, the genetically modified non-human animal is an ungulate.

[0027] In some embodiments of the first, second, or third aspect, the genetically modified non-human animal is a pig.

[0028] In some embodiments of the first, second, or third aspect, the genetically modified non-human animal is a non- human primate.

[0029] In some embodiments of the first, second, or third aspect, the genetically modified non-human animal is fetus.

[0030] Also disclosed herein are cells isolated from the genetically modified non-human animal of any embodiments of the first, second, or third aspects. In some embodiments, the cell is an islet cell. In some embodiments, the cell is a stem cell.

[0031] Also disclosed herein are tissues isolated from the genetically modified non-human animal of any embodiments of the first, second, or third aspects. In some embodiments, the tissue is a solid organ transplant. In some embodiments, the tissue is all or a portion of a liver. In some embodiments, the tissue is all or a portion of a kidney.

[0032] In a fourth aspect, disclosed herein are non-human cells comprising an exogenous nucleic acid sequence at least 95% identical to SEQ ID NO: 359 or SEQ ID NO: 502.

[0033] In some embodiments of the fourth aspect, the exogenous nucleic acid is at least 96% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the exogenous nucleic acid is at least 97% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the exogenous nucleic acid is at least 98% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the exogenous nucleic acid is at least 90% identical to SEQ ID NO: 359 or SEQ ID NO: 502. In some embodiments, the exogenous nucleic acid is 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.

[0034] In some embodiments of the fourth aspect, the non-human cell expresses human leukocyte antigen G1 (HLA-G1) on the cell surface.

[0035] In a fifth aspect, disclosed herein are non-human cells comprising an exogenous nucleic acid that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region.

[0036] In some embodiments of the fifth aspect, the modified 3' untranslated region comprises one or more deletions. In some embodiments, the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA.

[0037] In some embodiments of the fifth aspect, the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7. In some embodiments, the HLA-G is HLA-G1. In some embodiments, the HLA-G is HLA-G2.

[0038] In some embodiments of the fourth or fifth aspect, the non-human cell further comprises a second exogenous nucleic acid that encodes for a β-2-microglobulin (B2M) protein. In some embodiments, the B2M protein is a human B2M protein.

[0039] In a sixth aspect, disclosed herein are non-human cells comprising an exogenous nucleic acid at least 75% identical to SEQ ID NO: 240.

[0040] In some embodiments of the sixth aspect, the exogenous nucleic acid sequence is at least 80% identical to SEQ ID NO: 240.

[0041] In some embodiments, the exogenous nucleic acid sequence is at least 85% identical to SEQ ID NO: 240. In some embodiments, the exogenous nucleic acid sequence is at least 90% identical to SEQ ID NO: 240. In some embodiments, the exogenous nucleic acid sequence is at least 95% identical to SEQ ID NO: 240. In some embodiments, the exogenous nucleic acid sequence is 100% identical to SEQ ID NO: 240.

[0042] In some embodiments of the sixth aspect, the at least one non-human cell expresses a human CD47 protein.

[0043] In some embodiments of the sixth aspect, the non-human cell further comprises a second exogenous nucleic acid sequence that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region. In some embodiments, the modified 3' untranslated region comprises one or more deletions. In some embodiments, the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA. In some embodiments, the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7. In some embodiments, the HLA-G is HLA-G1. In some embodiments, the HLA-G is HLA-G2.In some embodiments, the second exogenous nucleic acid sequence is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.

[0044] In some embodiments of the fourth, fifth, or sixth aspects, the exogenous nucleic acid sequence is operatively linked to a constitutively active endogenous promoter.

[0045] In some embodiments of the fourth, fifth, or sixth aspects, the exogenous nucleic acid sequence is inserted in the non-human cell's genome at a ROSA 26 gene site.

[0046] In some embodiments of the fourth, fifth, or sixth aspects, the exogenous nucleic acid sequence is inserted in the non-human cell's genome at a site effective to reduce expression of a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a

MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a NOD-like receptor family CARD domain containing 5 (NLRC5), or a combination thereof in comparison to: a cell of the same species without the exogenous nucleic acid sequence or a cell of the same species wherein the exogenous nucleic acid is inserted in a different site.

[0047] In some embodiments of the fourth, fifth, or sixth aspects, the exogenous nucleic acid sequence is inserted in the non-human cell's genome at a site that reduces expression of a glycoprotein galactosyltransferase alpha 1,3 (GGTA1).

[0048] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell further comprises a genomic disruption in one or more genes selected from the list consisting of: a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a NOD-like receptor family CARD domain containing 5 (NLRC5), and any combination thereof.

[0049] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell further comprises a genomic disruption in one or more genes selected from the list consisting of: a component of an MHC I-specific enhanceosome, a transporter of an MHC I-binding peptide, a natural killer (NK) group 2D ligand, a CXC chemokine receptor (CXCR)3 ligand, MHC II transactivator (CIITA), C3, an endogenous gene not expressed in a human, and any combination thereof. In some embodiments, the non-human cell comprises the genomic disruption of the component of a MHC I-specific enhanceosome, wherein the component of a MHC I-specific enhanceosome is NOD-like receptor family CARD domain containing 5 (NLRC5). In some embodiments, the non-human cell comprises the genomic disruption of the transporter of a MHC I-binding peptide, wherein the transporter is transporter associated with antigen processing 1 (TAP1)

[0050] In some embodiments, the non-human cell comprises the genomic disruption of C3.

[0051] In some embodiments, the non-human cell comprises the genomic disruption of the NK group 2D ligand, wherein the NK group 2D ligand is MHC class I polypeptide-related sequence A (MICA) or MHC class I polypeptide-related sequence B (MICB).

[0052] In some embodiments, the non-human cell comprises the genomic disruption of the endogenous gene not expressed in a human, wherein the endogenous gene not expressed in a

human is glycoprotein galactosyltransferase alpha 1,3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), or β1,4 N-acetylgalactosaminyltransferase (B4GALNT2). In some embodiments, the non-human cell comprises the genomic disruption of a CXCR3 ligand, wherein the CXCR3 ligand is C-X-C motif chemokine 10 (CXCL10). In some embodiments, the genomic disruption reduces expression of the disrupted gene in comparison to a cell from the same species without the genomic disruption.

[0053] In some embodiments, the genomic disruption reduces protein expression from the disrupted gene in comparison to a cell from the same species without the genomic disruption.

[0054] Some embodiments of the fourth, fifth, or sixth aspects further comprise an additional exogenous nucleic acid sequence encoding an infected cell protein 47 (ICP47).

[0055] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell is a Laurasiatheria superorder cell.

[0056] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell is an ungulate cell.

[0057] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell is a pig cell.

[0058] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell is a non-human primate cell.

[0059] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell is a fetal cell.

[0060] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell is a stem cell.

[0061] In some embodiments of the fourth, fifth, or sixth aspects, the non-human cell is an islet cell.

[0062] Also disclosed herein are solid organ transplants comprising the non-human cell of any embodiment of the fourth, fifth, or sixth aspects.

[0063] Also disclosed herein are embryos comprising the non-human cell of any embodiment of the fourth, fifth, or sixth aspects.

[0064] In a seventh aspect, disclosed herein are methods comprising providing to a subject, at least one non-human cell of any embodiment of the fourth, fifth, or sixth aspects. In some

embodiments, the at least one non-human cell is a solid organ transplant. In some embodiments, the at least one non-human cell is a stem cell transplant. In some embodiments, the at least one non-human cell is an islet cell transplant.

[0065] Some embodiments of the seventh aspect comprise providing to the subject a tolerizing vaccine. In some embodiments, the tolerizing vaccine is provided prior to, concurrently with, or after the at least one non-human cell is provided to the subject. In some embodiments, the tolerizing vaccine comprises apoptotic cells. In some embodiments, the tolerizing vaccine comprises cells from the same species as the at least one non-human cell provided to the subject. In some embodiments, the tolerizing vaccine comprises cells that are genetically identical to the at least one non-human cell provided to the subject.

[0066] Some embodiments of the seventh aspect comprise providing an anti-CD40 antibody to the subject. In some embodiments, the anti-CD40 antibody is provided prior to, concurrently with, or after the at least one non-human cell is provided to the subject. In some embodiments, the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 487. In some embodiments, the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 488.

[0067] In an eight aspect, disclosed herein are systems for xenotransplantation comprising: a) at least one cell isolated from the genetically modified non-human animal of any embodiment of the first, second or third aspects; and b) a tolerizing vaccine, anti-CD40 antibody, or a combination thereof. In some embodiments, the at least one cell comprises an islet cell, a stem cell, or a combination thereof. In some embodiments, the at least one cell is a solid organ transplant. In some embodiments, the at least one cell is all or a portion of a liver. In some embodiments, the at least one cell is all or a portion of a kidney.

[0068] Some embodiments of the eighth aspect comprise the tolerizing vaccine. In some embodiments, the tolerizing vaccine comprises apoptotic cells. In some embodiments, the tolerizing vaccine comprises cells from the same species as the at least one cell. In some embodiments, the tolerizing vaccine comprises cells that are genetically identical to the at least one cell.

[0069] Some embodiments of the eighth aspect comprise or further comprise the anti-CD40 antibody. In some embodiments, the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 487. In some embodiments, the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 488.

[0070] In a ninth aspect, disclosed herein are systems for xenotransplantation comprising: a) at least one non-human cell of any one of claims 58-108; and b) a tolerizing vaccine, an anti-CD40 antibody, or a combination thereof. In some embodiments, the at least one cell comprises an islet cell, a stem cell, or a combination thereof. In some embodiments, the at least one cell is a solid organ transplant. In some embodiments, the at least one cell is all or a portion of a liver. In some embodiments, the at least one cell is all or a portion of a kidney.

[0071] Some embodiments of the ninth aspect comprise the tolerizing vaccine. In some embodiments, the tolerizing vaccine comprises apoptotic cells. In some embodiments, the tolerizing vaccine comprises cells from the same species as the at least one cell. In some embodiments, the tolerizing vaccine comprises cells that are genetically identical to the at least one cell.

[0072] Some embodiments of the ninth aspect comprise or further comprise the anti-CD40 antibody. In some embodiments, the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 487. In some embodiments, the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 488.

[0073]

[0074] Provided herein are methods comprising providing to an individual at least one engineered cell; wherein said engineered cell comprises at least two genomic modification resulting in inhibition of the immune response of said individual to said at least one engineered cell as measured by reduced effector function of at least one endogenous cell selected from a group consisting of T cells, B cells, monocytes, macrophages, Natural Killer (NK) cells, dendritic cells, and a combination thereof; and/or by increased immune cell regulation of at least one endogenous cell selected from a group including but not limited to CD4+ regulatory T cells, CD8+ regulatory T cells, CD8+ natural suppressor cells, Tr1 cells, regulatory B cells, B10 cells, myeloid-derived suppressor cells, and any combination thereof, as compared to an immune response of an individual contacted with a non-engineered counterpart cell. In some cases, the at least one engineered cell can be a solid organ transplant. In other cases, at least one engineered cell can be a stem cell transplant. In some cases, at least one engineered cell can be an islet cell transplant. An individual can be tolerized to an at least one engineered cell. In some cases, tolerization can occur before, during or, after an at least one engineered cell can be provided to an individual.

[0075] In some cases, tolerization can be facilitated by an administration of a vaccine. In some cases, tolerization can be an administration of at least one engineered cell. In some cases,

tolerization can be an administration of a vaccine and administration of at least one engineered cell. A vaccine can comprise apoptotic cells. A vaccine can also comprise viable cells. In some cases, reduced effector function can be selected from a group consisting of reduced proliferation; reduced cytokine expression, reduced expression of cytolytic effector molecules, reduced persistence, deletion, induction of anergy, increased immune cell regulation, and any combination thereof in response to exposure to said at least one engineered cell.

[0076] Disclosed herein can also be administering to an individual at least one additional treatment step. In some cases, at least one additional treatment step can be an immunosuppressive therapy. An immunosuppressive therapy can be selected from a group consisting of an anti-CD40 antibody, an anti-CD20 antibody, an anti-IL6 receptor antibody, $C_{51}H_{79}NO_{13}$ (Rapamycin), soluble tumor necrosis factor receptor (sTNFR), $C_{66}H_{99}N_{23}O_{17}S_2$ (compstatin), and any combination thereof. An individual may not be sensitized to a major histocompatibility complex (MHC). The anti-CD40 antibody can be an antagonistic antibody. The anti-CD40 antibody can be an anti-CD40 antibody that specifically binds to an epitope within the amino acid sequence: EPPTACREKQYLINSQCCSLCQPGQKLVSDCTEFTETECLPCGESEFLDTWNRETHCHQH KYCDPNLGLRVQQKGTSETDTICTCEEGWHCTSEACESCV (SEQ ID NO: 487). The anti-CD40 antibody can be an anti-CD40 antibody that specifically binds to an epitope within the amino acid sequence: EKQYLINSQCCSLCQPGQKLVSDCTEFTETECL (SEQ ID NO: 488).The anti-CD40 antibody can be a Fab' anti-CD40L monoclonal antibody fragment CDP7657. The anti-CD-40 antibody can be a FcR-engineered, Fc silent anti-CD40L monoclonal domain antibody. In some cases, an individual can be sensitized to a major histocompatibility complex (MHC). MHC can be human leukocyte antigen (HLA). An individual can be sensitized to a major histocompatibility complex (MHC) as determined by a positive response to a panel reactive antibody (PRA) screen analysis.

[0077] In some cases, an individual can have a calculated panel reactive antibody (cPRA) score from 0.1 to 100%. In some cases, a reduced effector function can be a reduced effector function of at least two endogenous cell types selected from a group consisting of T cells, B cells, monocytes, macrophages, Natural Killer (NK) cells, dendritic cells, and any combination thereof. A genome modification can be a gene disruption, deletion, induction of anergy, increased immune cell regulation, or a combination thereof. A gene can be selected from a group consisting of a C-X-C motif chemokine 10 (CXCL10), transporter associated with antigen processing 1 (TAP1), NOD-like receptor family CARD domain containing 5 (NLRC5), and any combination thereof. In some cases, an at least one engineered cell is a xenograft.

[0078] Disclosed herein can be an engineered polynucleic acid comprising at least two sequences encoding targeting oligonucleotides; wherein said targeting oligonucleotides comprise complementary sequences to at least one non-human genome sequence adjacent to a protospacer adjacent motif (PAM) sequence. In some cases, targeting oligonucleotides can be guide RNAs (gRNAs). A gRNA can comprise complementary sequences to a gene selected from a group consisting of GGTA1, Gal2-2, NLRC5, and any combination thereof. In some cases, gRNAs can comprise complementary sequences to GGTA1 and/or Gal2. A gRNA can comprise complementary sequences to NLRC5 and Gal2. In some cases, a targeting oligonucleotide can bind a first exon of said gene. A non-human genome can be a *Laurasiatheria* superorder animal or can be from a non-human primate. A *Laurasiatheria* super order animal can be an ungulate. In some cases, an ungulate can be a pig. A PAM sequence can be 5'-NGG-3' (SEQ ID NO: 265).

[0079] In some cases, a guide RNA can comprise at least one modification. A modification can be selected from a group consisting of 5'adenylate, 5' guanosine-triphosphate cap, 5'N^7-Methylguanosine-triphosphate cap, 5'triphosphate cap, 3'phosphate, 3'thiophosphate, 5'phosphate, 5'thiophosphate, Cis-Syn thymidine dimer, trimers, C12 spacer, C3 spacer, C6 spacer, dSpacer, PC spacer, rSpacer, Spacer 18, Spacer 9,3'-3' modifications, 5'-5' modifications, abasic, acridine, azobenzene, biotin, biotin BB, biotin TEG, cholesteryl TEG, desthiobiotin TEG, DNP TEG, DNP-X, DOTA, dT-Biotin, dual biotin, PC biotin, psoralen C2, psoralen C6, TINA, 3'DABCYL, black hole quencher 1, black hole quencer 2, DABCYL SE, dT-DABCYL, IRDye QC-1, QSY-21, QSY-35, QSY-7, QSY-9, carboxyl linker, thiol linkers, 2'deoxyribonucleoside analog purine, 2'deoxyribonucleoside analog pyrimidine, ribonucleoside analog, 2'-0-methyl ribonucleoside analog, sugar modified analogs, wobble/universal bases, fluorescent dye label, 2'fluoro RNA, 2'O-methyl RNA, methylphosphonate, phosphodiester DNA, phosphodiester RNA, phosphothioate DNA, phosphorothioate RNA, UNA, pseudouridine-5'-triphosphate, 5-methylcytidine-5'-triphosphate, and any combination thereof.

[0080] Disclosed herein can be a graft for xenotransplantation comprising at least one genomic disruption of SEQ ID NO: 261.

[0081] Disclosed herein can be a graft for xenotransplantation comprising at least one genomic disruption of SEQ ID NO: 262.

[0082] In some cases, a graft for xenotransplantation can further comprise at least one transgene. A transgene can be endogenous. A transgene can be engineered. A transgene can encode a human leukocyte antigen (HLA). An HLA can be HLA-G. A transgene can be CD47.

[0083] Provided herein is a genetically modified animal having a genomic disruption in two or more genes selected from a group consisting of: a component of an MHC I-specific enhanceosome, a transporter of an MHC I-binding peptide, a natural killer (NK) group 2D ligand, a CXC chemokine receptor (CXCR)3 ligand, MHC II transactivator (CIITA), C3, an endogenous gene not expressed in a human, and any combination thereof, wherein said genetically modified animal has reduced expression of said gene in comparison to a non-genetically modified counterpart animal. In some cases, a genetically modified animal can be a member of the *Laurasiatheria* superorder, wherein said member of the *Laurasiatheria* super order is an ungulate. An ungulate can be a pig.

[0084] In some cases, protein expression of said two or more genes can be absent in a genetically modified animal. In some cases, reduction of protein expression inactivates a function of said two or more genes. In some cases, a genetically modified animal can have reduced protein expression of three or more genes. A genetically modified animal can have reduced protein expression of a component of a MHC I-specific enhanceosome, wherein a component of a MHC I-specific enhanceosome can be a NOD-like receptor family CARD domain containing 5 (NLRC5). A genetically modified animal can comprise reduced protein expression of a transporter of a MHC I-binding peptide, wherein a transporter can be a transporter associated with antigen processing 1 (TAP1).

[0085] In some cases, a genetically modified animal can comprise reduced protein expression of C3. In some cases, a reduction of protein expression can inactivate a function of two or more genes. In some cases, a reduced protein expression of a NK group 2D ligand can be an MHC class I polypeptide-related sequence A (MICA) or MHC class I polypeptide-related sequence B (MICB). In some cases, reduced protein expression of an endogenous gene may not be expressed in a human, wherein said endogenous gene may not be expressed in a human can be glycoprotein galactosyltransferase alpha 1,3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), or β1,4 N-acetylgalactosaminyltransferase (B4GALNT2).

[0086] In some genetically modified animals described herein, is at least two genomic disruptions resulting in a reduced protein expression of a CXCR3 ligand, which can be C-X-C motif chemokine 10 (CXCL10).

[0087] Provided herein is at least one genetically modified animal further comprising one or more exogenous transgenes encoding at least one protein or functional fragment thereof, wherein said at least one protein is selected from an MHC I formation suppressor, a regulator of

complement activation, an inhibitory ligand for NK cells, a B7 family member, CD47, a serine protease inhibitor, galectin, and any combination thereof.

[0088] In some cases, the at least one protein can be at least one human protein. One or more exogenous transgenes encoding an MHC I formation suppressor can be infected cell protein 47 (ICP47). In some cases, one or more exogenous transgenes encoding a regulator of complement activation can be cluster of differentiation 46 (CD46), cluster of differentiation 55 (CD55), or cluster of differentiation 59 (CD59). In some cases, one or more exogenous transgenes encoding an inhibitory ligand for NK cells can be leukocyte antigen E (HLA-E), human leukocyte antigen G (HLA-G), or β-2-microglobulin (B2M). In other cases, one or more exogenous transgenes encoding HLA-G, wherein HLA-G can be HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7. In some cases, HLA-G can be HLA-G1.

[0089] In some genetically modified animal provided herein, are provided one or more exogenous transgenes encoding a B7 family member, wherein a B7 family member can be a programed death-ligand. A programed death-ligand can be programed death-ligand 1 (PD-L1) or programed death-ligand 2 (PD-L2). In some cases, one or more exogenous transgenes can encode both PD-L1 and PD-L2. In some cases, one or more exogenous transgenes can encode a serine protease inhibitor, wherein the serine protease inhibitor can be serine protease inhibitor 9 (Spi9). In some cases, one or more exogenous transgenes can encode a galectin, wherein the galectin can be galectin-9. In some cases, one or more exogenous transgenes can be inserted adjacent to a ubiquitous promoter. A ubiquitous promoter can be a Rosa26 promoter.

[0090] In some cases, one or more exogenous transgenes can be inserted adjacent to a promoter of a targeted gene, within said targeted gene, or adjacent to a protospacer adjacent motif (PAM) sequence. In some cases, protein expression of two or more genes can be reduced using a CRISPR/Cas system.

[0091] Provided herein is a genetically modified animal having a genomic disruption in at least one gene selected from a group consisting of a component of an MHC I-specific enhanceosome, a transporter of an MHC I-binding peptide, a natural killer (NK) group 2D ligand, a CXC chemokine receptor (CXCR) 3 ligand, MHC II transactivator (CIITA), C3, an endogenous gene not expressed in a human, and any combination thereof, wherein said genetically modified animal has reduced expression of said gene in comparison to a non-genetically modified counterpart animal and said genetically modified animal survives at least 22 days after birth. In some cases, a genetically modified animal can survive at least 23 days, 30 days, 35 days, 50 days, 70 days, 100 days, 150 days, 200 days, 250 days, 300 days, 350 days or 400 days after birth.

BRIEF DESCRIPTION OF THE DRAWINGS

[0092] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0093] FIG. 1 demonstrates an immunotherapeutic strategy centered on the use of genetically modified cell and organ grafts lacking functional expression of MHC class I. The need for maintenance immunosuppression required for the prevention of graft rejection is progressively reduced (or the applicability of transplantation of cell and organ xenografts and the transplantation of stem cell-derived cellular allografts and xenografts is progressively increased) when the transplantation of genetically modified cells and organs is combined with transient use of antagonistic anti-CD40 antibodies and even more when combined with the administration of tolerizing vaccines comprising apoptotic donor cells under the cover of anti-CD40 antibodies.

[0094] FIG. 2 demonstrates one strategy of making genetically modified pig islet cells and tolerizing vaccines. Two clonal populations of pigs are created. One population having at least GGTA1 knocked out can be used to create a tolerizing vaccine. The other clonal population of pigs that have at least GGTA1 and MHC I genes (*e.g.,* NRLC5) knocked out can be used for cell, tissues, and/or organ donors.

[0095] FIG. 3 demonstrates use of positive and tolerizing vaccines (also referred to as a negative vaccine).

[0096] FIG. 4 demonstrates an exemplary approach to extending the survival of xenografts in a subject with infusion of apoptotic donor splenocytes for tolerizing vaccination under the cover of transient immunosuppression.

[0097] FIG. 5 shows an exemplary approach to preventing rejection or extending survival of xenografts in a recipient in the absence of chronic and generalized immunosuppression of the xenograft recipient. This exemplary approach includes and integrates three components: i) genetically engineered islets with deficient and/or reduced expression of αGal, MHC class I, complement C3, and CXCL10 and transgenic expression of HLA-G; ii) genetically engineered donor apoptotic and non-apoptotic mononuclear cells (*e.g.,* splenocytes) with deficient and/or reduced expression of αGal, Neu5Gc, and Sda/CAD as well as transgenic expression of HLA-G with or without human CD47, human PD-L1, human PD-L2 (*e.g.,* the genetically engineered vaccine); and iii) the administration of transient immunosuppression including antagonistic anti-CD40 mAb, anti-CD20 mAb, rapamycin, and transient anti-inflammatory therapy including

compstatin (*e.g.,* the compstatin derivative APL-2), anti-IL-6 receptor mAb, and soluble TNF receptor.

[0098] FIG. 6 demonstrates an exemplary protocol for transplant rejection prophylaxis in a pig-to-cynomolgus monkey islet xenotransplantation. IE: islet equivalent; sTNFR: soluble TNF receptor (*e.g.,* etanercept); α-IL-6R: anti-interleukin 6 receptor; Tx'd: transplanted.

[0099] FIGs. 7A-7E demonstrate a strategy for cloning a px330-Gal2-1 plasmid targeting GGTA1. **FIG. 7A** shows a cloning strategy and oligonucleotides (SEQ ID NOs: 266-267, respectively, in order of appearance) for making a guide RNA targeting GGTA1. **FIG. 7B** shows an insertion site on the px330 plasmid (SEQ ID NO: 268). **FIG. 7C** shows a flow chart demonstrating the cloning and verification strategy. **FIG. 7D** shows a cloning site (SEQ ID NO: 270) and sequencing primers (SEQ ID NOs: 269 and 271, respectively, in order of appearance). **FIG. 7E** shows sequencing results (SEQ ID NOs: 272-274 respectively, in order of appearance).

[00100] FIGs. 8A-8E demonstrate a strategy for cloning a px330-CM1F plasmid targeting CMAH. **FIG. 8A** shows a cloning strategy and oligonucleotides (SEQ ID NOs: 275 and 276, respectively, in order of appearance) for making a guide RNA targeting CMAH1. **FIG. 8B** shows an insertion site on the px330 plasmid (SEQ ID NO: 277). **FIG. 8C** shows a flow chart demonstrating the cloning and verification strategy. **FIG. 8D** shows a cloning site (SEQ ID NO: 279) and sequencing primers (SEQ ID NOs: 278 and 280, respectively, in order of appearance). **FIG. 8E** shows sequencing results (SEQ ID NOs: 281-283, respectively, in order of appearance).

[00101] FIGs. 9A-9E demonstrate a strategy for cloning a px330-NL1_FIRST plasmid targeting NLRC5. **FIG. 9A** shows a cloning strategy and oligonucleotides (SEQ ID NOs: 284 and 285, respectively, in order of appearance) for making a guide RNA targeting NLRC5. **FIG. 9B** shows an insertion site on the px330 plasmid (SEQ ID NO: 286). **FIG. 9C** shows a flow chart demonstrating the cloning and verification strategy. **FIG. 9D** shows a cloning site (SEQ ID NO: 288) and sequencing primers (SEQ ID NOs: 287 and 289, respectively, in order of appearance). **FIG. 9E** shows sequencing results (SEQ ID NOs: 290-292, respectively, in order of appearance).

[00102] FIGs. 10A-10E demonstrate a strategy for cloning a px330/C3-5 plasmid targeting C3. **FIG. 10A** shows a cloning strategy and oligonucleotides (SEQ ID NOs: 293 and 294, respectively, in order of appearance) for making a guide RNA targeting C3. **FIG. 10B** shows an insertion site on the px330 plasmid (SEQ ID NO: 295). **FIG. 10C** shows a flow chart demonstrating the cloning and verification strategy. **FIG. 10D** shows a cloning site (SEQ ID NO: 297) and sequencing primers (SEQ ID NOs: 296 and 298, respectively, in order of

appearance). **FIG. 10E** shows sequencing results (SEQ ID NOs: 299-301, respectively, in order of appearance).

[00103] FIGs. 11A-11E demonstrate a strategy for cloning a px330/B41_second plasmid targeting B4GALNT2. **FIG. 11A** shows a cloning strategy and oligonucleotides (SEQ ID NOs: 302 and 303, respectively, in order of appearance)for making a guide RNA targeting B4GALNT2. **FIG. 11B** shows an insertion site on the px330 plasmid (SEQ ID NO: 304). **FIG. 11C** shows a flow chart demonstrating the cloning and verification strategy. **FIG. 11D** shows a cloning site (SEQ ID NO: 306) and sequencing primers (SEQ ID NOs: 305 and 307, respectively, in order of appearance). **FIG. 11E** shows sequencing results (SEQ ID NOs: 308-310, respectively, in order of appearance).

[00104] FIG. 12 demonstrates a map of Rosa26 locus sequenced in Example 2.

[00105] FIGs. 13A-13E demonstrates a strategy for cloning a px330/Rosa exon 1 plasmid targeting Rosa26. **FIG. 13A** shows a cloning strategy and oligonucleotides (SEQ ID NOs: 311-312, respectively, in order of appearance) for making a guide RNA targeting Rosa26. **FIG. 13B** shows an insertion site on the px330 plasmid (SEQ ID NO: 313). **FIG. 13C** shows a flow chart demonstrating the cloning and verification strategy. **FIG. 13D** shows a cloning site (SEQ ID NO: 315) and sequencing primers (SEQ ID NOs: 314 and 316, respectively, in order of appearance). **FIG. 13E** shows sequencing results (SEQ ID NOs: 317-319, respectively, in order of appearance).

[00106] FIG. 14A shows a map of the genomic sequence of HLA-G. **FIG. 14B** shows a map of the cDNA sequence of HLA-G.

[00107] FIG. 15 shows an exemplary microscopic view of porcine fetal fibroblasts transfected with pSpCas9(BB)-2A-GFP.

[00108] FIG. 16 shows a fluorescence *in situ* hybridization (FISH) to the GGTA1 gene by specific probes revealing the location on chromosome 1.

[00109] FIGs. 17A-17B demonstrate an example of phenotypic selection of cells with cas9/sgRNA-mediated GGTA1/NLCR5 disruption. **FIG. 17A** shows genetically modified cells, which do not express alpha-galactosidase. **FIG. 17B** shows non-genetically modified cells, which express alpha-galactosidase and were labeled with isolectin B4 (IB)-linked ferrous beads.

[00110] FIGs. 18A- 18B show sequencing of DNA isolated from fetal cells of two separate litters (Pregnancy 1: **FIG. 18A** or Pregnancy 2: **FIG. 18B**) subjected to PCR amplification of the GGTA1 (compared to *Sus scrofa* breed mixed chromosome 1, Sscrofa10.2 NCBI Reference

Sequence: NC_010443.4) target regions and the resulting amplicons were separated on 1% agarose gels. Amplicons were also analyzed by Sanger sequencing using the forward primer alone from each reaction. In **FIG. 18A**, the results are shown, aligned to reference and target gene sequences (SEQ ID NOs: 320-321, respectively), for fetuses 1-7 (SEQ ID NOs: 322-328, respectively) from Pregnancy 1's fetuses. Fetuses 1, 2, 4, 5, 6, and 7, were truncated 6 nucleotides after the target site for GGTA1. Fetus 3 was truncated 17 nucleotides after the cut site followed by a 2,511 (668-3179) nucleotide deletion followed by a single base substitution. Truncation, deletion and substitution from a single sequencing experiment containing the alleles from both copies of the target gene can only suggest a gene modification has occurred but not reveal the exact sequence for each allele. From this analysis it appears that all 7 fetuses have a single allele modification for GGTA1. In **FIG. 18B**, the results are shown, aligned to reference and target gene sequences (SEQ ID NOs: 329-330, respectively), for fetuses 1-5 (SEQ ID NOs: 331-335, respectively) from pregnancy 2 fetal DNA samples. Fetuses 1, 3, 4, and 5 were truncated 3 nucleotides from the GGTA1 gene target site. Fetus 2 had variability in Sanger sequencing that suggests a complex variability in DNA mutations or poor sample quality. However, fetal DNA template quality was sufficient for the generation of the GGTA1 gene screening experiment described above.

[00111] FIGs. 19A-19B show sequencing of DNA isolated from fetal cells of two separate litters (Pregnancy 1: **FIG. 19A** or Pregnancy 2: **FIG. 19B**) subjected to PCR amplification of the NLRC5 (consensus sequence) target regions and the resulting amplicons were separated on 1% agarose gels. Amplicons were also analyzed by Sanger sequencing using the forward primer alone from each reaction. In **FIG 19A**, the results are shown, aligned to reference and target gene sequences (SEQ ID NOs: 336-337, respectively) for fetuses 1, 3, 5, 6, and 7 (SEQ ID NOs: 338-342, respectively) from Pregnancy 1. Sequence analysis of the NLRC5 target site was unable to show consistent alignment suggesting an unknown complication in the sequencing reaction or varying DNA modifications between NLRC5 alleles that complicate the Sanger sequencing reaction and analysis. In **FIG. 19B**, the results are shown, aligned to reference and target gene sequences (SEQ ID NOs: 343-344, respectively) for fetuses 1-5 (SEQ ID NOs: 345-349, respectively) from Pregnancy 2. NLRC5 gene amplicons for fetuses 1-5 were all truncated 120 nucleotides downstream of the NLRC5 gene cut site.

[00112] FIGs. 20A-20B show data from fetal DNA (wt and 1-7 (**FIG. 20A**: Pregnancy 1) or 1-5 (**FIG. 20B**: Pregnancy 2) isolated from hind limb biopsies. Target genes were amplified by PCR and PCR products were separated on 1% agarose gels and visualized by fluorescent DNA stain. The amplicon band present in the wt lanes represent the unmodified DNA sequence. An

increase or decrease in size of the amplicon suggests an insertion or deletion within the amplicon, respectively. Variation in the DNA modification between alleles in one sample may make the band appear more diffuse. Pregnancy 1 (**FIG. 20A**) resulted in 7 fetuses while pregnancy 2 (**FIG. 20B**) resulted in 5 fetuses harvested at 45 and 43 days, respectively. A lack of band as in the NLRC5 gel in fetuses 1, 3, and 4 of **FIG. 20A** (bottom gel), suggests that the modification to the target region have disrupted the binding of DNA amplification primers. The presence of all bands in GGTA 1 in **FIG. 20A** (top gel) suggests that DNA quality was sufficient to generate DNA amplicons in the NLRC5 targeting PCR reactions. Fetuses 1, 2, 4, and 5 of Pregnancy 1 (**FIG. 20A**) have larger GGTA 1 amplicons than the WT suggesting an insertion within the target area. In fetus 3 of Pregnancy 1 (**FIG. 20A**), the GGTA 1 amplicon migrated faster than the WT control suggesting a deletion within the target area. Fetuses 6 and 7 of Pregnancy 1 (**FIG. 20A**) NLRC5 amplicons migrated faster than the WT suggesting a deletion within the target area. Fetuses 1-5 (**FIG. 20B**) GGTA1 amplicons were difficult to interpret by size and were diffuse as compared to the WT control. Fetuses 1-5 (**FIG. 20B**) NLRC5 amplicons were uniform in size and density as compared to the wild type control.

[00113] FIGs. 21A-21E shows phenotypic analysis of fetuses from two separate litters of pigs (**FIGs. 21A, 21B, 21C**: Pregnancy 1 or **FIGs. 21D-21E**: Pregnancy 2). Fetuses were harvested at day 45 (Pregnancy 1) or 43 days (Pregnancy 2) and processed for DNA and culture cell isolation. Tissue fragments and cells were plated in culture media for 2 days to allow fetal cells to adhere and grow. Wild type cells (fetal cells not genetically modified) and fetal cells from pregnancy 1 and 2 were removed from culture plates and labeled with IB4 lectin conjugated to Alexa fluor 488 or anti-porcine MHC class I antibody conjugated to FITC. Flow cytometric analysis is shown as histograms depicting the labeling intensity of the cells tested. The histograms for the WT cells are included in each panel to highlight the decrease in overall intensity of each group of fetal cells. There is a decrease in alpha Gal and MHC class I labeling in pregnancy 1 (**FIG. 21A**) indicated as a decrease in peak intensity. In pregnancy 2 (**FIG. 21B**) fetuses 1 and 3 have a large decrease in alpha gal labeling and significant reduction in MHC class 1 labeling as compared to WT fetal cells.

[00114] FIGs. 22A-22C show the impact of decreased MHC class I expression in cells from Fetus 3 (Pregnancy 1) as compared to wild type fetal cells from a genetic clone. The proliferative response of human CD8+ cells and CD4 T cells to porcine control fibroblast and NLRC5 knockout fetal cells were measured. **FIG. 22A**. Cells were gated as CD4 or CD8 before assessment of proliferation. **FIG. 22B**. CD8 T cell proliferation was reduced following treatments stimulation by porcine fetal GGTA1/NLRC5 knockout cells compared to control

unmodified porcine fibroblast. Almost a 55% reduction in CD8 T cells proliferation was observed when human responders were treated with porcine fetal GGTA1/NLRC5 knockout cells at 1:1 ratio. Wild type fetal cells elicited a 17.2% proliferation in human CD8 T cells whereas the MHC class I deficient cells from fetus 3 (Pregnancy 1) induced only a 7.6% proliferation. **FIG. 22C.** No differences were seen in CD8 T cells proliferative response at 1:5 and 1:10 ratio compared to unmodified fetal cells. No changes were observed in CD4 T cell proliferation in response to NLRC5 knockout and control unmodified porcine fetal cells at all ratios studied.

[00115] FIG. 23 shows live birth of GGTA1/NLRC5 knockout piglets generated using CRISPR/Cas technology.

[00116] FIGs. 24A-24C show DNA gel analysis of the genotypes of the piglets generated in Example 6. **FIG. 24A** shows the result of the first PCR experiment in Example 6. **FIG. 24B** shows the result of the second PCR experiment in Example 6. **FIG. 24C** shows the result of the third PCR experiment in Example 6.

[00117] FIG. 25A shows the sequencing data and sequence call (SEQ ID NO: 350) of part of NLRC5 gene of piglet #1. **FIG. 25B** shows the sequencing data and sequence call (SEQ ID NO: 351) of part of NLRC5 gene of piglet #2. **FIG. 25C** shows the sequencing data and sequence call (SEQ ID NO: 352) of part of NLRC5 gene of piglet #4. **FIG. 25D** shows the sequencing data and sequence call (SEQ ID NO: 353) of part of NLRC5 gene of piglet #5. **FIG. 25E** shows the sequencing data and sequence call (SEQ ID NO: 354) of part of NLRC5 gene of piglet #6. **FIG. 25F** shows the sequencing data and sequence call (SEQ ID NO: 355) of part of NLRC5 gene of piglet #7.

[00118] FIG. 26A shows the left arm of Rosa26 in Example 8 (SEQ ID NO: 356). **FIG. 26B** shows DNA gel analysis of the construct for homology recombination in Example 8. **FIG. 26C** shows the consensus sequence of amplicon based on paired read analysis in Example 8 (SEQ ID NO: 357). **FIGs. 26D** (SEQ ID NO: 358), **26E** (SEQ ID NO: 359), and **26F** (SEQ ID NO: 360) show homology directed recombination construct for inserting HLA-G1 at Rosa26 locus in Example 8.

[00119] FIG. 27A shows the sequence of the correct px330 plasmid (SEQ ID NO: 362) containing Rosa26 targeting oligo generated in Example 8, and sequencing primers (SEQ ID NOs: 361 and 363, respectively, in order of appearance). **FIG. 27B** shows the sequencing result of constructed px330 plasmid containing Rosa26 targeting oligo in Example 8. SEQ ID NOs:

364-366 are disclosed, respectively, in order of appearance. **FIG. 27C** shows restriction digestion of the constructed px330 plasmid containing Rosa26 targeting oligo in Example 8.

[00120] FIG. 28 shows the map of GalMet plasmid and oligos (SEQ ID NOs: 367-368, respectively, in order of appearance) used in Example 8.

[00121] FIG. 29 shows *in vitro* Cas9-mediated cleavage reactions of *in vitro* transcribed gRNA. Lane 1: Uncleaved pig Rosa26 (2000 bp). Lane 2: designed gRNA directed Cas9 cleavage of pig Rosa26; Lane 3: Uncleaved Pig GGTA1; Lane 4: designed gRNA directed Cas9 cleavage of GGTA1 template.

[00122] FIG. 30 shows sorting of genetically modified cell generated in Example 8 by flow cytometry.

[00123] FIG. 31 shows the construct for homology recombination of CD47 to GGTA1 locus generated in Example 9 (SEQ ID NO: 369).

[00124] FIG. 32 shows the sequence of the right arm (**FIG. 32A**; SEQ ID NO: 370) and the left arm (**FIG. 32B**; SEQ ID NO: 371) of GGTA1 locus in Example 9.

[00125] FIGs. 33A, 33B, and 33C show the sorting of unstained cells in Example 9.

[00126] FIGs. 34A, 34B, and 34C show the sorting of px330 stained cells in Example 9.

[00127] FIGs. 35A, 35B, and 35C show the sorting IB4 stained cells in Example 9.

[00128] FIGs. 36A, 36B, and 36C show the sorting of CD47/IB4 stained cells in Example 9.

[00129] FIGs. 37A, 37B, and 37C show the sorted IB4 stained cells CD47/IB4 stained cells in Example 9.

[00130] FIGs. 38A, 38B, and 38C show the sorted CD47/IB4 stained cells in Example 9.

[00131] FIG. 39 shows the gating strategy used for the selection of single cells and live cells for analysis. Total CD3+ cells were observed with in that population CD4+ and CD8+ cells were selected and counted for experimental parameters.

[00132] FIG. 40A and **40B** show **A.** unstimulated cells in quadrant 2 showed insignificant expansion when in culture conditions identical to the same cells stimulated with PHA. **B.** PHA stimulation induced 20.7% (CD3), 24.7% (CD4), 18.4% (CD8), and 21% (CD20) proliferation in lymphocytic samples suggesting the maximum amount of stimulation possible in this assay.

[00133] FIG. 41 shows flow cytometry results of a co-culture assay where CD8+ T cells were added to cultures of adherent WT or genetically engineered porcine fibroblasts at a dilution of

100:1, 50:1, 10:1, or 1:1.WT cells stimulated T cells to proliferate at 50:1, 10:1, and 1:1 ratios. GM cells #3 and #4 showed little effect at stimulating T cells at the 100:1, 50:1, and 10:1 ratios suggesting a complete abrogation of T cells proliferation response.

[00134] FIG. 42 shows flow cytometry results of a co-culture assay where CD4+ T cells were added to cultures of adherent WT or genetically engineered porcine fibroblasts at a dilution of 100:1, 50:1, 10:1, and 1:1. GM cells #3 and #4 showed little effect at stimulating T cells at the 100:1, 50:1, and 10:1 ratios suggesting a complete abrogation of T cells proliferation response.

[00135] FIG. 43 shows flow cytometry results of a co-culture assay where CD3+ T cells (overall CD 4 and CD8) were added to cultures of adherent WT or genetically engineered porcine fibroblasts at a dilution of 100:1, 50:1, 10:1, and 1:1. GM cells #3 and #4 showed little effect at stimulating T cells at the 100:1, 50:1, and 10:1 ratios suggesting a complete abrogation of T cells proliferation response.

[00136] FIG. 44 shows B cell proliferation inhibition by approximately 50% when incubated with GGTA1/NLRC5 knock out cells as compared to wild type cells.

[00137] FIG. 45 shows flow cytometry results of a co-culture assay where cytokines were measured by incubating human lymphocytes with WT or GM cells followed by the introduction of brefeldin A to block endocytosis causing the accumulation of the 4 cytokines intracellularly in endosomes. Fixation and permeabilization of the cells allows intracellular measurement of the accumulation of cytokines. Within the CD8 T cell population no IL2 stimulation was observed at 100:1 ratio moderate reductions in CD107a, Perforin and Granzyme were observed at the 100:1 ratio. Perforin and granzyme B double positive cells are significantly inhibited at the 100:1 and 10:1 ratios.

[00138] FIG. 46 shows flow cytometry results of a co-culture assay of human lymphocytes with WT or genetically modified porcine fibroblasts at a T cells vs FC ratio =10:1. Within the CD8 T cell population IL2 was stimulated at 10:1 ratio and reduced by approximately 40% in culture with genetically modified porcine cells. CD107a, expression was reduced by approximately 25%. Perforin expression was reduced by approximately 40% and Granzyme was unaffected at this ratio of incubation.

[00139] FIG. 47 shows flow cytometry results of a co-culture assay of human lymphocytes with WT or genetically modified porcine fibroblasts at a T cells vs FC ratio =10:1. Within CD3 cells CD107a was reduced by approximately 50%. Perforin and Granzyme B was also reduced after incubation with genetically modified cells and was reflected when compared as double positive cells retreating from quadrant 2.

[00140] FIG. 48 shows flow cytometry results of a co-culture assay of human lymphocytes with WT or genetically modified porcine fibroblasts at a T cells vs FC ratio =10:1. CD4+ T cells were activated less in the presence of GM cells to produce cytokines. IL2 expression was reduced by 40%. CD107a was reduced by approx. 50%. Perforin and Granzyme B were reduced by approximately 50% and 30%, respectively.

[00141] FIG. 49 shows flow cytometry results of a co-culture assay of human lymphocytes with WT or genetically modified porcine fibroblasts at a T cell vs FC ratio = 10:1. Among CD3 cells IFNγ expression was significantly reduced when lymphocytes were cultured with GM pig fibroblasts at a 10:1 ratio. TNFa expression was low in culture with WT cells but reduced when in culture with GM cells. Within this experiment Granzyme B was also dramatically reduced when incubated with GM cells as compared to WT cells.

[00142] FIG. 50 shows flow cytometry results of a co-culture assay of human lymphocytes with WT or genetically modified porcine fibroblasts at a T cell vs FC ratio = 10:1. Among CD4 cells IFNγ expression was significantly reduced when lymphocytes were cultured with GM pig fibroblasts at a 10:1 ratio. TNFa expression was low in culture with WT cells but reduced when in culture with GM cells. Within this experiment Granzyme B was also dramatically reduced when incubated with GM cells as compared to WT cells.

[00143] FIG. 51 shows flow cytometry results of a co-culture assay of human lymphocytes with WT or genetically modified porcine fibroblasts at a T cell vs FC ratio = 10:1. Among CD8 cells IFNγ expression was significantly reduced when lymphocytes were cultured with GM pig fibroblasts at a 10:1 ratio. TNFa expression was low in culture with WT cells but reduced when in culture with GM cells. Within this experiment Granzyme B was also dramatically reduced when incubated with GM cells as compared to WT cells.

[00144] FIG. 52 shows flow cytometry results of a co-culture assay of human lymphocytes with WT or genetically modified porcine fibroblasts at a T cell vs FC ratio = 10:1. NK cells (CD56+) have been shown to be activated in the absence of MHC class I expression on cells. IFNγ (y axis) and Granzyme B (x axis) were expressed in co-culture with WT cells but significantly reduced when in co-culture with GGTA1/NLRC5 knock out cells. No expression or change in TNFa expression was observed with GM cells as compared to WT cells.

[00145] FIG. 53 shows Human PBMC incubated with WT pig fibroblasts had a normal background percentage of IL10 expressing CD4 positive T cells (11%). GGTA1/NLRC5 knockout cells labeled #3 and #4 respectively (13.3 and 20.2%) had a marginal effect on IL10

expression. Pig fibroblasts expressing the human inspired HLAG1 protein optimized for expression in pigs induced 60.7% of human CD4+ T cells to produce IL10.

[00146] FIG. 54 shows that soluble HLA-G (100 ng/ml) blocks the proliferation of CD8+, CD8- and PBMCs in the culture with WT porcine islet. Q1 and Q2 showing proliferating (CFSE lo) and non-proliferating fractions (CFSE hi) fractions, respectively.

[00147] FIG. 55 shows the flow cytometry gating strategy used to analyze CD3, CD4, or CD8 populations for cytokine and effector function molecular analysis of cultured human T cells with genetically modified porcine fibroblasts (HLAG1 expressing), WT, or WT plus PT85 antibody.

[00148] FIG. 56 shows cytometry data of the CD4 population co-cultured with wild type pig fibroblasts, WT pig fibroblasts with the PT85 antibody, or HLAG1 expressing pig fibroblasts. Substantial decrease in cytokines levels (IL-2) and effector molecules secretion were observed with PT85 blocking or HLAG1 expressing cells at ratio of 10: and 1:1 of MLR culture. The PT85 blocking antibody was used to determine how much of the observed immune inhibitory effects were due to the NLRC5 knock out (MHC class 1 null) or the GGTA1 knock out. The PT85 antibody mimicked the effect of the NLRC5 knockdown in the presence of normal WT alpha-Gal surface expression. The HLAG1 protein expression on the surface of the cells had a profound inhibitory effect on CD4+ and CD8+ T cells cytokine production as well as effector function.

[00149] FIG. 57 shows cytometry data of the CD8 population co-cultured with either wild type pig fibroblasts, WT pig fibroblasts with the PT85 antibody, or HLAG1 expressing pig fibroblasts. Substantial decrease in cytokines levels (IL-2) and effector molecules secretion were observed with PT85 blocking or HLAG1 expressing cells at ratio of 10: and 1:1 of MLR culture. The PT85 blocking antibody was used to determine how much of the observed immune inhibitory effects were due to the NLRC5 knock out (MHC class 1 null) or the GGTA1 knock out. The PT85 antibody mimicked the effect of the NLRC5 knockdown in the presence of normal WT alpha-Gal surface expression within the CD8 population. The HLAG1 protein expression on the surface of the cells had a profound inhibitory effect on CD4+ and CD8+ T cells cytokine production as well as effector functions. The HLAG1 protein expression on the surface of the cells had a profound inhibitory effect on CD4+ and CD8+ T cells cytokine production as well as effector functions.

[00150] FIG. 58 shows cytometry data of the CD4 population co-cultured with wild type pig fibroblasts, WT pig fibroblasts with the PT85 antibody, or HLAG1 expressing pig fibroblasts. Substantial decrease in cytokines levels (TNF-a, IFN-g) and effector molecules secretion was

observed with PT85 blocking or HLAG1 expressing cells at ratio of 10: and 1:1 of MLR culture. The PT85 blocking antibody was used to determine how much of the observed immune inhibitory effects were due to the NLRC5 knock out (MHC class 1 null) or the GGTA1 knock out. The PT85 antibody mimicked the effect of the NLRC5 knockdown in the presence of normal WT alpha-Gal surface expression. The HLAG1 protein expression on the surface of the cells had a profound inhibitory effect on CD4+ and CD8+ T cells cytokine production as well as effector functions.

[00151] FIG. 59 shows cytometry data of the CD8 population co-cultured with wild type pig fibroblasts, WT pig fibroblasts with the PT85 antibody, or HLAG1 expressing pig fibroblasts. Substantial decrease in cytokines levels (TNF-a, IFN-g) and effector molecules secretion was observed with PT85 blocking or HLAG1 expressing cells at ratio of 10: and 1:1 of MLR culture. The PT85 blocking antibody was used to determine how much of the observed immune inhibitory effects were due to the NLRC5 knock out (MHC class 1 null) or the GGTA1 knock out. The PT85 antibody mimicked the effect of the NLRC5 knockdown in the presence of normal WT alpha-Gal surface expression. The HLAG1 protein expression on the surface of the cells had a profound inhibitory effect on CD4+ and CD8+ T cells cytokine production as well as effector functions.

[00152] FIG. 60 shows the flow gating scheme for the cellular proliferation/CFSE low population analysis.

[00153] FIG. 61 A and **B** shows flow cytometric analysis of a cellular proliferation (CFSE dilution) experiment of CD3, CD4, or CD8 populations among **A**. unstimulated cells or **B**. PHA stimulated cells (positive control or maximal dilution).

[00154] FIG. 62 shows that T cell proliferation was reduced following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. Substantial reduction in T cells (CD3) proliferation was observed when human responder were treated with SLA-I blocking PT-85 Abs or HLA-G expressing at 10:1 and 1:1 ratio. Not much difference was seen in T cells proliferative response at 100:1 and 50:1 ratio compared to unmodified/WT porcine fibroblast.

[00155] FIG. 63 shows that T cell proliferation was reduced following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. Substantial reduction in T cells (CD4) proliferation was observed when human responder were treated with SLA-I blocking

PT-85 Abs or HLA-G expressing at 10:1 and 1:1 ratio. Not much difference was seen in T cells proliferative response at 100:1 and 50:1 ratio compared to unmodified/WT porcine fibroblast.

[00156] FIG. 64 shows reduced T cell proliferation following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. Substantial reduction in T cells (CD8) proliferation was observed when human responder were treated with SLA-I blocking PT-85 Abs or HLA-G expressing at 10:1 and 1:1 ratio. Not much difference was seen in T cells proliferative response at 100:1 and 50:1 ratio compared to unmodified/WT porcine fibroblast.

[00157] FIG. 65 shows reduced T cell proliferation following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. No substantial reduction in B cells proliferation either with blocking SLA-I with PT-85 or HLA-G expression.

[00158] FIG. 66 shows that IFNγ is produced predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response. DKO #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. IFNγ is also produced by CD4 Th1 and CD8 cytotoxic T lymphocyte (CTL) effector T cells after antigen-specific immunity develops.

[00159] FIG. 67 shows GMC-SF production among genetically modified cells cultured with human immune cells and controls. Double knock out (DKO) cells had no ability to stimulate GM-CSF production. HLAG1 had significantly reduced expression. DKO #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately.

[00160] FIG. 68 shows IL-17 A expression among genetically modified cells cultured with human immune cells. DKO and HLAG1 transgenic cells both had no ability to induce a pro inflammatory response from human PBMC.

[00161] FIG. 69 shows Fractalkine expression among genetically modified porcine cells cultured with human immune cells. HLAG1 expression remains a significant inhibitor of T cells activation and fractalkine production though expressed on a log scale.

[00162] FIG. 70 shows TNF alpha expression among genetically modified porcine cells cultured with human immune cells.

[00163] FIG. 71 shows the IL-6 production among genetically modified porcine cells cultured with human immune cells.

[00164] FIG. 72 shows IL-4 production among genetically modified porcine cells cultured with human immune cells.

[00165] FIG. 73 shows MIP 1 alpha production among genetically modified porcine cells cultured with human immune cells.

[00166] FIG. 74 shows MIP 1 beta production among genetically modified porcine cells cultured with human immune cells.

[00167] FIG. 75 shows that T cell proliferation was reduced following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. Substantial reduction in T cells (CD3) proliferation was observed when human responder were treated with SLA-I blocking PT-85 Abs or HLA-G expressing at 10:1 and 1:1 ratio. Not much difference was seen in T cells proliferative response at 100:1 and 50:1 ratio compared to unmodified/WT porcine fibroblast.

[00168] FIG. 76 shows that T cell proliferation was reduced following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. Substantial reduction in T cells (CD4) proliferation was observed when human responder were treated with SLA-I blocking PT-85 Abs or HLA-G expressing at 10:1 and 1:1 ratio. Not much difference was seen in T cells proliferative response at 100:1 and 50:1 ratio compared to unmodified/WT porcine fibroblast.

[00169] FIG. 77 shows reduced T cell proliferation following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. Substantial reduction in T cells (CD8) proliferation was observed when human responder were treated with SLA-I blocking PT-85 Abs or HLA-G expressing at 10:1 and 1:1 ratio. Not much difference was seen in T cells proliferative response at 100:1 and 50:1 ratio compared to unmodified/WT porcine fibroblast.

[00170] FIG. 78 shows reduced T cell proliferation following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. No substantial reduction in B cells proliferation either with blocking SLA-I with PT-85 or HLA-G expression

[00171] FIG. 79 shows IFN gamma expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells

were conducted in a separate experiment with human donor #2 (**FIG. 79B**) (but not human donor #1; **FIG. 79A**), and therefore include matching unstimulated and wild type cell controls.

[00172] FIG. 80 shows GM-CSF gamma expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells were conducted in a separate experiment with human donor #2 (**FIG. 80B**) (but not human donor #1; **FIG. 80A**), and therefore include matching unstimulated and wild type cell controls.

[00173] FIG. 81 shows IL-2 expression after co-culture of human donor #1 mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately.

[00174] FIG. 82 shows IL-17 alpha expression after co-culture of human mixed lymphocytes from two donors (**FIG. 82A** and **B**) and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. DKO and HLA-G1 transgenic cells both had no ability to induce a pro inflammatory response from human PBMC.

[00175] FIG. 83 shows Fractalkine expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells were conducted in a separate experiment with human donor #2 (**FIG. 83B**) (but not human donor #1; **FIG. 83A**), and therefore include matching unstimulated and wild type cell controls. HLA-G1 expression remains a significant inhibitor of T cells activation and fractalkine production though expressed on a log scale.

[00176] FIG. 84 shows TNF alpha expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells were conducted in a separate experiment with human donor #2 (**FIG. 84B**) (but not human donor #1; **FIG. 84A**), and therefore include matching unstimulated and wild type cell controls.

[00177] FIG. 85 shows IL-6 expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells were conducted in a separate experiment with human donor #2 (**FIG. 85B**) (but not human donor #1; **FIG. 85A**), and therefore include matching unstimulated and wild type cell controls.

[00178] FIG. 86 shows IL-4 expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells were conducted in a separate experiment with human donor #2 (**FIG. 86B**) (but not human donor #1; **FIG. 86A**), and therefore include matching unstimulated and wild type cell controls.

[00179] FIG. 87 shows MIP-1 alpha expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells were conducted in a separate experiment with human donor #2 (**FIG. 87B**) (but not human donor #1; **FIG. 87A**), and therefore include matching unstimulated and wild type cell controls.

[00180] FIG. 88 shows MIP-1 beta expression after co-culture of human mixed lymphocytes and porcine genetically modified cells. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLA-G1 transgenic cells were conducted in a separate experiment with human donor #2 (**FIG. 88B**) (but not human donor #1; **FIG. 88A**), and therefore include matching unstimulated and wild type cell controls.

[00181] FIG. 89 shows the CRISPR/Cas construct within the PX333 vector.

[00182] FIG. 90 shows transfection schematic of primary porcine fibroblast using constructs: GGTA1-10/B4GALNT2 (condition 2), NLRC5-6/B4GALNT2 (condition 3), GGTA1-10/B4GALNT2 and NLRC5-6/B4GALNT2 (condition 4), Condition 1 (WT): cells only.

[00183] FIG. 91 shows genetically Modified Selection using Magnetic Bead Sorting.

[00184] FIG. 92 shows Genetically Modified Selection using Cell Sort of SLA I + / IB4 + (top right); SLA I + / IB4 – (bottom right); SLA I - / IB4 + (top left); and SLA I - / IB4 (bottom left).

[00185] FIG. 93 shows flow cytometric analysis of Condition 2: GGTA1-10/B4GALNT2.

[00186] FIG. 94 shows flow cytometric analysis of Condition 3: NLRC5-6/B4GALNT2.

[00187] FIG. 95 shows flow cytometric analysis of Condition 4: GGTA1-10/B4GALNT2 + NLRC5-6/B4GALNT2.

[00188] FIG. 96 shows flow cytometric analysis of Condition 2: GGTA1-10/B4GALNT2 post sort. Each population was sorted to verify that the right population was acquired post sorting and there was no cross-samples from other gates.

[00189] FIG. 97 shows flow cytometric analysis of Condition 3: NLRC5-6/B4GALNT2. Each population was sorted to verify that the right population was acquired post sorting and there was no cross-samples from other gates.

[00190] FIG. 98 shows flow cytometric analysis of Condition 4: GGTA1-10/B4GALNT2 + NLRC5-6/B4GALNT2. Each population was sorted to verify that the right population was acquired post sorting and there was no cross-samples from other gates.

[00191] FIGs. 99A and **99B** show flow cytometric analysis of IB4 lectin among **A.** WT unstained, all cells unstained, WT negative, and condition #2 Gal negative fraction cultured with WT or PFF1. **B**. Side scatter vs forward scatter of condition #4 Gal negative fraction, WT positive, Conditions #2 Gal Positive fraction. Condition #3Gal positive fraction or conditions #4 Gal positive fraction cultured with WT or PFF1.

[00192] FIG. 100 shows flow cytometric quantification of condition 1 (WT), 2, 3, and 4 (left to right, respectively) genetically modified cells.

[00193] FIGs. 101 A. and **101 B.** shows flow cytometric analysis of SLAI among **A.** WT unstained, All cells unstained, WT negative, and condition #2 Gal negative fraction cultured with WT or PFF1. **B**. Side scatter vs forward scatter of condition #4 Gal negative fraction, WT positive, Conditions #2 Gal Positive fraction. Condition #3Gal positive fraction or conditions #4 Gal positive fraction cultured with WT or PFF1.

[00194] FIG. 102 shows flow cytometric quantification of SLA1 (FITC) among **A.** Condition 3 cells and **B**. Condition 4 cells.

[00195] FIG. 103 A. and **103 B.** show confocal microscopy of **A**. imaging results of WT porcine cells and genetically modified condition 2, 3, and 4 cells. **B**. slides of imaged produced.

[00196] FIG. 104 shows sequencing results of NLRC5 sequencing of condition and condition 4 cell lines. SEQ ID NOs: 372-376 are disclosed, respectively, in order of appearance.

[00197] FIG. 105 shows a table of PCR oligos and target sequences (column two) for GG1, Gal2-1, Gal 2-2, Gal 2-3, Gal 2-4, Gal 2-5, GGTA1-10, GGTA1-11, GGTA1-16, NL1, NLRC5-6, NLRC5-7, NLRC5-8. SEQ ID NOs: 377-404 are disclosed, respectively, in order of appearance in column 2. SEQ ID NOs: 405-413 are disclosed, respectively, in order of appearance in column 4. SEQ ID NOs: 414-422 are disclosed, respectively, in order of appearance in column 6.

[00198] FIG. 106 shows a table of PCR oligos and target sequences (column two) for CM1F, CM2RS, CM3RS, CM4RS. SEQ ID NOs: 423-430 are disclosed, respectively, in order of

appearance in column 2. SEQ ID NOs: 431-434 are disclosed, respectively, in order of appearance in column 4. SEQ ID NOs: 435-437 are disclosed, respectively, in order of appearance in column 6.

[00199] FIG. 107 A. and **107 B**. show a table of **A.** Target sequences for gRNAs for B41, C3-9_1, C3-9_2, C3-5_1, C3-5_2, C3-15RS_1, C3-15RS_2. SEQ ID NOs: 438-447 are disclosed, respectively, in order of appearance in column 2. **B**. Deletion screening primer sequences and their respective target sequence for Gal 1. SEQ ID NOs: 448-453 are disclosed, respectively, in order of appearance in column 2.

[00200] FIG. 108 shows an overview of a Gal2-2 (B4GALNT2) vector and cloning strategy. A nucleotide sequence for a portion of the vector is disclosed (SEQ ID NO: 454), as well as two oligos: Gal2-2_Forward (SEQ ID NO): 455) and Gal2-2_Reverse (SEQ ID NO: 456).

[00201] FIG. 109 shows the expected Gal2-2 (B4GALNT2) clone sequence upon correct insertion based on the vector and cloning strategy of FIG. 113 (top panel). SEQ ID NOs: 457-459 are disclosed, respectively, in order of appearance. The sequencing results of the constructed plasmid (SEQ ID NO: 462) are aligned against the expected sequence (SEQ ID NOs: 460-461) in the bottom panel.

[00202] FIG. 110 A. and **B. A.** shows the Gal2-1 (B4GALNT2) target site within GGTA1 gene (SEQ ID NO: 464) and two oligos (Gal2-1_screen_Forward_1, SEQ ID NO: 463; and Gal2-1_screen_Reverse_1, SEQ ID NO: 465). **B**. shows Gal2-1_screen_1 primer set, Gal2-1_screen primer set PCR product observed on gel and expected amplicon size of 303 bp. The strong single band observed at expected amplicon size product was sequence verified and was shown to include Gal2-1 target cut-sites desired for screening.

[00203] FIG. 111 A. and **111 B**. **A**. shows the CM1F target site within CMAH gene (SEQ ID NO: 467) and two oligos (CM1F-1_screen_Forward_1, SEQ ID NO: 466; and CM1F-1_screen_Reverse_1, SEQ ID NO: 468). **B**. shows CM1F_screen_1 primer set expected amplicon size of 309 bp, CM1F_screen primer set PCR product observed on gel. A strong band observed at the expected amplicon size; faint band observed at ~600 bp as well. Product at approximately 300 bp was sequence verified and was shown to include the target cut-site as desired for screening.

[00204] FIG. 112 A. and 112 B. **A**. shows NL1_First target site within NLRC5 gene (SEQ ID NO: 470) and two oligos (NLR amp2 forward, SEQ ID NO: 469; and NLR amp2 reverse, SEQ ID NO: 471). **B.** shows NLR amp 2 primer set expected amplicon size: 217 bp, NLR amp 2 primer set PCR product observed on gel, the strong single band observed at the expected

amplicon size. The product was sequence verified and was shown to include NL1_First target cut-site as desired for screening.

[00205] FIG. 113 A to 113 I represent exon 1 genomic modifications of Gal2-2 and NLRC5 genes. **A.** shows the location of screening primers for Gal. **B**. Gal2-2 PCR Screen using Gal2-2 screen 1 primers. **C**. sequence results for Gal 2-2. SEQ ID NOs: 472-478 are disclosed respectively, in order of appearance. **D.** GGTA1-10 PCR screen using GGTA1-10,11 screen primers. **E**. NLRC5-6 Screen Primers Location **F**. NLRC5-6 set A (NLRC5-678 screen primers) **G**. NLRC5-6 Sequence Results from Set A. SEQ ID NOs: 479-486 are disclosed respectively, in order of appearance. **H**. NLRC5-6 set B
(NLRC5-678 Forward and NLR1st screen 2 Reverse screen primers) **I.** NLRC5-6 set C
(NLRC5-678 Forward and NLR1st screen 2 Reverse screen primers).

[00206] FIGs. 114 A-C show live births of GGTA1/NLRC5 knockout/HLA-G1 knockin piglets generated using CRISPR/Cas technology.

[00207] FIG. 115 shows the sequencing results confirming insertion of HLA-G1 into the ROSA gene site. SEQ ID NO: 499 is disclosed.

[00208] FIG. 116 shows the sequence results confirming correct construction of the homology directed recombination construct for inserting HLA-G1 at Rosa26 locus in Example 8. SEQ ID NO: 500 is disclosed.

[00209] FIG. 117 shows the sequence of a left arm corresponding to the Rosa26 locus that can be used in the constuction of a homology targeting vector for insertion of HLA-G1, or another sequence, into the Rosa26 locus. SEQ ID NO: 501 is disclosed.

[00210] FIG. 118 shows the sequence of a modified HLA-G encoding sequence that can be used in the constuction of a homology targeting vector for insertion of HLA-G1 into a genetic loci such as a Rosa26 locus. SEQ ID NO: 502 is disclosed.

[00211] FIG. 119 shows the sequence of a right arm corresponding to the Rosa26 locus that can be used in the constuction of a homology targeting vector for insertion of HLA-G1, or another sequence, into the Rosa26 locus. SEQ ID NO: 503 is disclosed.

DETAILED DESCRIPTION OF THE DISCLOSURE

[00212] The following description and examples illustrate embodiments of the invention in detail. It is to be understood that this invention is not limited to the particular embodiments described herein and as such can vary. Those of skill in the art will recognize that there are

numerous variations and modifications of this invention, which are encompassed within its scope.

[00213] Graft rejection can be prevented by methods tempering the immune response, including those described herein. For example, one method described herein to prevent transplantation rejection or prolong the time to transplantation rejection without or with minimal immunosuppressive drug use, an animal, *e.g.,* a donor non-human animal, could be altered, *e.g.,* genetically. Subsequently, the cells, organs, and/or tissues of the altered animal, *e.g.,* a donor non-human animal, can be harvested and used in allografts or xenografts. Alternatively, cells can be extracted from an animal, *e.g.,* a human or non-human animal (including but not limited to primary cells) or cells can be previously extracted animal cells, *e.g.,* cell lines. These cells can be used to create a genetically altered cell.

[00214] Transplant rejection (*e.g.,* T cells-mediated transplant rejection) can be prevented by chronic immunosuppression. However, immunosuppression is costly and associated with the risk of serious side effects. To circumvent the need for chronic immunosuppression, a multifaceted, T cell-targeted rejection prophylaxis was developed (**FIG. 1**) that

i) utilizes genetically modified grafts lacking functional expression of MHC class I, thereby interfering with activation of $CD8^+$ T cells with direct specificity and precluding cytolytic effector functions of these $CD8^+$ T cells,

ii) interferes with B cell (and other APC)-mediated priming and memory generation of anti-donor T cells using induction immunotherapy comprising antagonistic anti-CD40 mAbs (and depleting anti-CD20 mAbs and a mTOR inhibitor), and/or

iii) depletes anti-donor T cells with indirect specificity via peritransplant infusions of apoptotic donor cell vaccines.

[00215] Described herein are genetically modified non-human animals (such as non-human primates or a genetically modified animal that is member of the *Laurasiatheria* superorder, *e.g.,* ungulates) and organs, tissues, or cells isolated therefrom, tolerizing vaccines, and methods for treating or preventing a disease in a recipient in need thereof by transplantation of an organ, tissue, or cell isolated from a non-human animal. An organ, tissue, or cell isolated from a non-human animal (such as non-human primates or a genetically modified animal that is member of the *Laurasiatheria* superorder, *e.g.,* ungulates) can be transplanted into a recipient in need thereof from the same species (an allotransplant) or a different species (a xenotransplant). A recipient can be tolerized with a tolerizing vaccine and/or one or more immunomodulatory agents (*e.g.,* an

antibody). In embodiments involving xenotransplantation the recipient can be a human. Suitable diseases that can be treated are any in which an organ, tissue, or cell of a recipient is defective or injured, (*e.g.,* a heart, lung, liver, vein, skin, or pancreatic islet cell) and a recipient can be treated by transplantation of an organ, tissue, or cell isolated from a non-human animal.

[00216] Human Leukocyte Antigen G (HLA-G) HLA-G can be a potent immuno-inhibitory and tolerogenic molecule. Accordingly, in one aspect, disclosed herein are genetically modified non-human animals and cells comprising an exogenous nucleic acid sequence encoding for an HLA-G protein. The genetically modified non-human animals and cells can also comprise one or more additional genetic modifications, such as any of the genetic modifications (e.g., knock-ins, knock-outs, gene disruptions, etc.) disclosed herein.

DEFINITIONS

[00217] The term *"about"* in relation to a reference numerical value and its grammatical equivalents as used herein can include the numerical value itself and a range of values plus or minus 10% from that numerical value. For example, the amount *"about 10"* includes 10 and any amounts from 9 to 11. For example, the term *"about"* in relation to a reference numerical value can also include a range of values plus or minus 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% from that value.

[00218] The term "non-human animal" and its grammatical equivalents as used herein includes all animal species other than humans, including non-human mammals, which can be a native animal or a genetically modified non-human animal. A non-human mammal includes, an ungulate, such as an even-toed ungulate (*e.g.,* pigs, peccaries, hippopotamuses, camels, llamas, chevrotains (mouse deer), deer, giraffes, pronghorn, antelopes, goat-antelopes (which include sheep, goats and others), or cattle) or an odd-toed ungulate (*e.g.,* horse, tapirs, and rhinoceroses), a non-human primate (*e.g.,* a monkey, or a chimpanzee), a Canidae (*e.g.,* a dog) or a cat. A non-human animal can be a member of the *Laurasiatheria* superorder. The *Laurasiatheria* superorder can include a group of mammals as described in Waddell *et al.*, *Towards Resolving the Interordinal Relationships of Placental Mammals.* Systematic Biology 48 (1): 1–5 (1999). Members of the *Laurasiatheria* superorder can include Eulipotyphla (hedgehogs, shrews, and moles), Perissodactyla (rhinoceroses, horses, and tapirs), Carnivora (carnivores), Cetartiodactyla (artiodactyls and cetaceans), Chiroptera (bats), and Pholidota (pangolins). A member of *Laurasiatheria* superorder can be an ungulate described herein, *e.g.,* an odd-toed ungulate or even-toed ungulate. An ungulate can be a pig. A member can be a member of Carnivora, such as a cat, or a dog. In some cases, a member of the *Laurasiatheria* superorder can be a pig.

[00219] The term "pig" and its grammatical equivalents as used herein can refer to an animal in the genus *Sus*, within the *Suidae* family of even-toed ungulates. For example, a pig can be a wild pig, a domestic pig, mini pigs, a *Sus scrofa* pig, a *Sus scrofa domesticus* pig, or inbred pigs.

[00220] The term "transgene" and its grammatical equivalents as used herein can refer to a gene or genetic material that can be transferred into an organism. For example, a transgene can be a stretch or segment of DNA containing a gene that is introduced into an organism. The gene or genetic material can be from a different species. The gene or genetic material can be synthetic. When a transgene is transferred into an organism, the organism can then be referred to as a transgenic organism. A transgene can retain its ability to produce RNA or polypeptides (*e.g.*, proteins) in a transgenic organism. A transgene can comprise a polynucleotide encoding a protein or a fragment (*e.g.*, a functional fragment) thereof. The polynucleotide of a transgene can be an exogenous polynucleotide. A fragment (*e.g.*, a functional fragment) of a protein can comprise at least or at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% of the amino acid sequence of the protein. A fragment of a protein can be a functional fragment of the protein. A functional fragment of a protein can retain part or all of the function of the protein.

[00221] The term "exogenous nucleic acid sequence" can refer to a gene or genetic material that was transferred into a cell or animal that originated outside of the cell or animal. An exogenous nucleic acid sequence can by synthetically produced. An exogenous nucleic acid sequence can be from a different species, or a different member of the same species. An exogenous nucleic acid sequence can be another copy of an endogenous nucleic acid sequence.

[00222] The term "genetic modification" and its grammatical equivalents as used herein can refer to one or more alterations of a nucleic acid, *e.g.*, the nucleic acid within an organism's genome. For example, genetic modification can refer to alterations, additions, and/or deletion of genes. A genetically modified cell can also refer to a cell with an added, deleted and/or altered gene. A genetically modified cell can be from a genetically modified non-human animal. A genetically modified cell from a genetically modified non-human animal can be a cell isolated from such genetically modified non-human animal. A genetically modified cell from a genetically modified non-human animal can be a cell originated from such genetically modified non-human animal.

[00223] The term "gene knock-out" or "knock-out" can refer to any genetic modification that reduces the expression of the gene being "knocked out." Reduced expression can include no expression. The genetic modification can include a genomic disruption.

[00224] The term *"islet"* or *"islet cells"* and their grammatical equivalents as used herein can refer to endocrine (*e.g.,* hormone-producing) cells present in the pancreas of an organism. For example, islet cells can comprise different types of cells, including, but not limited to, pancreatic α cells, pancreatic β cells, pancreatic δ cells, pancreatic F cells, and/or pancreatic ε cells. Islet cells can also refer to a group of cells, cell clusters, or the like.

[00225] The term "condition" condition and its grammatical equivalents as used herein can refer to a disease, event, or change in health status.

[00226] The term *"diabetes"* and its grammatical equivalents as used herein can refer to is a disease characterized by high blood sugar levels over a prolonged period. For example, the term *"diabetes"* and its grammatical equivalents as used herein can refer to all or any type of diabetes, including, but not limited to, type 1, type 2, cystic fibrosis-related, surgical, gestational diabetes, and mitochondrial diabetes. In some cases, diabetes can be a form of hereditary diabetes.

[00227] The term *"phenotype"* and its grammatical equivalents as used herein can refer to a composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties, phenology, behavior, and products of behavior. Depending on the context, the term "phenotype" can sometimes refer to a composite of a population's observable characteristics or traits.

[00228] The term *"disrupting"* and its grammatical equivalents as used herein can refer to a process of altering a gene, *e.g.,* by deletion, insertion, mutation, rearrangement, or any combination thereof. For example, a gene can be disrupted by knockout. Disrupting a gene can be partially reducing or completely suppressing expression (*e.g.,* mRNA and/or protein expression) of the gene. Disrupting can also include inhibitory technology, such as shRNA, siRNA, microRNA, dominant negative, or any other means to inhibit functionality or expression of a gene or protein.

[00229] The term *"gene editing"* and its grammatical equivalents as used herein can refer to genetic engineering in which one or more nucleotides are inserted, replaced, or removed from a genome. For example, gene editing can be performed using a nuclease (*e.g.,* a natural-existing nuclease or an artificially engineered nuclease).

[00230] The term *"transplant rejection"* and its grammatical equivalents as used herein can refer to a process or processes by which an immune response of an organ transplant recipient mounts a reaction against the transplanted material (*e.g.,* cells, tissues, and/or organs) sufficient to impair or destroy the function of the transplanted material.

[00231] The term *"hyperacute rejection"* and its grammatical equivalents as used herein can refer to rejection of a transplanted material or tissue occurring or beginning within the first 24 hours after transplantation. For example, hyperacute rejection can encompass but is not limited to *"acute humoral rejection"* and *"antibody-mediated rejection"*.

[00232] The term "negative vaccine", "tolerizing vaccine" and their grammatical equivalents as used herein, can be used interchangeably. A tolerizing vaccine can tolerize a recipient to a graft or contribute to tolerization of the recipient to the graft if used under the cover of appropriate immunotherapy. This can help to prevent transplantation rejection.

[00233] The term "recipient", "subject" and their grammatical equivalents as used herein, can be used interchangeably. A recipient or a subject can be a human or non-human animal. A recipient or a subject can be a human or non-human animal that will receive, is receiving, or has received a transplant graft, a tolerizing vaccine, and/or other composition disclosed in the application. A recipient or subject can also be in need of a transplant graft, a tolerizing vaccine and/or other composition disclosed in the application. In some cases, a recipient can be a human or non-human animal that will receive, is receiving, or has received a transplant graft.

[00234] Some numerical values disclosed throughout are referred to as, for example, "X is at least or at least about 100; or 200 [or any numerical number]." This numerical value includes the number itself and all of the following:

i) X is at least 100;

ii) X is at least 200;

iii) X is at least about 100; and

iv) X is at least about 200.

All these different combinations are contemplated by the numerical values disclosed throughout. All disclosed numerical values should be interpreted in this manner, whether it refers to an administration of a therapeutic agent or referring to days, months, years, weight, dosage amounts, etc., unless otherwise specifically indicated to the contrary.

[00235] The ranges disclosed throughout are sometimes referred to as, for example, "X is administered on or on about day 1 to 2; or 2 to 3 [or any numerical range]." This range includes the numbers themselves (*e.g.*, the endpoints of the range) and all of the following:

i) X being administered on between day 1 and day 2;

ii) X being administered on between day 2 and day 3;

iii) X being administered on between about day 1 and day 2;

iv) X being administered on between about day 2 and day 3;

v) X being administered on between day 1 and about day 2;

vi) X being administered on between day 2 and about day 3;

vii) X being administered on between about day 1 and about day 2; and

viii) X being administered on between about day 2 and about day 3.

All these different combinations are contemplated by the ranges disclosed throughout. All disclosed ranges should be interpreted in this manner, whether it refers to an administration of a therapeutic agent or referring to days, months, years, weight, dosage amounts, etc., unless otherwise specifically indicated to the contrary.

[00236] The terms "and/or" and "any combination thereof" and their grammatical equivalents as used herein, can be used interchangeably. These terms can convey that any combination is specifically contemplated. Solely for illustrative purposes, the following phrases "A, B, and/or C" or "A, B, C, or any combination thereof" can mean "A individually; B individually; C individually; A and B; B and C; A and C; and A, B, and C."

[00237] The term "or" can be used conjunctively or disjunctively, unless the context specifically refers to a disjunctive use.

I. GENETICALLY MODIFIED NON-HUMAN ANIMALS

[00238] Provided herein are genetically modified non-human animals that can be donors of cells, tissues, and/or organs for transplantation. A genetically modified non-human animal can be any desired species. For example, a genetically modified non-human animal described herein can be a genetically modified non-human mammal. A genetically modified non-human mammal can be a genetically modified ungulate, including a genetically modified even-toed ungulate (*e.g.,* pigs, peccaries, hippopotamuses, camels, llamas, chevrotains (mouse deer), deer, giraffes, pronghorn, antelopes, goat-antelopes (which include sheep, goats and others), or cattle) or a genetically modified odd-toed ungulate (*e.g.,* horse, tapirs, and rhinoceroses), a genetically modified non-human primate (*e.g.,* a monkey, or a chimpanzee) or a genetically modified Canidae (*e.g.,* a dog). A genetically modified non-human animal can be a member of the *Laurasiatheria* superorder. A genetically modified non-human animal can be a non-human primate, *e.g.,* a monkey, or a chimpanzee. If a non-human animal is a pig, the pig can be at least or at least about 1, 5, 50, 100, or 300 pounds, *e.g.,* the pig can be or be about between 5 pounds to 50 pounds; 25 pounds

to 100 pounds; or 75 pounds to 300 pounds. In some cases, a non-human animal is a pig that has given birth at least one time.

[00239] A genetically modified non-human animal can be of any age. For example, the genetically modified non-human animal can be a fetus; from or from about 1 day to 1 month; from or from about 1 month to 3 months; from or from about 3 months to 6 months; from or from about 6 months to 9 months; from or from about 9 months to 1 year; from or from about 1 year to 2 years. A genetically modified non-human animal can be a non-human fetal animal, perinatal non-human animal, neonatal non-human animal, preweaning non-human animal, young adult non-human animal, or an adult non-human animal.

[00240] A genetically modified non-human animal can survive for at least a period of time after birth. For example the genetically modified non-human animal can survive for at least 1 day, 2 days, 3 days, 1 week, 2 week, 3 week, 1 month, 2 months, 4 months, 8 months, 1 year, 2 years, 5 years, or 10 years after birth. Multiple genetically modified animals (e.g., a pig) can be born in a litter. A litter of genetically modified animal can have at least 30%, 50%, 60%, 80%, or 90% survival rate, e.g., number of animals in a litter that survive after birth divided by the total number of animals in the litter.

[00241] A genetically modified non-human animal can comprise reduced expression of one or more genes compared to a non-genetically modified counterpart animal. The reduction of expression of a gene can result from mutations on one or more alleles of the gene. For example, a genetically modified animal can comprise a mutation on two or more alleles of a gene. In some cases, such genetically modified animal can be a diploid animal.

[00242] A genetically modified non-human animal can comprise reduced expression of one or more genes compared to a non-genetically modified counterpart animal. A genetically modified non-human animal can comprise reduced expression of two or more genes compared to a non-genetically modified counterpart animal. A genetically modified animal can have a genomic disruption in at least one gene selected from a group consisting of a component of an MHC I-specific enhanceosome, a transporter of an MHC I-binding peptide, a natural killer (NK) group 2D ligand, a CXC chemokine receptor (CXCR)3 ligand, MHC II transactivator (CIITA), C3, an endogenous gene not expressed in a human, and any combination thereof.

[00243] In some cases a genetically modified animal has reduced expression of a gene in comparison to a non-genetically modified counterpart animal. In some cases, a genetically modified animal survives at least 22 days after birth. In other cases, a genetically modified animal can survive at least or at least about 23 to 30, 25 to 35, 35 to 45, 45 to 55, 55 to 65, 65 to

75, 75 to 85, 85 to 95, 95 to 105, 105 to 115, 115 to 225, 225 to 235, 235 to 245, 245 to 255, 255 to 265, 265 to 275, 275 to 285, 285 to 295, 295 to 305, 305 to 315, 315 to 325, 325 to 335, 335 to 345, 345 to 355, 355 to 365, 365 to 375, 375 to 385, 385 to 395, or 395 to 400 days after birth.

[00244] A non-genetically modified counterpart animal can be an animal substantially identical to the genetically modified animal but without genetic modification in the genome. For example, a non-genetically modified counterpart animal can be a wild-type animal of the same species as the genetically modified animal.

[00245] A genetically modified non-human animal can provide cells, tissues or organs for transplanting to a recipient or subject in need thereof. A recipient or subject in need thereof can be a recipient or subject known or suspected of having a condition. The condition can be treated, prevented, reduced, eliminated, or augmented by the methods and compositions disclosed herein. The recipient can exhibit low or no immuno-response to the transplanted cells, tissues or organs. The transplanted cells, tissues or organs can be non-recognizable by CD8+ T cells, NK cells, or CD4+ T cells of the recipient (*e.g.*, a human or another animal). The genes whose expression is reduced can include MHC molecules, regulators of MHC molecule expression, and genes differentially expressed between the donor non-human animal and the recipient (*e.g.*, a human or another animal). The reduced expression can be mRNA expression or protein expression of the one or more genes. For example, the reduced expression can be protein expression of the one or more genes. Reduced expression can also include no expression. For example an animal, cell, tissue or organ with reduced expression of a gene can have no expression (*e.g.*, mRNA and/or protein expression) of the gene. Reduction of expression of a gene can inactivate the function of the gene. In some cases, when expression of a gene is reduced in a genetically modified animal, the expression of the gene is absent in the genetically modified animal.

[00246] A genetically modified non-human animal can comprise reduced expression of one or more MHC molecules compared to a non-genetically modified counterpart animal. For example, the non-human animal can be an ungulate, *e.g.*, a pig, with reduced expression of one or more swine leukocyte antigen (SLA) class I and/or SLA class II molecules.

[00247] A genetically modified non-human animal can comprise reduced expression of any genes that regulate major histocompatibility complex (MHC) molecules (*e.g.*, MHC I molecules and/or MHC II molecules) compared to a non-genetically modified counterpart animal. Reducing expression of such genes can result in reduced expression and/or function of MHC molecules (*e.g.*, MHC I molecules and/or MHC II molecules). In some cases, the one or more genes whose expression is reduced in the non-human animal can comprise one or more of the

following: components of an MHC I-specific enhanceosome, transporters of a MHC I-binding peptide, natural killer group 2D ligands, CXC chemical receptor (CXCR) 3 ligands, complement component 3 (C3), and major histocompatibility complex II transactivator (CIITA). In some cases, the component of a MHC I-specific enhanceosome can be NLRC5. In some cases, the component of a MHC I-specific enhanceosome can also comprise regulatory factor X (RFX) (*e.g.,* RFX1), nuclear transcription factor Y (NFY), and cAMP response element-binding protein (CREB). In some instances, the transporter of a MHC I-binding peptide can be Transporter associated with antigen processing 1 (TAP1). In some cases, the natural killer (NK) group 2D ligands can comprise MICA and MICB. For example, the genetically modified non-human animal can comprise reduced expression of one or more of the following genes: NOD-like receptor family CARD domain containing 5 (NLRC5), Transporter associated with antigen processing 1 (TAP1), C-X-C motif chemokine 10 (CXCL10), MHC class I polypeptide-related sequence A (MICA), MHC class I polypeptide-related sequence B (MICB), complement component 3 (C3), and CIITA. A genetically modified animal can comprise reduced expression of one or more of the following genes: a component of an MHC I-specific enhanceosome (*e.g.,* NLRC5), a transporter of an MHC I-binding peptide (TAP1), and C3.

[00248] A genetically modified non-human animal can comprise reduced expression compared to a non-genetically modified counterpart of one or more genes expressed at different levels between the non-human animal and a recipient receiving a cell, tissue, or organ from the non-human animal. For example, the one or more genes can be expressed at a lower level in a human than in the non-human animal. In some cases, the one or more genes can be endogenous genes of the non-human animal. The endogenous genes are in some cases genes not expressed in another species. For example, the endogenous genes of the non-human animal can be genes that are not expressed in a human. For example, in some cases, homologs (*e.g.,* orthologs) of the one or more genes do not exist in a human. In another example, homologs (*e.g.,* orthologs) of the one or more genes can exist in a human but are not expressed.

[00249] In some cases, a non-human animal can be a pig, and the recipient can be a human. In these cases, the one or more genes can be any genes expressed in a pig but not in a human. For example, the one or more genes can comprise glycoprotein galactosyltransferase alpha 1, 3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), and β1,4 N-acetylgalactosaminyltransferase (B4GALNT2). A genetically modified non-human animal can comprise reduced expression of B4GALNT2, GGTA1, or CMAH, where the reduced expression is in comparison to a non-genetically modified counterpart animal. A genetically modified non-human animal can comprise reduced expression of B4GALNT2 and

GGTA1, where the reduced expression is in comparison to a non-genetically modified counterpart animal. A genetically modified non-human animal can comprise reduced expression of B4GALNT2 and CMAH, where the reduced expression is in comparison to a non-genetically modified counterpart animal. A genetically modified non-human animal can comprise reduced expression of B4GALNT2, GGTA1, and CMAH, where the reduced expression is in comparison to a non-genetically modified counterpart animal.

[00250] The genetically modified non-human animal can comprise reduced expression compared to a non-genetically modified counterpart of one or more of any of the genes disclosed herein, including NLRC5, TAP1, CXCL10, MICA, MICB, C3, CIITA, GGTA1, CMAH, and B4GALNT2.

[00251] A genetically modified non-human animal can comprise one or more genes whose expression is reduced, *e.g.,* where genetic expression is reduced. The one or more genes whose expression is reduced include but are not limited to NOD-like receptor family CARD domain containing 5 (NLRC5), Transporter associated with antigen processing 1 (TAP1), Glycoprotein galactosyltransferase alpha 1,3 (GGTA1), Putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), C-X-C motif chemokine 10 (CXCL10), MHC class I polypeptide-related sequence A (MICA), MHC class I polypeptide-related sequence B (MICB), class II major histocompatibility complex transactivator (CIITA), Beta-1,4-N-Acetyl-Galactosaminyl Transferase 2 (B4GALNT2), complemental component 3 (C3), and/or any combination thereof.

[00252] A genetically modified non-human animal can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more genes whose expression is disrupted. For illustrative purposes, and not to limit various combinations a person of skill in the art can envision, a genetically modified non-human animal can have NLRC5 and TAP1 individually disrupted. A genetically modified non-human animal can also have both NLRC5 and TAP1 disrupted. A genetically modified non-human animal can also have NLRC5 and TAP1, and in addition to one or more of the following GGTA1, CMAH, CXCL10, MICA, MICB, B4GALNT2, or CIITA genes disrupted; for example "NLRC5, TAP1, and GGTA1" or "NLRC5, TAP1, and CMAH" can be disrupted. A genetically modified non-human animal can also have NLRC5, TAP1, GGTA1, and CMAH disrupted. Alternatively, a genetically modified non-human animal can also have NLRC5, TAP1, GGTA1, B4GALNT2, and CMAH disrupted. In some cases, a genetically modified non-human animal can have C3 and GGTA1 disrupted. In some cases, a genetically modified non-human animal can have reduced expression of NLRC5, C3, GGTA1,

B4GALNT2, CMAH, and CXCL10. In some cases, a genetically modified non-human animal can have reduced expression of TAP1, C3, GGTA1, B4GALNT2, CMAH, and CXCL10. In some cases, a genetically modified non-human animal can have reduced expression of NLRC5, TAP1, C3, GGTA1, B4GALNT2, CMAH, and CXCL10. A B4GALNT2 gene can be a Gal2-2 or Gal 2-1.

[00253] Lack of MHC class I expression on transplanted human cells can cause the passive activation of natural killer (NK) cells (Ohlen *et al.*, 1989). Lack of MHC class I expression could be due to NLRC5, TAP1, or B2M gene deletion. NK cell cytotoxicity can be overcome by the expression of the human MHC class 1 gene, HLA-E, can stimulate the inhibitory receptor CD94/NKG2A on NK cells to prevent cell killing (Weiss *et al.*, 2009; Lilienfeld *et al.*, 2007; Sasaki *et al.*, 1999). Successful expression of the HLA-E gene can be dependent on co-expression of the human B2M (beta 2 microglobulin) gene and a cognate peptide (Weiss *et al.*, 2009; Lilienfeld *et al.*, 2007; Sasaki *et al.*, 1999; Pascasova *et al.*, 1999). A nuclease mediated break in the stem cell DNA can allow for the insertion of one or multiple genes via homology directed repair. The HLA-E and hB2M genes in series can be integrated in the region of the nuclease mediated DNA break thus preventing expression of the target gene (for example, NLRC5) while inserting the transgenes.

[00254] Expression levels of genes can be reduced to various extents. For example, expression of one or more genes can be reduced by or by about 100%. In some cases, expression of one or more genes can be reduced by or by about 99%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50% of normal expression, *e.g.,* compared to the expression of non-modified controls. In some cases, expression of one or more genes can be reduced by at least or to at least about 99% to 90%; 89% to 80%, 79% to 70%; 69% to 60%; 59% to 50% of normal expression, *e.g.,* compared to the expression of non-modified controls. For example, expression of one or more genes can be reduced by at least or at least about 90% or by at least or at least about 90% to 99% of normal expression.

[00255] Expression can be measured by any known method, such as quantitative PCR (qPCR), including but not limited to PCR, real-time PCR (*e.g.,* Sybr-green), and/or hot PCR. In some cases, expression of one or more genes can be measured by detecting the level of transcripts of the genes. For example, expression of one or more genes can be measured by Northern blotting, nuclease protection assays (*e.g.,* RNase protection assays), reverse transcription PCR, quantitative PCR (*e.g.,* real-time PCR such as real-time quantitative reverse transcription PCR), *in situ* hybridization (*e.g.,* fluorescent in situ hybridization (FISH)), dot-blot analysis, differential

display, serial analysis of gene expression, subtractive hybridization, microarrays, nanostring, and/or sequencing (*e.g.,* next-generation sequencing). In some cases, expression of one or more genes can be measured by detecting the level of proteins encoded by the genes. For example, expression of one or more genes can be measured by protein immunostaining, protein immunoprecipitation, electrophoresis (*e.g.,* SDS-PAGE), Western blotting, bicinchoninic acid assay, spectrophotometry, mass spectrometry, enzyme assays (*e.g.,* enzyme-linked immunosorbent assays), immunohistochemistry, flow cytometry, and/or immunoctyochemistry. Expression of one or more genes can also be measured by microscopy. The microscopy can be optical, electron, or scanning probe microscopy. Optical microscopy can comprise use of bright field, oblique illumination, cross-polarized light, dispersion staining, dark field, phase contrast, differential interference contrast, interference reflection microscopy, fluorescence (*e.g.,* when particles, *e.g.,* cells, are immunostained), confocal, single plane illumination microscopy, light sheet fluorescence microscopy, deconvolution, or serial time-encoded amplified microscopy. Expression of MHC I molecules can also be detected by any methods for testing expression as described herein.

Disrupted Genes

[00256] Cells, organs, and/or tissues having different combinations of disrupted genes described herein, can result in cells, organs, and/or tissues that are less susceptible to rejection when transplanted into a recipient. For example, the inventors have found that disrupting (*e.g.,* reducing expression of) certain genes, such as NLRC5, TAP1, GGTA1, B4GALNT2, CMAH, CXCL10, MICA, MICB, C3, and/or CIITA, can increase the likelihood of graft survival. In some cases, at least two genes are disrupted. For example, GGTA1-10 and Gal2-2 can be disrupted. In some cases, GGTA1-10, Gal2-2, and NLRC5-6 can be disrupted. In other cases, NLRC5-6 and Gal2-2 can be disrupted.

[00257] In some cases, the disruptions are not limited to solely these genes. It is contemplated that genetic homologues (*e.g.,* any mammalian version of the gene) of the genes within this applications are covered. For example, genes that are disrupted can exhibit a certain identity and/or homology to genes disclosed herein, *e.g.,* NLRC5, TAP1, GGTA1, B4GALNT2, CMAH, CXCL10, MICA, MICB, C3, and/or CIITA. Therefore, it is contemplated that a gene that exhibits at least or at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% homology (at the nucleic acid or protein level) can be disrupted, *e.g.,* a gene that exhibits at least or at least about from 50% to 60%; 60% to 70%; 70% to 80%; 80% to 90%; or 90% to 99% homology. It is also contemplated that a gene that exhibits at least or at least about

50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 99%, or 100% identity (at the nucleic acid or protein level) can be disrupted, *e.g.,* a gene that exhibits at least or at least about from 50% to 60%; 60% to 70%; 70% to 80%; 80% to 90%; or 90% to 99% identity. Some genetic homologues are known in the art, however, in some cases, homologues are unknown. However, homologous genes between mammals can be found by comparing nucleic acid (DNA or RNA) sequences or protein sequences using publically available databases such as NCBI BLAST. Genomic sequences, cDNA and protein sequences of exemplary genes are shown in Table 1.

[00258] Gene suppression can also be done in a number of ways. For example, gene expression can be reduced by knock out, altering a promoter of a gene, and/or by administering interfering RNAs (knockdown). This can be done at an organism level or at a tissue, organ, and/or cellular level. If one or more genes are knocked down in a non-human animal, cell, tissue, and/or organ, the one or more genes can be reduced by administrating RNA interfering reagents, *e.g.,* siRNA, shRNA, or microRNA. For example, a nucleic acid which can express shRNA can be stably transfected into a cell to knockdown expression. Furthermore, a nucleic acid which can express shRNA can be inserted into the genome of a non-human animal, thus knocking down a gene with in a non-human animal.

[00259] Disruption methods can also comprise overexpressing a dominant negative protein. This method can result in overall decreased function of a functional wild-type gene. Additionally, expressing a dominant negative gene can result in a phenotype that is similar to that of a knockout and/or knockdown.

[00260] In some cases a stop codon can be inserted or created (*e.g.,* by nucleotide replacement), in one or more genes, which can result in a nonfunctional transcript or protein (sometimes referred to as knockout). For example, if a stop codon is created within the middle of one or more genes, the resulting transcription and/or protein can be truncated, and can be nonfunctional. However, in some cases, truncation can lead to an active (a partially or overly active) protein. In some cases, if a protein is overly active, this can result in a dominant negative protein, *e.g.,* a mutant polypeptide that disrupts the activity of the wild-type protein.

[00261] This dominant negative protein can be expressed in a nucleic acid within the control of any promoter. For example, a promoter can be a ubiquitous promoter. A promoter can also be an inducible promoter, tissue specific promoter, and/or developmental specific promoter.

[00262] The nucleic acid that codes for a dominant negative protein can then be inserted into a cell or non-human animal. Any known method can be used. For example, stable transfection

can be used. Additionally, a nucleic acid that codes for a dominant negative protein can be inserted into a genome of a non-human animal.

[00263] One or more genes in a non-human animal can be knocked out using any method known in the art. For example, knocking out one or more genes can comprise deleting one or more genes from a genome of a non-human animal. Knocking out can also comprise removing all or a part of a gene sequence from a non-human animal. It is also contemplated that knocking out can comprise replacing all or a part of a gene in a genome of a non-human animal with one or more nucleotides. Knocking out one or more genes can also comprise inserting a sequence in one or more genes thereby disrupting expression of the one or more genes. For example, inserting a sequence can generate a stop codon in the middle of one or more genes. Inserting a sequence can also shift the open reading frame of one or more genes. In some cases, knock out can be performed in a first exon of a gene. In other cases, knock out can be performed in a second exon of a gene.

[00264] Knockout can be done in any cell, organ, and/or tissue in a non-human animal. For example, knockout can be whole body knockout, *e.g.,* expression of one or more genes is reduced in all cells of a non-human animal. Knockout can also be specific to one or more cells, tissues, and/or organs of a non-human animal. This can be achieved by conditional knockout, where expression of one or more genes is selectively reduced in one or more organs, tissues or types of cells. Conditional knockout can be performed by a Cre-lox system, where cre is expressed under the control of a cell, tissue, and/or organ specific promoter. For example, one or more genes can be knocked out (or expression can be reduced) in one or more tissues, or organs, where the one or more tissues or organs can include brain, lung, liver, heart, spleen, pancreas, small intestine, large intestine, skeletal muscle, smooth muscle, skin, bones, adipose tissues, hairs, thyroid, trachea, gall bladder, kidney, ureter, bladder, aorta, vein, esophagus, diaphragm, stomach, rectum, adrenal glands, bronchi, ears, eyes, retina, genitals, hypothalamus, larynx, nose, tongue, spinal cord, or ureters, uterus, ovary, testis, and/or any combination thereof. One or more genes can also be knocked out (or expression can be reduced) in one types of cells, where one or more types of cells include trichocytes, keratinocytes, gonadotropes, corticotropes, thyrotropes, somatotropes, lactotrophs, chromaffin cells, parafollicular cells, glomus cells melanocytes, nevus cells, merkel cells, odontoblasts, cementoblasts corneal keratocytes, retina muller cells, retinal pigment epithelium cells, neurons, glias (*e.g.,* oligodendrocyte astrocytes), ependymocytes, pinealocytes, pneumocytes (*e.g.,* type I pneumocytes, and type II pneumocytes), clara cells, goblet cells, G cells, D cells, Enterochromaffin-like cells, gastric chief cells, parietal cells, foveolar cells, K cells, D cells, I cells, goblet cells, paneth cells, enterocytes,

microfold cells, hepatocytes, hepatic stellate cells (*e.g.,* Kupffer cells from mesoderm), cholecystocytes, centroacinar cells, pancreatic stellate cells, pancreatic α cells, pancreatic β cells, pancreatic δ cells, pancreatic F cells, pancreatic ε cells, thyroid (*e.g.,* follicular cells), parathyroid (*e.g.,* parathyroid chief cells), oxyphil cells, urothelial cells, osteoblasts, osteocytes, chondroblasts, chondrocytes, fibroblasts, fibrocytes, myoblasts, myocytes, myosatellite cells, tendon cells, cardiac muscle cells, lipoblasts, adipocytes, interstitial cells of cajal, angioblasts, endothelial cells, mesangial cells (*e.g.,* intraglomerular mesangial cells and extraglomerular mesangial cells), juxtaglomerular cells, macula densa cells, stromal cells, interstitial cells, telocytes simple epithelial cells, podocytes, kidney proximal tubule brush border cells, sertoli cells, leydig cells, granulosa cells, peg cells, germ cells, spermatozoon ovums, lymphocytes, myeloid cells, endothelial progenitor cells, endothelial stem cells, angioblasts, mesoangioblasts, pericyte mural cells, and/or any combination thereof.

[00265] Conditional knockouts can be inducible, for example, by using tetracycline inducible promoters, development specific promoters. This can allow for eliminating or suppressing expression of a gene/protein at any time or at a specific time. For example, with the case of a tetracycline inducible promoter, tetracycline can be given to a non-human animal any time after birth. If a non-human animal is a being that develops in a womb, then promoter can be induced by giving tetracycline to the mother during pregnancy. If a non-human animal develops in an egg, a promoter can be induced by injecting, or incubating in tetracycline. Once tetracycline is given to a non-human animal, the tetracycline will result in expression of cre, which will then result in excision of a gene of interest.

[00266] A cre/lox system can also be under the control of a developmental specific promoter. For example, some promoters are turned on after birth, or even after the onset of puberty. These promoters can be used to control cre expression, and therefore can be used in developmental specific knockouts.

[00267] It is also contemplated that any combinations of knockout technology can be combined. For example, tissue specific knockout can be combined with inducible technology, creating a tissue specific, inducible knockout. Furthermore, other systems such developmental specific promoter, can be used in combination with tissues specific promoters, and/or inducible knockouts.

[00268] In some cases, gene editing can be useful to design a knockout. For example, gene editing can be performed using a nuclease, including CRISPR associated proteins (Cas proteins, *e.g.,* Cas9), Zinc finger nuclease (ZFN), Transcription Activator-Like Effector Nuclease

(TALEN), and maganucleases. Nucleases can be naturally existing nucleases, genetically modified, and/or recombinant. For example, a CRISPR/Cas system can be suitable as a gene editing system.

[00269] It is also contemplated that less than all alleles of one or more genes of a non-human animal can be knocked out. For example, in diploid non-human animals, it is contemplated that one of two alleles are knocked out. This can result in decreased expression and decreased protein levels of genes. Overall decreased expression can be less than or less than about 99%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or 20%; *e.g.,* from or from about 99% to 90%; 90% to 80%; 80% to 70%; 70% to 60%; 60% to 50%; 50% to 40%; 40% to 30%, or 30% to 20%; compared to when both alleles are functioning, for example, not knocked out and/or knocked down. Additionally, overall decrease in protein level can be the same as the decreased in overall expression. Overall decrease in protein level can be about or less than about 99%, 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, or 20%, *e.g.,* from or from about 99% to 90%; 90% to 80%; 80% to 70%; 70% to 60%; 60% to 50%; 50% to 40%; 40% to 30%, or 30% to 20%; compared to when both alleles are functioning, for example, not knocked out and/or knocked down. However, it is also contemplated that all alleles of one or more genes in a non-human animal can be knocked out.

[00270] Knockouts of one or more genes can be verified by genotyping. Methods for genotyping can include sequencing, restriction fragment length polymorphism identification (RFLPI), random amplified polymorphic detection (RAPD), amplified fragment length polymorphism detection (AFLPD), PCR (*e.g.,* long range PCR, or stepwise PCR), allele specific oligonucleotide (ASO) probes, and hybridization to DNA microarrays or beads. For example, genotyping can be performed by sequencing. In some cases, sequencing can be high fidelity sequencing. Methods of sequencing can include Maxam-Gilbert sequencing, chain-termination methods (*e.g.,* Sanger sequencing), shotgun sequencing, and bridge PCR. In some cases, genotyping can be performed by next-generation sequencing. Methods of next-generation sequencing can include massively parallel signature sequencing, colony sequencing, pyrosequencing (*e.g.,* pyrosequencing developed by 454 Life Sciences), single-molecule rea-time sequencing (*e.g.,* by Pacific Biosciences), Ion semiconductor sequencing (*e.g.,* by Ion Torrent semiconductor sequencing), sequencing by synthesis (*e.g.,* by Solexa sequencing by Illumina), sequencing by ligation (*e.g.,* SOLiD sequencing by Applied Biosystems), DNA nanoball sequencing, and heliscope single molecule sequencing. In some cases, genotyping of a non-human animal herein can comprise full genome sequencing analysis. In some cases, knocking out of a gene in an animal can be validated by sequencing (*e.g.,* next-generation

sequencing) a part of the gene or the entire gene. For example, knocking out of NLRC5 gene in a pig can be validated by next generation sequencing of the entire NLRC5. The next generation sequencing of NLRC5 can be performed using *e.g.* using forward primer 5'-gctgtggcatatggcagttc -3' (SEQ ID No. 1) and reverse primer 5'-tccatgtataagtctttta-3' (SEQ ID No. 2), or forward primer 5'- ggcaatgccagatcctcaac -3' (SEQ ID No. 3) and reverse primer 5'-tgtctgatgtctttctcatg -3' (SEQ ID No. 4).

Table 1. Genomic sequences, cDNA and proteins of exemplary disrupted genes*

	Genomic sequence	**cDNA**		**protein**	
Gene	SEQ ID No.	SEQ ID No.	Accession No.	SEQ ID No.	Accession No.
NLRC5	5	6	KC514136.1	7	AGG68119.1
TAP1	8	9	NM_001044581	10	NP_001038046.1
GGTA1	11	12	AF221508	13	NP_998975.1
CMAH	14	15	NM_001113015	16	NP_001106486.1
CXCL10	17	18	NM_001008691.1	19	NP_001008691.1
CIITA	20	21	XM_013995652.1	22	XP_013851106.1
B4GALNT2	23	24	NM_001244330.1	25	NP_001231259.1
C3	26	27	NM_214009.1	28	NP_999174.1
MICA	29	30	NM_000247.2	31	NP_000238.1
MICB	32	33	NM_001289160.1	34	NP_001276089.1

*The sequences for Table 1 can be found in Table 18.

Transgenes

[00271] Transgenes, or exogenous nucleic acid sequences, can be useful for overexpressing endogenous genes at higher levels than without the transgenes. Additionally, exogenous nucleic acid sequences can be used to express exogenous genes. Transgenes can also encompass other types of genes, for example, a dominant negative gene.

[00272] A transgene of protein X can refer to a transgene comprising an exogenous nucleic acid sequence encoding protein X. As used herein, in some cases, a transgene encoding protein X can be a transgene encoding 100% or about 100% of the amino acid sequence of protein X. In some cases, a transgene encoding protein X can encode the full or partial amino sequence of protein X. For example, the transgene can encode at least or at least about 99%, 95%, 90%, 80%, 70%,

60%, 50%, 40%, 30%, 20%, 10%, or 5%, *e.g.,* from or from about 99% to 90%; 90% to 80%; 80% to 70%; 70% to 60%; or 60% to 50%; of the amino acid sequence of protein X. Expression of a transgene can ultimately result in a functional protein, *e.g.,* a partially or fully functional protein. As discussed above, if a partial sequence is expressed, the ultimate result can be in some cases a nonfunctional protein or a dominant negative protein. A nonfunctional protein or dominant negative protein can also compete with a functional (endogenous or exogenous) protein. A transgene can also encode an RNA (*e.g.,* mRNA, shRNA, siRNA, or microRNA). In some cases, where a transgene encodes for an mRNA, this can in turn be translated into a polypeptide (*e.g.,* a protein). Therefore, it is contemplated that a transgene can encode for protein. A transgene can, in some instances, encode a protein or a portion of a protein. Additionally, a protein can have one or more mutations (*e.g.,* deletion, insertion, amino acid replacement, or rearrangement) compared to a wild-type polypeptide. A protein can be a natural polypeptide or an artificial polypeptide (*e.g.,* a recombinant polypeptide). A transgene can encode a fusion protein formed by two or more polypeptides.

[00273] Where a transgene, or exogenous nucleic acid sequence, encodes for an mRNA based on a naturally occurring mRNA (e.g., an mRNA normally found in another species), the mRNA can comprise one or more modifications in the 5' or 3' untranslated regions. The one or more modifications can comprise one or more insertions, on or more deletions, or one or more nucleotide changes, or a combination thereof. The one or more modifications can increase the stability of the mRNA. The one or more modifications can remove a binding site for an miRNA molecule, such as an miRNA molecule that can inhibit translation or stimulate mRNA degradation. For example, an mRNA encoding for a HLA-G protein can be modified to remove a biding site for an miR148 family miRNA. Removal of this binding site can increase mRNA stability.

[00274] Transgenes can be placed into an organism, cell, tissue, or organ, in a manner which produces a product of the transgene. For example, disclosed herein is a non-human animal comprising one or more transgenes. One or more transgenes can be in combination with one or more disruptions as described herein. A transgene can be incorporated into a cell. For example, a transgene can be incorporated into an organism's germ line. When inserted into a cell, a transgene can be either a complementary DNA (cDNA) segment, which is a copy of messenger RNA (mRNA), or a gene itself residing in its original region of genomic DNA (with or without introns).

[00275] A transgene can comprise a polynucleotide encoding a protein of a species and expressing the protein in an animal of a different species. For example, a transgene can comprise a polynucleotide encoding a human protein. Such a polynucleotide can be used express the human protein (e.g., CD47) in a non-human animal (e.g., a pig). In some cases, the polynucleotide can be synthetic, e.g., different from any native polynucleotide in sequence and/or chemical characteristics.

[00276] The polynucleotide encoding a protein of species X can be optimized to express the protein in an animal of a species Y. There may be codon usage bias (e.g., differences in the frequency of occurrence of synonymous codons in coding DNA). A codon can be a series of nucleotides (e.g., a series of 3 nucleotides) that encodes a specific amino acid residue in a polypeptide chain or for the termination of translation (stop codons). Different species may have different preference in the DNA codons. The optimized polynucleotide can encode a protein of species X, in some cases with codons of a species Y, so that the polynucleotide can express the protein more efficiently in the species Y, compared to the native gene encoding the protein of species X. In some cases, an optimized polynucleotide can express a protein at least 5%, 10%, 20%, 40%, 80%, 90%, 1.5 folds, 2 folds, 5 folds, or 10 folds more efficiently in species Y than a native gene of species X encoding the same protein.

[00277] Human Leukocyte Antigen G (HLA-G)

[00278] HLA-G can be a potent immuno-inhibitory and tolerogenic molecule. HLA-G expression in a human fetus can enable the human fetus to elude the maternal immune response. Neither stimulatory functions nor responses to allogeneic HLA-G have been reported to date. HLA-G can be a non-classical HLA class I molecule. It can differ from classical MHC class I molecules by its genetic diversity, expression, structure, and function. HLA-G can be characterized by a low allelic polymorphism. Expression of HLA-G can be restricted to trophoblast cells , adult thymic medulla , and stem cells . However, HLA-G neo-expression may be induced in pathological conditions such as cancers, multiple sclerosis, inflammatory diseases, or viral infections.

[00279] Seven isoforms of HLA-G have been identified. The different isoforms can be products of alternative splicing. Four of these can be membrane bound (HLA-G1 to -G4), and 3 can be soluble isoforms (HLA-G5 to -G7). HLA-G1 and HLA-G5 isoforms present the typical structure of the classical HLA class I molecules formed by a 3 globular domain (α1-α3) heavy-chain, noncovalently associated to β-2-microglobulin (B2M) and a nonapeptide. The truncated isoforms

lack 1 or 2 domains, although they all contain the α1 domain, and they are all B2M-free isoforms.

[00280] HLA-G can exerts an immuno-inhibitory function through direct binding to inhibitory receptors, e.g., ILT2/CD85j/LILRB1, ILT4/CD85d/LILRB2, or KIR2DL4/CD158d.

[00281] ILT2 can be expressed by B cells, some T cells, some NK cells, and monocytes/dendritic cells. ILT4 can be myeloid-specific and its expression can be restricted to monocytes/dendritic cells. KIR2DL4 can be a specific receptor for HLA-G. It can be expressed by the $CD56^{bright}$ subset of NK cells. ILT2 and ILT4 receptors can bind a wide range of classical HLA molecules through the α3 domain and B2M. However, HLA-G can be their ligand of highest affinity.

[00282] ILT2-HLA-G interaction can mediate the inhibition of, for example: i) NK and antigen-specific CD8+ T cell cytolytic function, ii) alloproliferative response of CD4+T cells, and iii) maturation and function of dendritic cells. ILT2-HLA-G interaction can impede both naïve and memory B cell function in vitro and in vivo. HLA-G can inhibit B cell proliferation, differentiation, and Ig secretion in both T cell-dependent and –independent models of B cell activation. HLA-G can act as a negative B cell regulator in modulating B cell Ab secretion. HLA-G can also induce the differentiation of regulatory T cells, which can then inhibit allogeneic responses themselves may participate in the tolerance of allografts.

[00283] The expression of HLA-G by tumor cells can enable the escape of immunosurveillance mediated by host T lymphocytes and NK cells. Thus, the expression of HLA-G by malignant cells may prevent tumor immune eradication by inhibiting the activity of tumor-infiltrating NK cells, cytotoxic T lymphocytes (CTLs), and antigen presenting cells (APCs).

[00284] The HLA-G structure variation, particularly its monomeric/multimeric status and its association with B2M, can play a role in the biological function of HLA-G, its regulation and its interactions with the inhibitory receptors ILT2 and ILT4.

[00285] ILT2 and ILT4 inhibitory receptors may have a higher affinity for HLA-G multimers than monomeric structures. HLA-G1 and HLA-G5 (HLA-G1/5) can form dimers through disulphide bonds between unique cysteine residues at positions 42 (Cys42–Cys42), within the α1 domain. Dimers of B2M-associated HLA-G1 may bind ILT2 and ILT4 with higher affinity than monomers. This increased affinity of dimers may be due to an oblique orientation that exposes the ILT2- and ILT4-binding sites of the α3 domain, making it more accessible to the receptors. Both ILT2 and ILT4 can bind the HLA-G α3 domain at the level of F195 and Y197 residues.

[00286] ILT2 and ILT4 bind differently to their HLA-G isoforms. ILT2 may recognize only B2M-associated HLA-G structures, whereas ILT4 may recognize both B2M-associated and B2M-free HLA-G heavy chains. B2M-free heavy chains have been detected at the cell surface and in culture supernatants of HLA-G-expressing cells. Furthermore, B2M-free HLA-G heavy chains may be the main structure produced by human villous trophoblast cells. The presence of (B2M-free) α1 - α3 structures (HLA-G2 and G-6 isoforms) was shown in the circulation of human heart transplant recipients and may be associated with better allograft acceptance. The α1 - α3 structure may bind only to ILT4 but not ILT2. However, α1 - α3 dimers (with dimerization of α1- α3 monomers achieved through disulfide bonds between two free cysteines in position 42) may be tolerogenic in vivo in an allogeneic murine skin transplantation model. An (α1 - α3)x2 synthetic molecule may inhibit the proliferation of tumor cell lines that did not express ILT4. This may indicate the existence of yet unknown receptors for HLA-G.

[00287] Accordingly, in one aspect, disclosed herein are genetically modified non-human animals and cells comprising an exogenous nucleic acid sequence encoding for an HLA-G protein. The genetically modified non-human animals and cells can also comprise one or more additional genetic modifications, such as any of the genetic modifications (e.g., knock-ins, knock-outs, gene disruptions, etc.) disclosed herein. For example, the genetically modified non-human animals and cells can also comprise another exogenous nucleic acid sequence encoding a B2M protein.

[00288] A non-human animal can comprise one or more transgenes comprising one or more polynucleotide inserts. The polynucleotide inserts can encode one or proteins or functional fragments thereof. For example, a non-human genetically modified animal can comprise one or more exogenous nucleic acid sequences encoding one or more proteins or functional fragments thereof. In some cases, a non-human animal can comprise one or more transgenes comprising one or more polynucleotide inserts encoding proteins that can reduce expression and/or function of MHC molecules (*e.g.*, MHC I molecules and/or MHC II molecules). The one or more transgenes can comprise one or more polynucleotide inserts encoding MHC I formation suppressors, regulators of complement activations, inhibitory ligands for NK cells, B7 family members, CD47, serine protease inhibitors, galectins, and/or any fragments thereof. In some cases, the MHC I formation suppressors can be infected cell protein 47 (ICP47). In some cases, regulators of complement activation can comprise cluster of differentiation 46 (CD46), cluster of differentiation 55 (CD55), and cluster of differentiation 59 (CD59). In some cases, inhibitory ligands for NK cells can comprise leukocyte antigen E (HLA-E), human leukocyte antigen G (HLA-G), and β-2-microglobulin (B2M). An inhibitory ligand for NK cells can be an isoform of

HLA-G, *e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7. For example, inhibitory ligand for NK cells can be HLA-G1. A transgene of HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7) can refer to a transgene comprising a nucleotide sequence encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7). As used herein, in some cases, a transgene encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7) can be a transgene encoding 100% or about 100% of the amino acid sequence of HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7). In other cases, a transgene encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7) can be a transgene encoding the full or partial sequence of HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7). For example, the transgene can encode at least or at least about 99%, 95%, 90%, 80%, 70%, 60%, or 50% of the amino acid sequence of HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7). For example, the transgene can encode 90% of the HLA-G amino acid sequence. A transgene can comprise polynucleotides encoding a functional (*e.g.*, a partially or fully functional) HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7). In some cases, the one or more transgenes can comprise one or more polynucleotide inserts encoding one or more of ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), and B2M. The HLA-G genomic DNA sequence can have 8 exons by which alternative splicing results in 7 isoforms. The HLA-G1 isoform can exclude exon 7. The HLA-G2 isoform can exclude exon 3 and 7. Translation of intron 2 or intron 4 can result secreted isoforms due to the loss of the transmembrane domain expression. The maps of the genomic sequence and cDNA of HLA-G are shown in **FIGs. 14A-14B**. In some cases, B7 family members can comprise CD80, CD86, programed death-ligand 1 (PD-L1), programed death-ligand 2 (PD-L2), CD275, CD276, V-set domain containing T cell activation inhibitor 1 (VTCN1), platelet receptor Gi24, natural cytotoxicity triggering receptor 3 ligand 1 (NR3L1), and HERV-H LTR-associating 2 (HHLA2). For example, a B7 family member can be PD-L1 or PD-L2. In some cases, a serine protease inhibitor can be serine protease inhibitor 9 (Spi9). In some cases, galectins can comprise galectin-1, galectin-2, galectin-3, galectin-4, galectin-5, galectin-6, galectin-7, galectin-8, galectin-9, galectin-10, galectin-11, galectin-12, galectin-13, galectin-14, and galectin-15. For example, a galectin can be galectin-9.

[00289] A genetically modified non-human animal can comprise reduced expression of one or more genes and one or more transgenes disclosed herein. In some cases, a genetically modified non-human animal can comprise reduced expression of one or more of NLRC5, TAP1,

CXCL10, MICA, MICB, C3, CIITA, GGTA1, CMAH, and B4GALNT2, and one or more transgenes comprising one or more polynucleotide inserts encoding one or more of ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, PD-L1, PD-L2, CD47, Spi9, and galectin-9. In some cases, a genetically modified non-human animal can comprise reduced expression GGTA1, CMAH, and B4GALNT2, and exogenous polynucleotides encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), CD47 (*e.g.*, human CD47), PD-L1 (*e.g.*, human PD-L1), and PD-L2 (*e.g.*, human PD-L2). In some cases, a genetically modified non-human animal can comprise reduced expression GGTA1, CMAH, and B4GALNT2, and exogenous polynucleotides encoding HLA-E, CD47 (*e.g.*, human CD47), PD-L1 (*e.g.*, human PD-L1), and PD-L2 (*e.g.*, human PD-L2). In some cases, a genetically modified non-human animal can comprise reduced expression NLRC5, C3, CXC10, GGTA1, CMAH, and B4GALNT2, and exogenous polynucleotides encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), CD47 (*e.g.*, human CD47), PD-L1 (*e.g.*, human PD-L1), and PD-L2 (*e.g.*, human PD-L2). In some cases, a genetically modified non-human animal can comprise reduced expression TAP1, C3, CXC10GGTA1, CMAH, and B4GALNT2, and exogenous polynucleotides encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), CD47 (*e.g.*, human CD47), PD-L1 (*e.g.*, human PD-L1), and PD-L2 (*e.g.*, human PD-L2). In some cases, a genetically modified non-human animal can comprise reduced expression NLRC5, C3, CXC10, GGTA1, CMAH, and B4GALNT2, and exogenous polynucleotides encoding HLA-E, CD47 (*e.g.*, human CD47), PD-L1 (*e.g.*, human PD-L1), and PD-L2 (*e.g.*, human PD-L2). In some cases, a genetically modified non-human animal can comprise reduced expression TAP1, C3, CXC10, GGTA1, CMAH, and B4GALNT2, and exogenous polynucleotides encoding HLA-E. In some cases, a genetically modified non-human animal can comprise reduced expression of GGTA1 and a transgene comprising one or more polynucleotide inserts encoding HLA-E. In some cases, a genetically modified non-human animal can comprise reduced expression of GGTA1 and a transgene comprising one or more polynucleotide inserts encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7). In some cases, a genetically modified non-human animal can comprise a transgene comprising one or more polynucleotide inserts encoding HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7) inserted adjacent to a Rosa26 promoter, *e.g.*, a porcine Rosa26 promoter. In some cases, a genetically modified non-human animal can comprise reduced expression of NLRC5, C3, GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where

the proteins comprise HLA-G1, Spi9, PD-L1, PD-L2, CD47, and galectin-9. In some cases, a genetically modified non-human animal can comprise reduced expression of TAP1, C3, GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the proteins comprise HLA-G1, Spi9, PD-L1, PD-L2, CD47, and galectin-9. In some cases, a genetically modified non-human animal can comprise reduced expression of NLRC5, TAP1, C3, GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the proteins comprise HLA-G1, Spi9, PD-L1, PD-L2, CD47, and galectin-9. In some cases, a genetically modified non-human animal can comprise reduced protein expression of NLRC5, C3, GGTA1, and CXCL10, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the protein comprise HLA-G1 or HLA-E. In some cases, a genetically modified non-human animal can comprise reduced protein expression of TAP1, C3, GGTA1, and CXCL10, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the protein comprise HLA-G1 or HLA-E. In some cases, a genetically modified non-human animal can comprise reduced protein expression of NLRC5, TAP1, C3, GGTA1, and CXCL10, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the protein comprise HLA-G1 or HLA-E. In some cases, CD47, PD-L1, and PD-L2 encoded by the transgenes herein can be human CD47, human PD-L1 and human PD-L2.

[00290] A genetically modified non-human animal can comprise a transgene inserted in a locus in the genome of the animal. In some cases, a transgene can be inserted adjacent to the promoter of or inside a targeted gene. In some cases, insertion of the transgene can reduce the expression of the targeted gene. The targeted gene can be a gene whose expression is reduced disclosed herein. For example, a transgene can be inserted adjacent to the promoter of or inside one or more of NLRC5, TAP1, CXCL10, MICA, MICB, C3, CIITA, GGTA1, CMAH, and B4GALNT2. In some cases, a transgene can be inserted adjacent to the promoter of or inside GGTA1. In some cases, a transgene (e.g., a CD47 transgene) can be inserted adjacent to a promoter that allows the transgene to selectively expression in certain types of cells. For example, a CD47 transgene can be inserted adjacent to promoter that allows the CD47 transgene to selectively express in blood cells and splenocytes. One of such promoters can be GGTA1 promoters.

[00291] For example, a non-human animal can comprise one or more transgenes (e.g., exogenous nucleic acid sequences) comprising one or more polynucleotide inserts of Infected cell protein 47 (ICP47), Cluster of differentiation 46 (CD46), Cluster of differentiation 55 (CD55), Cluster of differentiation 59 (CD 59), HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-

G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, Spi9, PD-L1, PD-L2, CD47, galectin-9, any functional fragments thereof, or any combination thereof. Polynucleotide encoding for ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), or B2M can encode one or more of ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, Spi9, PD-L1, PD-L2, CD47, or galectin-9 human proteins. A non-human animal can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more transgenes. For example, a non-human animal can comprise one or more transgene comprising ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, Spi9, PD-L1, PD-L2, CD47, galectin-9, any functional fragments thereof, or any combination thereof. A non-human animal can also comprise a single transgene encoding ICP47. A non-human animal can sometimes comprise a single transgene encoding CD59. A non-human animal can sometimes comprise a single transgene encoding HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7). A non-human animal can sometimes comprise a single transgene encoding HLA-E. A non-human animal can sometimes comprise a single transgene encoding B2M. A non-human animal can also comprise two or more transgenes, where the two or more transgenes are ICP47, CD46, CD55, CD59, and/or any combination thereof. For example, two or more transgenes can comprise CD59 and CD46 or CD59 and CD55. A non-human animal can also comprise three or more transgenes, where the three or more transgenes can comprise ICP47, CD46, CD55, CD59, or any combination thereof. For example, three or more transgenes can comprise CD59, CD46, and CD55. A non-human animal can also comprise four or more transgenes, where the four or more transgenes can comprise ICP47, CD46, CD55, and CD59. A non-human animal can comprise four or more transgenes comprising ICP47, CD46, CD55, and CD59.

[00292] A combination of transgenes and gene disruptions can be used. A non-human animal can comprise one or more reduced genes and one or more transgenes. For example, one or more genes whose expression is reduced can comprise any one of NLRC5, TAP1, GGTA1, B4GALNT2, CMAH, CXCL10, MICA, MICB, C3, CIITA, and/or any combination thereof, and one or more transgene can comprise ICP47, CD46, CD55, CD 59, any functional fragments thereof, and/or any combination thereof. For example, solely to illustrate various combinations, one or more genes whose expression is disrupted can comprise NLRC5 and one or more transgenes comprise ICP47. One or more genes whose expression is disrupted can also comprise TAP1, and one or more transgenes comprise ICP47. One or more genes whose expression is disrupted can also comprise NLRC5 and TAP1, and one or more transgenes comprise ICP47.

One or more genes whose expression is disrupted can also comprise NLRC5, TAP1, and GGTA1, and one or more transgenes comprise ICP47. One or more genes whose expression is disrupted can also comprise NLRC5, TAP1, B4GALNT2, and CMAH, and one or more transgenes comprise ICP47. One or more genes whose expression is disrupted can also comprise NLRC5, TAP1, GGTA1, B4GALNT2, and CMAH, and one or more transgenes comprise ICP47. One or more genes whose expression is disrupted can also comprise NLRC5 and one or more transgenes comprise CD59. One or more genes whose expression is disrupted can also comprise TAP1, and one or more transgenes comprise CD59. One or more genes whose expression is disrupted can also comprise NLRC5 and TAP1, and one or more transgenes comprise CD59. One or more genes whose expression is disrupted can also comprise NLRC5, TAP1, and GGTA1, and one or more transgenes comprise CD59. One or more genes whose expression is disrupted can also comprise NLRC5, TAP1, B4GALNT2, and CMAH, and one or more transgenes comprise CD59. One or more genes whose expression is disrupted can also comprise NLRC5, TAP1, GGTA1, B4GALNT2, and CMAH, and one or more transgenes comprise CD59.

[00293] In some cases, a first exon of a gene is genetically modified. For example, one or more first exons of a gene that can be genetically modified can be a gene selected from a group consisting of NLRC5, TAP1, GGTA1, B4GALNT2, CMAH, CXCL10, MICA, MICB, C3, CIITA, and any combination thereof. For example, **FIG. 112 A** shows a guide RNA targeted a first exon of an NLCR5 gene. In other cases, a second exon of a gene is targeted. For example, **FIG. 105, FIG. 106,** and **FIG. 107** show relevant sequences for primer pairs to generate first and second exon targeting guide RNAs as well as primer sequences to determine genetic modification by sequencing.

[00294] Transgenes that can be used and are specifically contemplated can include those genes that exhibit a certain identity and/or homology to genes disclosed herein, for example, ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, Spi9, PD-L1, PD-L2, CD47, galectin-9, any functional fragments thereof, and/or any combination thereof. Therefore, it is contemplated that if gene that exhibits at least or at least about 60%, 70%, 80%, 90%, 95%, 98%, or 99% homology, *e.g.,* at least or at least about 99% to 90%; 90% to 80%; 80% to 70%; 70% to 60% homology; (at the nucleic acid or protein level), it can be used as a transgene. It is also contemplated that a gene that exhibits at least or at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, identity *e.g.,* at least or at least about 99% to 90%; 90% to 80%; 80% to 70%; 70% to 60% identity; (at the nucleic acid or protein level) can be used as a transgene.

[00295] A non-human animal can also comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more dominant negative transgenes. Expression of a dominant negative transgenes can suppress expression and/or function of a wild type counterpart of the dominant negative transgene. Thus, for example, a non-human animal comprising a dominant negative transgene X, can have similar phenotypes compared to a different non-human animal comprising an X gene whose expression is reduced. One or more dominant negative transgenes can be dominant negative NLRC5, dominant negative TAP1, dominant negative GGTA1, dominant negative CMAH, dominant negative B4GALNT2, dominant negative CXCL10, dominant negative MICA, dominant negative MICB, dominant negative CIITA, dominant negative C3, or any combination thereof.

[00296] Also provided is a non-human animal comprising one or more transgenes that encodes one or more nucleic acids that can suppress genetic expression, *e.g.,* can knockdown a gene. RNAs that suppress genetic expression can comprise, but are not limited to, shRNA, siRNA, RNAi, and microRNA. For example, siRNA, RNAi, and/or microRNA can be given to a non-human animal to suppress genetic expression. Further, a non-human animal can comprise one or more transgene encoding shRNAs. shRNA can be specific to a particular gene. For example, a shRNA can be specific to any gene described in the application, including but not limited to, NLRC5, TAP1, GGTA1, B4GALNT2, CMAH, CXCL10, MICA, MICB, B4GALNT2, CIITA, C3, and/or any combination thereof.

[00297] When transplanted to a subject, cells, tissues, or organs from the genetically modified non-human animal can trigger lower immune responses (*e.g.,* transplant rejection) in the subject compared to cells, tissues, or organs from a non-genetically modified counterpart. In some cases, the immune responses can include the activation, proliferation and cytotoxicity of T cells (*e.g.,* CD8+ T cells and/or CD4+ T cells) and NK cells. Thus, phenotypes of genetically modified cells disclosed herein can be measured by co-culturing the cells with NK cells, T cells (*e.g.,* CD8+ T cells or CD4+ T cells), and testing the activation, proliferation and cytotoxicity of the NK cells or T cells. In some cases, the T cells or NK cells activation, proliferation and cytotoxicity induced by the genetically modified cells can be lower than that induced by non-genetically modified cells. In some cases, phenotypes of genetically modified cells herein can be measured by Enzyme-Linked ImmunoSpot (ELISPOT) assays.

[00298] One or more transgenes can be from different species. For example, one or more transgenes can comprise a human gene, a mouse gene, a rat gene, a pig gene, a bovine gene, a dog gene, a cat gene, a monkey gene, a chimpanzee gene, or any combination thereof. For

example, a transgene can be from a human, having a human genetic sequence. One or more transgenes can comprise human genes. In some cases, one or more transgenes are not adenoviral genes.

[00299] A transgene can be inserted into a genome of a non-human animal in a random or site-specific manner. For example, a transgene can be inserted to a random locus in a genome of a non-human animal. These transgenes can be fully functional if inserted anywhere in a genome. For instance, a transgene can encode its own promoter or can be inserted into a position where it is under the control of an endogenous promoter. Alternatively, a transgene can be inserted into a gene, such as an intron of a gene or an exon of a gene, a promoter, or a non-coding region. A transgene can be integrated into a first exon of a gene.

[00300] Sometimes, more than one copy of a transgene can be inserted into more than a random locus in a genome. For example, multiple copies can be inserted into a random locus in a genome. This can lead to increased overall expression than if a transgene was randomly inserted once. Alternatively, a copy of a transgene can be inserted into a gene, and another copy of a transgene can be inserted into a different gene. A transgene can be targeted so that it could be inserted to a specific locus in a genome of a non-human animal.

[00301] Expression of a transgene can be controlled by one or more promoters. A promoter can be a ubiquitous, tissue-specific promoter or an inducible promoter. Expression of a transgene that is inserted adjacent to a promoter can be regulated. For example, if a transgene is inserted near or next to a ubiquitous promoter, the transgene will be expressed in all cells of a non-human animal. Some ubiquitous promoters can be a CAGGS promoter, an hCMV promoter, a PGK promoter, an SV40 promoter, or a Rosa26 promoter.

[00302] A promoter can be endogenous or exogenous. For example, one or more transgenes can be inserted adjacent to an endogenous or exogenous Rosa26 promoter. Further, a promoter can be specific to a non-human animal. For example, one or more transgenes can be inserted adjacent to a porcine Rosa26 promoter.

[00303] Tissue specific promoter (which can be synonymous with cell-specific promoters) can be used to control the location of expression. For example, one or more transgenes can be inserted adjacent to a tissue-specific promoter. Tissue-specific promoters can be a FABP promoter, a Lck promoter, a CamKII promoter, a CD19 promoter, a Keratin promoter, an Albumin promoter, an aP2 promoter, an insulin promoter, an MCK promoter, an MyHC promoter, a WAP promoter, or a Col2A promoter. For example, a promoter can be a pancreas-specific promoter, *e.g.,* an insulin promoter.

[00304] Inducible promoters can be used as well. These inducible promoters can be turned on and off when desired, by adding or removing an inducing agent. It is contemplated that an inducible promoter can be a Lac, tac, trc, trp, araBAD, phoA, recA, proU, cst-1, tetA, cadA, nar, PL, cspA, T7, VHB, Mx, and/or Trex.

[00305] A non-human animal or cells as described herein can comprise a transgene encoding insulin. A transgene encoding insulin can be a human gene, a mouse gene, a rat gene, a pig gene, a cattle gene, a dog gene, a cat gene, a monkey gene, a chimpanzee gene, or any other mammalian gene. For example, a transgene encoding insulin can be a human gene. A transgene encoding insulin can also be a chimeric gene, for example, a partially human gene.

[00306] Expression of transgenes can be measured by detecting the level of transcripts of the transgenes. For example, expression of transgenes can be measured by Northern blotting, nuclease protection assays (*e.g.,* RNase protection assays), reverse transcription PCR, quantitative PCR (*e.g.,* real-time PCR such as real-time quantitative reverse transcription PCR), in situ hybridization (*e.g.,* fluorescent in situ hybridization (FISH)), dot-blot analysis, differential display, Serial analysis of gene expression, subtractive hybridization, microarrays, nanostring, and/or sequencing (*e.g.,* next-generation sequencing). In some cases, expression of transgenes can be measured by detecting proteins encoded by the genes. For example, expression of one or more genes can be measured by protein immunostaining, protein immunoprecipitation, electrophoresis (*e.g.,* SDS-PAGE), Western blotting, bicinchoninic acid assay, spectrophotometry, mass spectrometry, enzyme assays (*e.g.,* enzyme-linked immunosorbent assays), immunohistochemistry, flow cytometry, and/or immunocytochemistry. In some cases, expression of transgenes can be measured by microscopy. The microscopy can be optical, electron, or scanning probe microscopy. In some cases, optical microscopy comprises use of bright field, oblique illumination, cross-polarized light, dispersion staining, dark field, phase contrast, differential interference contrast, interference reflection microscopy, fluorescence (*e.g.,* when particles, *e.g.,* cells, are immunostained), confocal, single plane illumination microscopy, light sheet fluorescence microscopy, deconvolution, or serial time-encoded amplified microscopy.

[00307] Insertion of transgenes can be validated by genotyping. Methods for genotyping can include sequencing, restriction fragment length polymorphism identification (RFLPI), random amplified polymorphic detection (RAPD), amplified fragment length polymorphism detection (AFLPD), PCR (*e.g.,* long range PCR, or stepwise PCR), allele specific oligonucleotide (ASO) probes, and hybridization to DNA microarrays or beads. In some cases, genotyping can be

performed by sequencing. In some cases, sequencing can be high fidelity sequencing. Methods of sequencing can include Maxam-Gilbert sequencing, chain-termination methods (*e.g.,* Sanger sequencing), shotgun sequencing, and bridge PCR. In some cases, genotyping can be performed by next-generation sequencing. Methods of next-generation sequencing can include massively parallel signature sequencing, colony sequencing, pyrosequencing (*e.g.,* pyrosequencing developed by 454 Life Sciences), single-molecule rea-time sequencing (*e.g.,* by Pacific Biosciences), Ion semiconductor sequencing (*e.g.,* by Ion Torrent semiconductor sequencing), sequencing by synthesis (*e.g.,* by Solexa sequencing by Illumina), sequencing by ligation (*e.g.,* SOLiD sequencing by Applied Biosystems), DNA nanoball sequencing, and heliscope single molecule sequencing. In some cases, genotyping of a non-human animal herein can comprise full genome sequencing analysis.

[00308] In some cases, insertion of a transgene in an animal can be validated by sequencing (*e.g.,* next-generation sequencing) a part of the transgene or the entire transgene. For example, insertion of a transgene adjacent to a Rosa26 promoter in a pig can be validated by next generation sequencing of Rosa exons 1 to 4, *e.g.,* using the forward primer 5'-cgcctagagaagaggctgtg-3' (SEQ ID No. 35), and reverse primer 5'-ctgctgtggctgtggtgtag -3' (SEQ ID No. 36).

Table 2. cDNA sequences of exemplary transgenes*

SEQ ID No.	Gene	Accession No.
37	CD46	NM_213888
38	CD55	AF228059.1
39	CD59	AF020302
40	ICP47	EU445532.1
41	HLA-G1	NM_002127.5
42	HLA-E	NM_005516.5
43	Human β-2-microglobulin	NM_004048.2
44	Human PD-L1	NM_001267706.1
45	Human PD-L2	NM_025239.3
46	Human Spi9	NM_004155.5
47	Human CD47	NM_001777.3
48	Human galectin-9	NM_009587.2

*The sequences for Table 2 can be found in Table 18.

Table 3. Sequences of proteins encoded by exemplary transgenes*

SEQ ID No.	Protein	Accession No.
49	CD46	NP_999053.1
50	CD55	AAG14412.1
51	CD59	AAC67231.1
52	ICP47	ACA28836.1
53	HLA-G1	NP_002118.1
54	HLA-E	NP_005507.3
55	Human β-2-microglobulin	NP_004039.1
56	Human PD-L1	NP_001254635.1
57	Human PD-L2	NP_079515.2
58	Human Spi9	NP_004146.1
59	Human CD47	NP_001768.1
60	Human galectin-9	NP_033665.1

*The sequences for Table 3 can be found in Table 18.

Populations of Non-Human Animals

[00309] Provided herein is a single non-human animal and also a population of non-human animals. A population of non-human animals can be genetically identical. A population of non-human animals can also be phenotypical identical. A population of non-human animals can be both phenotypical and genetically identical.

[00310] Further provided herein is a population of non-human animals, which can be genetically modified. For example, a population can comprise at least or at least about 2, 5, 10, 50, 100, or 200, non-human animals as disclosed herein. The non-human animals of a population can have identical phenotypes. For example, the non-human animals of a population can be clones. A population of non-human animal can have identical physical characteristics. The non-human animals of a population having identical phenotypes can comprise a same transgene(s). The non-human animals of a population having identical phenotypes can also comprise a same gene(s) whose expression is reduced. The non-human animals of a population having identical phenotypes can also comprise a same gene(s) whose expression is reduced and comprise a same transgene(s). A population of non-human animals can comprise at least or at least about 2, 5, 10, 50, 100, or 200, non-human animals having identical phenotypes. For example, the phenotypes of any particular litter can have the identical phenotype (*e.g.*, in one example, anywhere from 1

to about 20 non-human animals). The non-human animals of a population can be pigs having identical phenotypes.

[00311] The non-human animals of a population can have identical genotypes. For example, all nucleic acid sequences in the chromosomes of non-human animals in a population can be identical. The non-human animals of a population having identical genotypes can comprise a same transgene(s). The non-human animals of a population having identical genotypes can also comprise a same gene(s) whose expression is reduced. The non-human animals of a population having identical genotypes can also comprise a same gene(s) whose expression is reduced and comprise a same transgene(s). A population of non-human animals can comprise at least or at least about 2, 5, 50, 100, or 200 non-human animals having identical genotypes. The non-human animals of a population can be pigs having identical genotypes.

[00312] Cells from two or more non-human animals with identical genotypes and/or phenotypes can be used in a tolerizing vaccine. In some cases, a tolerizing vaccine disclosed herein can comprise a plurality of the cells (*e.g.*, genetically modified cells) from two or more non-human animals (*e.g.*, pigs) with identical genotypes and/or phenotypes. A method for immunotolerizing a recipient to a graft can comprise administering to the recipient a tolerizing vaccine comprising a plurality of cells (*e.g.*, genetically modified cells) from two or more non-human animals with identical genotypes or phenotypes.

[00313] Cells from two or more non-human animals with identical genotypes and/or phenotypes can be used in transplantation**.** In some cases, a graft (*e.g.*, xenograft or allograft) can comprise a plurality of cells from two or more non-human animals with identical genotypes and/or phenotypes. In embodiments of the methods described herein, *e.g.*, a method for treating a disease in a subject in need thereof, can comprise transplanting a plurality of cells (*e.g.*, genetically modified cells) from two or more non-human animals with identical genotypes and/or phenotypes.

[00314] Populations of non-human animals can be generated using any method known in the art. In some cases, populations of non-human animals can be generated by breeding. For example, inbreeding can be used to generate a phenotypically or genetically identical non-human animal or population of non-human animals. Inbreeding, for example, sibling to sibling or parent to child, or grandchild to grandparent, or great grandchild to great grandparent, can be used. Successive rounds of inbreeding can eventually produce a phenotypically or genetically identical non-human animal. For example, at least or at least about 2, 3, 4, 5, 10, 20, 30, 40, or 50 generations of inbreeding can produce a phenotypically and/or a genetically identical non-human

animal. It is thought that after 10-20 generations of inbreeding, the genetic make-up of a non-human animal is at least 99% pure. Continuous inbreeding can lead to a non-human animal that is essentially isogenic, or close to isogenic as a non-human animal can be without being an identical twin.

[00315] Breeding can be performed using non-human animals that have the same genotype. For example, the non-human animals have the same gene(s) whose expression is reduced and/or carry the same transgene(s). Breeding can also be performed using non-human animals having different genotypes. Breeding can be performed using a genetically modified non-human animal and non-genetically modified non-human animal, for example, a genetically modified female pig and a wild-type male pig, or a genetically modified male pig and a wild-type female pig. All these combinations of breeding can be used to produce a non-human animal of desire.

[00316] Populations of genetically modified non-human animals can also be generated by cloning. For example, the populations of genetically modified non-human animal cells can be asexually producing similar populations of genetically or phenotypically identical individual non-human animals. Cloning can be performed by various methods, such as twinning (*e.g.*, splitting off one or more cells from an embryo and grow them into new embryos), somatic cell nuclear transfer, or artificial insemination. More details of the methods are provided throughout the disclosure.

II. GENETICALLY MODIFIED CELLS

[00317] Disclosed herein are one or more genetically modified cells that can be used to treat or prevent disease. These genetically modified cells can be from genetically modified non-human animals. For example, genetically modified non-human animals as disclosed above can be processed so that one or more cells are isolated to produce isolated genetically modified cells. These isolated cells can also in some cases be further genetically modified cells. However, a cell can be modified *ex vivo*, *e.g.*, outside an animal using modified or non-modified human or non-human animal cells. For example, cells (including human and non-human animal cells) can be modified in culture. It is also contemplated that a genetically modified cell can be used to generate a genetically modified non-human animal described herein. In some cases, the genetically modified cell can be isolated from a genetically modified animal. In some cases, the genetically modified cell can be derived from a cell from a non-genetically modified animal. Isolation of cells can be performed by methods known in the art, including methods of primary cell isolation and culturing. It is specifically contemplated that a genetically modified cell is not extracted from a human.

[00318] Therefore, anything that can apply to the genetically modified non-human animals including the various methods of making as described throughout can also apply herein. For example, all the genes that are disrupted and the transgenes that are overexpressed are applicable in making genetically modified cells used herein. Further, any methods for testing the genotype and expression of genes in the genetically modified non-human animals described throughout can be used to test the genetic modification of the cells.

[00319] A genetically modified cell can be from a member of the *Laurasiatheria* superorder or a non-human primate. Such genetically modified cell can be isolated from a member of the *Laurasiatheria* superorder or a non-human primate. Alternatively, such genetically modified cell can be originated from a member of the *Laurasiatheria* superorder or a non-human primate. For example, the genetically modified cell can be made from a cell isolated from a member of the *Laurasiatheria* superorder or a non-human primate, *e.g.,* using cell culturing or genetic modification methods.

[00320] Genetically modified cells, *e.g.,* cells from a genetically modified animal or cells made *ex vivo*, can be analyzed and sorted. In some cases, genetically modified cells can be analyzed and sorted by flow cytometry, *e.g.,* fluorescence-activated cell sorting. For example, genetically modified cells expressing a transgene can be detected and purified from other cells using flow cytometry based on a label (*e.g.,* a fluorescent label) recognizing the polypeptide encoded by the transgene.

[00321] In some cases, genetically modified cells can reduce, inhibit, or eliminate an immune response. For example, a genetic modification can decrease cellular effector function, decrease proliferation, decrease, persistence, and/or reduce expression of cytolytic effector molecules such as Granzyme B and CD107alpha in an immune cell. An immune cell can be a monocyte and/or macrophage. In some cases, T cell-derived cytokines, such as IFN-g, can activate macrophages via secretion of IFN-gamma. In some cases, T cell activation is inhibited and may cause a macrophage to also be inhibited.

[00322] Stem cells, including, non-human animal and human stem cells can be used. Stem cells do not have the capability to generating a viable human being. For example, stem cells can be irreversibly differentiated so that they are unable to generate a viable human being. Stem cells can be pluripotent, with the caveat that the stem cells cannot generate a viable human.

[00323] As discussed above in the section regarding the genetically modified non-human animals, the genetically modified cells can comprise one or more genes whose expression is reduced. The same genes as disclosed above for the genetically modified non-human animals

can be disrupted. For example, a genetically modified cell comprising one or more genes whose expression is disrupted, *e.g.,* reduced, where the one or more genes comprise NLRC5, TAP1, GGTA1, B4GALNT2, CMAH, CXCL10, MICA, MICB, C3, CIITA and/or any combination thereof. Further, the genetically modified cell can comprise one or more transgenes comprising one or more polynucleotide inserts. For example, a genetically modified cell can comprise one or more transgenes comprising one or more polynucleotide inserts of ICP47, CD46, CD55, CD 59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, Spi9, PD-L1, PD-L2, CD47, galectin-9, any functional fragments thereof, or any combination thereof. A genetically modified cell can comprise one or more reduced genes and one or more transgenes. For example, one or more genes whose expression is reduced can comprise any one of NLRC5, TAP1, GGTA1, B4GALNT2, CMAH, CXCL10, MICA, MICB, CIITA, and/or any combination thereof, and one or more transgene can comprise ICP47, CD46, CD55, CD 59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, Spi9, PD-L1, PD-L2, CD47, galectin-9, any functional fragments thereof, and/or any combination thereof. In some cases, a genetically modified cell can comprise reduced expression of NLRC5, C3, GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the proteins comprise HLA-G1, Spi9, PD-L1, PD-L2, CD47, and galectin-9. In some cases, a genetically modified cell can comprise reduced expression of TAP1, C3, GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the proteins comprise HLA-G1, Spi9, PD-L1, PD-L2, CD47, and galectin-9. In some cases, a genetically modified cell can comprise reduced expression of NLRC5, TAP1, C3, GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the proteins comprise HLA-G1, Spi9, PD-L1, PD-L2, CD47, and galectin-9. In some cases, CD47, PD-L1, and PD-L2 encoded by the transgenes herein can be human CD47, human PD-L1 and human PD0-L2. In some cases, the genetically modified cell can be coated with CD47 on its surface. Coating of CD47 on the surface of a cell can be accomplished by biotinylating the cell surface followed by incubating the biotinylated cell with a streptavidin-CD47 chimeric protein. The coated CD47 can be human CD47.

[00324] As discussed above in the section regarding the genetically modified non-human animals, the genetically modified cell can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more disrupted genes. A genetically modified cell can also comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more transgenes.

[00325] As discussed in detail above, a genetically modified cell, *e.g.,* porcine cell, can also comprise dominant negative transgenes and/or transgenes expressing one or more knockdown genes. Also as discussed above, expression of a transgene can be controlled by one or more promoters.

[00326] A genetically modified cell can be one or more cells from tissues or organs, the tissues or organs including brain, lung, liver, heart, spleen, pancreas, small intestine, large intestine, skeletal muscle, smooth muscle, skin, bones, adipose tissues, hairs, thyroid, trachea, gall bladder, kidney, ureter, bladder, aorta, vein, esophagus, diaphragm, stomach, rectum, adrenal glands, bronchi, ears, eyes, retina, genitals, hypothalamus, larynx, nose, tongue, spinal cord, or ureters, uterus, ovary and testis. For example, a genetically modified cell, *e.g.,* porcine cell, can be from brain, heart, liver, skin, intestine, lung, kidney, eye, small bowel, or pancreas. In some cases, a genetically modified cell can be from a pancreas. More specifically, pancreas cells can be islet cells. Further, one or more cells can be pancreatic α cells, pancreatic β cells, pancreatic δ cells, pancreatic F cells (*e.g.,* PP cells), or pancreatic ε cells. For example, a genetically modified cell can be pancreatic β cells. Tissues or organs disclosed herein can comprise one or more genetically modified cells. The tissues or organs can be from one or more genetically modified animals described in the application, *e.g.,* pancreatic tissues such as pancreatic islets from one or more genetically modified pigs.

[00327] A genetically modified cell, *e.g.,* porcine cell, can comprise one or more types of cells, where the one or more types of cells include Trichocytes, keratinocytes, gonadotropes, corticotropes, thyrotropes, somatotropes, lactotrophs, chromaffin cells, parafollicular cells, glomus cells melanocytes, nevus cells, Merkel cells, odontoblasts, cementoblasts corneal keratocytes,, retina Muller cells, retinal pigment epithelium cells, neurons, glias (*e.g.,* oligodendrocyte astrocytes), ependymocytes, pinealocytes, pneumocytes (*e.g.,* type I pneumocytes, and type II pneumocytes), clara cells, goblet cells, G cells, D cells, ECL cells, gastric chief cells, parietal cells, foveolar cells, K cells, D cells, I cells, goblet cells, paneth cells, enterocytes, microfold cells, hepatocytes, hepatic stellate cells (*e.g.,* Kupffer cells from mesoderm), cholecystocytes, centroacinar cells, pancreatic stellate cells, pancreatic α cells, pancreatic β cells, pancreatic δ cells, pancreatic F cells (*e.g.,* PP cells), pancreatic ε cells, thyroid (*e.g.,* follicular cells), parathyroid (*e.g.,* parathyroid chief cells), oxyphil cells, urothelial cells, osteoblasts, osteocytes, chondroblasts, chondrocytes, fibroblasts, fibrocytes, myoblasts, myocytes, myosatellite cells, tendon cells, cardiac muscle cells, lipoblasts, adipocytes, interstitial cells of cajal, angioblasts, endothelial cells, mesangial cells (*e.g.,* intraglomerular mesangial cells and extraglomerular mesangial cells), juxtaglomerular cells, macula densa cells, stromal cells,

interstitial cells, telocytes simple epithelial cells, podocytes, kidney proximal tubule brush border cells, sertoli cells, leydig cells, granulosa cells, peg cells, germ cells, spermatozoon ovums, lymphocytes, myeloid cells, endothelial progenitor cells, endothelial stem cells, angioblasts, mesoangioblasts, and pericyte mural cells. A genetically modified cell can potentially be any cells used in cell therapy. For example, cell therapy can be pancreatic β cells supplement or replacement to a disease such as diabetes.

[00328] A genetically modified cell, *e.g.,* porcine cell, can be from (*e.g.,* extracted from) a non-human animal. One or more cells can be from a mature adult non-human animal. However, one or more cells can be from a fetal or neonatal tissue.

[00329] Depending on the disease, one or more cells can be from a transgenic non-human animal that has grown to a sufficient size to be useful as an adult donor, *e.g.,* an islet cell donor. In some cases, non-human animals can be past weaning age. For example, non-human animals can be at least or at least about six months old. In some cases, non-human animals can be at least or at least about 18 months old. A non-human animal in some cases, survive to reach breeding age. For example, islets for xenotransplantation can be from neonatal (*e.g.,* age 3-7 days) or pre-weaning (*e.g.,* age 14 to 21 days) donor pigs. One or more genetically modified cells, *e.g.,* porcine cells, can be cultured cells. For example, cultured cells can be from wild-type cells or from genetically modified cells (as described herein). Furthermore, cultured cells can be primary cells. Primary cells can be extracted and frozen, *e.g.,* in liquid nitrogen or at -20°C to -80°C. Cultured cells can also be immortalized by known methods, and can be frozen and stored, *e.g.,* in liquid nitrogen or at -20°C to -80°C.

[00330] Genetically modified cells, *e.g.,* porcine cells, as described herein can have a lower risk of rejection, when compared to when a wild-type non-genetically modified cell is transplanted.

[00331] Disclosed herein is a vector comprising a polynucleotide sequence of ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, Spi9, PD-L1, PD-L2, CD47, galectin-9, any functional fragments thereof, or any combination thereof. These vectors can be inserted into a genome of a cell (by transfection, transformation, viral delivery, or any other known method). These vectors can encode ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M Spi9, PD-L1, PD-L2, CD47, and/or galectin-9 proteins or functional fragments thereof.

[00332] Vectors contemplated include, but not limited to, plasmid vectors, artificial/mini-chromosomes, transposons, and viral vectors. Further disclosed herein is an isolated or

synthetic nucleic acid comprising an RNA, where the RNA is encoded by any sequence in Table 2. RNA can also encode for any sequence that exhibits at least or at least about 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100% homology to any sequence in Table 2. RNA can also encode for any sequence that exhibits at least or at least about 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100% identity to any sequence in Table 2.

[00333] RNA can be a single-chain guide RNA. The disclosure also provides an isolated or synthesized nucleic acid comprising any sequence in Table 1. RNA can also provide an isolated or synthesized nucleic acid that exhibits at least or at least about 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100% homology to any sequence in Table 1. RNA can also provide an isolated or synthesized nucleic acid that exhibits at least or at least about 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100% identity to any sequence in Table 1.

[00334] Guide RNA sequences can be used in targeting one or more genes in a genome of a non-human animal. For example, guide RNA sequence can target a single gene in a genome of non-human animal. In some cases, guide RNA sequences can target one or more target sites of each of one or more genes in a genome of a non-human animal.

[00335] Genetically modified cells can also be leukocytes, lymphocytes, B lymphocytes, or any other cell such as islet cells, islet beta cells, or hepatocytes. These cells can be fixed or made apopototic by any method disclosed herein, *e.g.,* by ECDI fixation.

[00336] A genetically modified cells can be derived (*e.g.,* retrieved) from a non-human fetal animal, perinatal non-human animal, neonatal non-human animal, preweaning non-human animal, young adult non-human animal, adult non-human animal, or any combination thereof. In some cases, a genetically modified non-human animal cell can be derived from an embryonic tissue, *e.g.,* an embryonic pancreatic tissue. For example, a genetically modified cell can be derived (*e.g.,* retrieved) from an embryonic pig pancreatic tissue from embryonic day 42 (E42).

[00337] The term "fetal animal" and its grammatical equivalents can refer to any unborn offspring of an animal. The term "perinatal animal" and its grammatical equivalents can refer to an animal immediately before or after birth. For example, a perinatal period can start from 20th to 28th week of gestation and ends 1 to 4 weeks after birth. The term "neonatal animal" and its grammatical equivalents can refer to any new born animals. For example, a neonatal animal can be an animal born within a month. The term "preweaning non-human animal" and its grammatical equivalents can refer to any animal before being withdrawn from the mother's milk.

[00338] Genetically modified non-human animal cells can be formulated into a pharmaceutical composition. For example, the genetically modified non-human animal cells can be combined

with a pharmaceutically acceptable excipient. An excipient that can be used is saline. The pharmaceutical composition can be used to treat patients in need of transplantation.

[00339] A genetically modified cell can comprise reduced expression of any genes, and/or any transgenes disclosed herein. Genetic modification of the cells can be done by using any of the same method as described herein for making the genetically modified animals. In some cases, a method of making a genetically modified cell originated from a non-human animal can comprise reducing expression of one or more genes and/or inserting one or more transgenes. The reduction of gene expression and/or transgene insertion can be performed using any methods described in the application, *e.g.*, gene editing.

Genetically modified cells derived from stem cells

[00340] Genetically modified cells can be a stem cell. These genetically modified stem cells can be used to make a potentially unlimited supply of cells that can be subsequently processed into fixed or apoptotic cells by the methods disclosed herein. As discussed above, stem cells are not capable of generating a viable human being.

[00341] The production of hundreds of millions of insulin-producing, glucose-responsive pancreatic beta cells from human pluripotent stem cells provides an unprecedented cell source for cell transplantation therapy in diabetes (Pagliuca *et al.*, 2014). Other human stem cell-(embryonic, pluripotent, placental, induced pluripotent, etc.) derived cell sources for cell transplantation therapy in diabetes and in other diseases are being developed.

[00342] These stem cell-derived cellular grafts are subject to rejection. The rejection can be mediated by CD8+ T cells. In Type 1 diabetic recipients, human stem cell-derived functional beta cells are subject to rejection and autoimmune recurrence. Both are thought to be mediated by CD8+ T cells.

[00343] To interfere with activation and effector function of these allo-reactive and auto-reactive CD8+ T cells, established molecular methods of gene modification, including CRISP/Cas9 gene targeting, can be used to mutate the NLRC5, TAP1, and/or B2M genes in human stem cells for the purpose of preventing cell surface expression of functional MHC class I in the stem cell-derived, partially or fully differentiated cellular graft. Thus, transplanting human stem cell-derived cellular grafts lacking functional expression of MHC class I can minimize the requirements of immunosuppression otherwise required to prevent rejection and autoimmune recurrence.

[00344] However, lack of MHC class I expression on transplanted human cells will likely cause the passive activation of natural killer (NK) cells (Ohlen et al, 1989). NK cell cytotoxicity can be overcome by the expression of the human MHC class 1 gene, HLA-E, which stimulates the inhibitory receptor CD94/NKG2A on NK cells to prevent cell killing (Weiss *et al.*, 2009; Lilienfeld *et al.*, 2007; Sasaki *et al.*, 1999). Successful expression of the HLA-E gene was dependent on co-expression of the human B2M (beta 2 microglobulin) gene and a cognate peptide (Weiss *et al.*, 2009; Lilienfeld *et al.*, 2007; Sasaki *et al.*, 1999; Pascasova *et al.*, 1999). A nuclease mediated break in the stem cell DNA allows for the insertion of one or multiple genes via homology directed repair. The HLA-E and hB2M genes in series can be integrated in the region of the nuclease mediated DNA break thus preventing expression of the target gene (for example, NLRC5) while inserting the transgenes.

[00345] To further minimize, if not eliminate, the need for maintenance immunosuppression in recipients of stem cell derived cellular grafts lacking functional expression of MHC class I, recipients of these grafts can also be treated with tolerizing apoptotic donor cells disclosed herein.

[00346] The methods for the production of insulin-producing pancreatic beta cells (Pagliuca *et al.*, 2014) can potentially be applied to non-human (*e.g.*, pig) primary isolated pluripotent, embryonic stem cells or stem-like cells (Goncalves *et al.*, 2014; Hall *et al.* V. 2008). However, the recipient of these insulin-producing pancreatic beta cells likely has an active immune response that threatens the success of the graft. To overcome antibody-mediated and CD8+ T cell immune attack, the donor animal can be genetically modified before isolation of primary non-human pluripotent, embryonic stem cells or stem-like cells to prevent the expression of the GGTA1, CMAH, B4GalNT2, or MHC class I-related genes as disclosed throughout the application. The pluripotent, embryonic stem cells or stem-like cells isolated from genetically modified animals could then be differentiated into millions of insulin-producing pancreatic beta cells.

[00347] Xenogeneic stem cell-derived cell transplants can be desirable in some cases. For example, the use of human embryonic stem cells may be ethically objectionable to the recipient. Therefore, human recipients may feel more comfortable receiving a cellular graft derived from non-human sources of embryonic stem cells.

[00348] Non-human stem cells may include pig stem cells. These stem cells can be derived from wild-type pigs or from genetically engineered pigs. If derived from wild-type pigs, genetic engineering using established molecular methods of gene modification, including CRISP/Cas9

gene targeting, may best be performed at the stem cell stage. Genetic engineering may be targeted to disrupt expression of NLRC5, TAP1, and/or B2M genes to prevent functional expression of MHC class I. Disrupting genes such as NLRC5, TAP1, and B2M in the grafts can cause lack of functional expression of MHC class I on graft cells including on islet beta cells, thereby interfering with the post-transplant activation of autoreactive CD8+ T cells. Thus, this can protect the transplant, *e.g.,* transplanted islet beta cells, from the cytolytic effector functions of autoreactive CD8+ T cells.

[00349] However, as genetic engineering of stem cells may alter their potential for differentiation, an approach can be to generate stem cell lines from genetically engineered pigs, including those pigs, in whom the expression of NLRC5, TAP1, and/or B2M genes has been disrupted.

[00350] Generation of stem cells from pigs genetically modified to prevent the expression also of the GGTA1, CMAH, B4GalNT2 genes or modified to express transgenes that encode for complement regulatory proteins CD46, CD55, or CD59, as disclosed throughout the application, could further improve the therapeutic use of the insulin-producing pancreatic beta cells or other cellular therapy products. Likewise, the same strategy as described herein can be used in other methods and compositions described throughout.

[00351] Like in recipients of human stem cell-derived cellular grafts lacking functional expression of MHC class I, the need for maintenance immunosuppression in recipients of pig stem cell-derived grafts can be further minimized by peritransplant treatments with tolerizing apoptotic donor cells.

III. TOLERIZING VACCINES

[00352] Traditionally, vaccines are used to confer immunity to a host. For example, injecting an inactivated virus with adjuvant under the skin can lead to temporary or permanent immunity to the active and/or virulent version of the virus. This can be referred to as a positive vaccine (**FIG. 3**). However, inactivated cells (*e.g.,* cells from a donor or an animal genetically different from the donor) that are injected intravenously can result in tolerance of donor cells or cells with similar cellular markers. This can be referred to as a tolerizing vaccine (also referred to as a negative vaccine) (**FIG. 3**). The inactive cells can be injected without an adjuvant. Alternatively, the inactive cells can be injected with an adjuvant. These tolerizing vaccines can be advantageous in transplantation, for example, in xenotransplantation, by tolerizing a recipient and preventing rejection. Tolerization can be conferred to a recipient without the use of

immunosuppressive therapies. However, in some cases, other immunosuppressive therapies in combination with tolerizing vaccines can decrease transplantation rejection.

[00353] FIG. 4 demonstrates an exemplary approach to extending the survival of transplanted grafts (*e.g.*, xenografts) in a subject (*e.g.*, a human or a non-human primate) with infusion (*e.g.*, intravenous infusion) of apoptotic cells from the donor for tolerizing vaccination under the cover of transient immunosuppression. A donor can provide xenografts for transplantation (*e.g.*, islets), as well as cells (*e.g.*, splenocytes) as a tolerizing vaccine. The tolerizing vaccine cells can be apoptotic cells (*e.g.*, by ECDI fixation) and administered to the recipient before (*e.g.*, the first vaccine, on day 7 before the transplantation) and after the transplantation (*e.g.*, the booster vaccine, on day 1 after the transplantation). The tolerizing vaccine can provide transient immunosuppression that extends the time of survival of the transplanted grafts (*e.g.*, islets).

[00354] Tolerizing vaccines can comprise one or more of the following types of cells: i) apoptotic cells comprising genotypically identical cells with reduced expression of GGTA1 alone, or GGTA1 and CMAH, or GGTA1, CMAH, and B4GALNT2. This can minimize or eliminate cell-mediated immunity and cell-dependent antibody-mediated immunity to organ, tissue, cell, and cell line grafts (*e.g.*, xenografts) from animals that are genotypically identical with the apoptotic cell vaccine donor animal, or from animals that have undergone additional genetic modifications (*e.g.*, suppression of NLRC5, TAP1, MICA, MICB, CXCL10, C3, CIITA genes or expression of transgenes comprising two or more polynucleotide inserts of ICP47, CD46, CD55, HLA-E, HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, CD59, or any functional fragments thereof), but are genotypically similar to the donor animal from which the apoptotic cell vaccine is derived; ii) apoptotic stem cell (*e.g.*, embryonic, pluripotent, placental, induced pluripotent, etc.)-derived donor cells (*e.g.*, leukocytes, lymphocytes, T lymphocytes, B lymphocytes, red blood cells, graft cells, or any other donor cell) for minimizing or eliminating cell-mediated immunity and cell-dependent antibody-mediated immunity to organ, tissue, cell, and cell line grafts (*e.g.*, xenografts) from animals that are genotypically identical with the apoptotic cell vaccine donor animal or from animals that have undergone additional genetic modifications (*e.g.*, suppression of NLRC5, TAP1, MICA, MICB, CXCL10, C3, CIITA genes or expression of transgenes comprising two or more polynucleotide inserts of ICP47, CD46, CD55, HLA-E, HLA-G (*e.g.*, HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, CD59, or any functional fragments thereof), but are genotypically similar to the donor animal from which the apoptotic stem cell-derived cell vaccine is derived; iii) apoptotic stem cell (*e.g.*, embryonic, pluripotent, placental, induced pluripotent, etc.)-derived donor cells (leukocytes, lymphocytes, T lymphocytes, B

lymphocytes, red blood cells, graft cells such as functional islet beta cells, or any other donor cell) for minimizing or eliminating cell-mediated immunity and cell-dependent antibody-mediated immunity to organ, tissue, cell, and cell grafts (*e.g.,* allografts) that are genotypically identical with the human stem cell line or to grafts (*e.g.,* allografts) derived from the same stem cell line that have undergone genetic modifications (*e.g.,* suppression of NLRC5, TAP1, MICA, MICB, CXCL10, C3, CIITA genes) but are otherwise genotypically similar to the apoptotic human stem cell-derived donor cell vaccine; iv) apoptotic donor cells, where the cells are made apoptotic by UV irradiation, gamma-irradiation, or other methods not involving incubation in the presence of ECDI. In some cases, tolerizing vaccine cells can be adminstered, *e.g.,* infused (in some cases repeatedly infused) to a subject in need thereof. Tolerizing vaccines can be produced by disrupting (*e.g.,* reducing expression) one or more genes from a cell. For example, genetically modified cells as described throughout the application can be used to make a tolerizing vaccine. For example, cells can have one or more genes that can be disrupted (*e.g.,* reduced expression) including glycoprotein galactosyltransferase alpha 1, 3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), B4GALNT2, and/or any combination thereof. For example, a cell can have disrupted GGTA1 only, or disrupted CMAH only, or disrupted B4GALNT2 only. A cell can also have disrupted GGTA1 and CMAH, disrupted GGTA1 and B4GALNT2, or disrupted CMAH and B4GALNT2. A cell can have disrupted GGTA1, CMAH, and B4GALNT2. In some cases, the disrupted gene does not include GGTA1. A cell can also express NLRC5 (endogenously or exogenously), while GGTA1 and/or CMAH are disrupted. A cell can also have disrupted C3.

[00355] A tolerizing vaccine can be produced with cells comprising additionally expressing one or more transgenes, *e.g.,* as described throughout the application. For example, a tolerizing vaccine can comprise a cell comprising one or more transgenes comprising one or more polynucleotide inserts of Infected cell protein 47 (ICP47), Cluster of differentiation 46 (CD46), Cluster of differentiation 55 (CD55), Cluster of differentiation 59 (CD 59), HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, PD-L1, PD-L2, CD47, any functional fragments thereof, or any combination thereof. In some cases, a tolerizing vaccine can comprise a genetically modified cell comprising reduced protein expression of GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the proteins comprise HLA-G1, PD-L1, PD-L2, and CD47. In some cases, a tolerizing vaccine can comprise a genetically modified cell comprising reduced protein expression of GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where

the proteins comprise HLA-E, PD-L1, PD-L2, and CD47. In some cases, a tolerizing vaccine can comprise a cell coated with CD47 on its surface. Coating of CD47 on the surface of a cell can be accomplished by biotinylating the cell surface followed by incubating these biotinylated cells with a streptavidin-CD47 chimeric protein. For example, a tolerizing vaccine can comprise a cell coated with CD47 on its surface, where the cell comprises reduced protein expression of GGTA1, CMAH, and B4GALNT2, and transgenes comprising polynucleotides encoding proteins or functional fragments thereof, where the proteins comprise HLA-G1, PD-L1, and PD-L2. A CD47-coated cell can be a non-apoptotic cell. Alternative, a CD47 coated cell can be an apoptotic cell.

[00356] In some cases, tolerization may comprise administration of a genetically modified graft. A graft can be a cell, tissue, organ, or a combination. In some cases, immunosuppression is combined with a vaccine or tolerizing graft. In some cases, expression of HLA-G1 on a graft and an MHC or HLA class I deficiency of a graft may have tolerogenic activity independent from administration of a vaccine.

[00357] When administered in a subject, a cell of a tolerizing vaccine can have a circulation half-life. A cell of a tolerizing vaccine can have a circulation half-life of at least or at least about 0.1, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 36, 48, 60, or 72 hours. For example, the circulation half-life of the tolerizing vaccine can be from or from about 0.1 to 0.5; 0.5 to 1.0; 1.0 to 2.0; 1.0 to 3.0; 1.0 to 4.0; 1.0 to 5.0; 5 to 10; 10 to 15; 15 to 24; 24 to 36; 36 to 48; 48 to 60; or 60 to 72 hours. A cell in a tolerizing vaccine can be treated to enhance its circulation half-life. Such treatment can include coating the cell with a protein, *e.g.,* CD47. A cell treated to enhance its circulation half-life can be a non-apoptotic cell. A cell treated to enhance its circulation half-life can be an apoptotic cell. Alternatively, a cell in a tolerizing vaccine can be genetically modified (*e.g.,* insertion of a transgene such as CD47 in its genome) to enhance its circulation half-life. A cell genetically modified to enhance its circulation half-life can be a non-apoptotic cell. A cell genetically modified to enhance its circulation half-life can be an apoptotic cell.

[00358] A tolerizing vaccine can have both one or more disrupted genes (*e.g.,* reduced expression) and one or more transgenes. Any genes and/or transgenes as described herein can be used.

[00359] A cell that comprises one or more disrupted genes (*e.g.,* reduced expression) can be used as, or be a part of, a tolerizing vaccine. In other words, a cell that comprises one or more disrupted genes can be or can be made into a tolerizing vaccine.

[00360] A tolerizing vaccine can have the same genotype and/or phenotype as cells, organs, and/or tissues used in transplantation. Sometimes, the genotype and/or phenotype of a tolerizing vaccine and a transplant are different. A tolerizing vaccine used for a transplant recipient can comprise cells from the transplant graft donor. A tolerizing vaccine used for a transplant recipient can comprise cells that are genetically and/or phenotypically different from the transplant graft. In some cases, a tolerizing vaccine used for a transplant recipient can comprise cells from the transplant graft donor and cells that are genetically and/or phenotypically different from the transplant graft. The cells that are genetically and/or phenotypically different from the transplant graft can be from an animal of the same species of the transplant graft donor.

[00361] A source of cells for a tolerizing vaccine can be from a human or non-human animal.

[00362] Cells as disclosed throughout the application can be made into a tolerizing vaccine. For example, a tolerizing vaccine can be made of one or more transplanted cells disclosed herein. Alternatively, a tolerizing vaccine can be made of one or more cells that are different from any of the transplanted cells. For example, the cells made into a tolerizing vaccine can be genotypically and/or phenotypically different from any of the transplanted cells. However in some cases, the tolerizing vaccine will express NLRC5 (endogenously or exogenously). A tolerizing vaccine can promote survival of cells, organs, and/or tissues in transplantation. A tolerizing vaccine can be derived from non-human animals that are genotypically identical or similar to donor cells, organs, and/or tissues. For example, a tolerizing vaccine can be cells derived from pigs (*e.g.,* apoptotic pig cells) that are genotypically identical or similar to donor pig cells, organs, and/or tissues. Subsequently, donor cells, organs, and/or tissues can be used in allografts or xenografts. In some cases, cells for a tolerizing vaccine can be from genetically modified animals (*e.g.,* pigs) with reduced expression of GGTA1, CMAH, and B4GalNT2, and having transgenes encoding HLA-G (or HLA-E-), human CD47, human PD-L1 and human PD-L2. Graft donor animals can be generated by further genetically modifying the animals (*e.g.,* pigs) for tolerizing vaccine cells. For example, graft donor animals can be generated by disrupting additional genes (*e.g.,* NLRC5 (or TAP1), C3, and CXCL10) in the abovementioned animals for tolerizing vaccines cells (**FIG. 5**).

[00363] A tolerizing vaccine can comprise non-human animal cells (*e.g.,* non-human mammalian cells). For example, non-human animal cells can be from a pig, a cat, a cow, a deer, a dog, a ferret, a gaur, a goat, a horse, a mouse, a mouflon, a mule, a rabbit, a rat, a sheep, or a primate. Specifically, non-human animal cells can be porcine cells. A tolerizing vaccine can also comprise genetically modified non-human animal cells. For example, genetically modified non-

human animal cells can be dead cells (*e.g.*, apoptotic cells). A tolerizing vaccine can also comprise any genetically modified cells disclosed herein.

Treatment of cells to make a tolerizing vaccine

[00364] A tolerizing vaccine can comprise cells treated with a chemical. In some cases, the treatment can induce apoptosis of the cells. Without being bound by theory, the apoptotic cells can be picked up by host antigen presenting cells (*e.g.*, in the spleen) and presented to host immune cells (*e.g.*, T cells) in a non-immunogenic fashion that leads to induction of anergy in the immune cells (*e.g.*, T cells).

[00365] Tolerizing vaccines can comprise apoptotic cells and non-apoptotic cells. An apoptotic cell in a tolerizing vaccine can be genetically identical to a non-apoptotic cell in the tolerizing vaccine. Alternatively, an apoptotic cell in a tolerizing vaccine can be genetically different from a non-apoptotic cell in the tolerizing vaccine. Tolerizing vaccines can comprise fixed cells and non-fixed cells. A fixed cell in a tolerizing vaccine can be genetically identifical to a non-fixed cell in the tolerizing vaccine. Alternatively, a fixed cell in a tolerizing vaccine can be genetically different from a non-fixed cell in the tolerizing vaccine. In some cases, the fixed cell can be a 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (ECDI)-fixed cell.

[00366] Cells in a tolerizing vaccine can be fixed using a chemical, *e.g.*, ECDI. The fixation can make the cells apoptotic. A tolerizing vaccine, cells, kits and methods disclosed herein can comprise ECDI and/or ECDI treatment. For example, a tolerizing vaccine can be cells, *e.g.*, the genetically modified cell as disclosed herein, that are treated with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (ECDI). In other words, the genetically modified cells as described throughout can be treated with ECDI to create a tolerizing vaccine. A tolerizing vaccine can then be used in transplantation to promote survival of cells, organs, and/or tissues that are transplanted. It is also contemplated that ECDI derivatives, functionalized ECDI, and/or substituted ECDI can also be used to treat the cells for a tolerizing vaccine. In some cases, cells for a tolerizing vaccine can be treated with any suitable carbodiimide derivatives, *e.g.*, ECDI, N, N′-diisopropylcarbodiimide (DIC), N,N′-dicyclohexylcarbodiimide (DCC), and other carbodiimide derivatives understood by those in the art.

[00367] Cells for tolerizing vaccines can also be made apoptotic methods not involving incubation in the presence of ECDI, *e.g.*, other chemicals or irradiation such as UV irradiation or gamma-irradiation.

[00368] ECDI can chemically cross-link free amine and carboxyl groups, and can effectively induce apoptosis in cells, organs, and/or tissues, *e.g.*, from animal that gave rise to both a

tolerizing vaccine and a donor non-human animal. In other words, the same genetically modified animal can give rise to a tolerizing vaccine and cells, tissues and/or organs that are used in transplantation. For example, the genetically modified cells as disclosed herein can be treated with ECDI. This ECDI fixation can lead to the creation of a tolerizing vaccine.

[00369] Genetically modified cells that can be used to make a tolerizing vaccine can be derived from: a spleen (including splenic B cells), liver, peripheral blood (including peripheral blood B cells), lymph nodes, thymus, bone marrow, or any combination thereof. For example, cells can be spleen cells, *e.g.,* porcine spleen cells. In some cases, cells can be expanded *ex-vivo*. In some cases, cells can be derived from fetal, perinatal, neonatal, preweaning, and/or young adult, non-human animals. In some cases, cells can be derived from an embryo of a non-human animal.

[00370] Cells in a tolerizing vaccine can also comprise two or more disrupted (*e.g.,* reduced expression) genes, where the two or more disrupted genes can be glycoprotein galactosyltransferase alpha 1,3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, and B4GALNT2, any functional fragments thereof, or any combination thereof. In some cases, the two or more disrupted genes do not include GGTA1. As described above, disruption can be a knockout or suppression of gene expression. Knockout can be performed by gene editing, for example, by using a CRISPR/Cas system. Alternatively, suppression of gene expression can be done by knockdown, for example, using RNA interference, shRNA, one or more dominant negative transgenes. In some cases, cells can further comprise one or more transgenes as disclosed herein. For example, one or more transgenes can be CD46, CD55, CD59, or any combination thereof.

[00371] Cells in a tolerizing vaccine can also be derived from one or more donor non-human animals. In some cases, cells can be derived from the same donor non-human animal. Cells can be derived from one or more recipient non-human animals. In some cases, cells can be derived from two or more non-human animals (*e.g.,* pig).

[00372] A tolerizing vaccine can comprise from or from about 0.001 and about 5.0, *e.g.,* from or from about 0.001 and 1.0, endotoxin unit per kg bodyweight of a prospective recipient. For example, a tolerizing vaccine can comprise from or from about 0.01 to 5.0; 0.01 to 4.5; 0.01 to 4.0, 0.01 to 3.5; 0.01 to 3.0; 0.01 to 2.5; 0.01 to 2.0; 0.01 to 1.5; 0.01 to 1.0; 0.01 to 0.9; 0.01 to 0.8; 0.01 to 0.7; 0.01 to 0.6; 0.01 to 0.5; 0.01 to 0.4; 0.01 to 0.3; 0.01 to 0.2; or 0.01 to 0.1 endotoxin unit per kg bodyweight of a prospective recipient.

[00373] A tolerizing vaccine can comprise from or from about 1 to 100 aggregates, per µl. For example, a tolerizing vaccine can comprise from or from about 1 to 5; 1 to 10, or 1 to 20 aggregate per µl. A tolerizing vaccine can comprise at least or at least about 1, 5, 10, 20, 50, or 100 aggregates.

[00374] A tolerizing vaccine can trigger a release from or from about 0.001 pg/ml to 10.0 pg/ml, *e.g.*, from or from about 0.001 pg/ml to 1.0 pg/ml, IL-1 beta when about 50,000 frozen to thawed human peripheral blood mononuclear cells are incubated with about 160,000 cells of the tolerizing vaccine (*e.g.*, pig cells). For example, a tolerizing vaccine triggers a release of from or from about 0.001 to 10.0; 0.001 to 5.0; 0.001 to 1.0; 0.001 to 0.8; 0.001 to 0.2; or 0.001 to 0.1 pg/ml IL-1 beta when about 50,000 frozen to thawed human peripheral blood mononuclear cells are incubated with about 160,000 cell of the tolerizing vaccine (*e.g.*, pig cells). A tolerizing vaccine can trigger a release of from or from about 0.001 to 2.0 pg/ml, *e.g.*, from or from about 0.001 to 0.2 pg/ml, IL-6 when about 50,000 frozen to thawed human peripheral blood mononuclear cells are incubated with about 160,000 cells of the tolerizing vaccine (*e.g.*, pig cells). For example, a tolerizing vaccine can trigger a release of from or from about 0.001 to 2.0; 0.001 to 1.0; 0.001 to 0.5; or 0.001 to 0.1 pg/ml IL-6 when about 50,000 frozen to thawed human peripheral blood mononuclear cells are incubated with about 160,000 cells of the tolerizing vaccine (*e.g.*, pig cells).

[00375] A tolerizing vaccine can comprise more than or more than about 60%, *e.g.*, more than or more than about 85%, Annexin V positive, apoptotic cells after a 4 hour or after about 4 hours post-release incubation at 37°C. For example, a tolerizing vaccine comprises more than 60%, 70%, 80%, 90%, or 99% Annexin V positive, apoptotic cells after about a 4 hour post-release incubation at 37°C.

[00376] A tolerizing vaccine can include from or from about 0.01% to 10%, *e.g.*, from or from about 0.01% to 2%, necrotic cells. For example, a tolerizing vaccine includes from or from about 0.01% to 10%; 0.01% to 7.5%, 0.01% to 5%; 0.01% to 2.5%; or 0.01% to 1% necrotic cells.

[00377] Administering a tolerizing vaccine comprising ECDI-treated cells, organs, and/or tissues before, during, and/or after administration of donor cells can induce tolerance for cells, organs, and/or tissues in a recipient (*e.g.*, a human or a non-human animal). ECDI-treated cells can be administered by intravenous infusion.

[00378] Tolerance induced by infusion of a tolerizing vaccine comprising ECDI-treated splenocytes is likely dependent on synergistic effects between an intact programmed death 1

receptor - programmed death ligand 1 signaling pathway and $CD4^+CD25^+Foxp3^+$ regulatory T cells.

[00379] Cells in a telorizing vaccine can be made into apoptotic cells (*e.g.,* tolerizing vaccines) not only by ECDI fixation, but also through other methods. For example, any of the genetically modified cells as disclosed throughout, *e.g.,* non-human cells animal cells or human cells (including stem cells), can be made apopototic by exposing the genetically modified cells to UV irradiation. The genetically modified cells can also be made apopototic by exposing it to gamma-irradiation. Other methods, not involving ECDI are also comtemplated, for example, by EtOH fixation.

[00380] Cells in a tolerizing vaccine, *e.g.,* ECDI-treated cells, antigen-coupled cells, and/or epitope-coupled cells can comprise donor cells (*e.g.,* cells from the donor of transplant grafts). Cells in a tolerizing vaccine, *e.g.,* ECDI-treated cells, antigen-coupled cells, and/or epitope-coupled cells can comprise recipient cells (*e.g.,* cells from the recipient of transplant grafts). Cells in a tolerizing vaccine, *e.g.,* ECDI-treated cells, antigen-coupled cells, and/or epitope-coupled cells can comprise third party (*e.g.,* neither donor nor recipient) cells. In some cases, third party cells are from a non-human animal of the same species as a recipient and/or donor. In other cases, third party cells are from a non-human animal of a different species as a recipient and/or donor.

[00381] ECDI-treatment of cells can be performed in the presence of one or more antigens and/or epitopes. ECDI-treated cells can comprise donor, recipient and/or third party cells. Likewise, antigens and/or epitopes can comprise donor, recipient and/or third party antigens and/or epitopes. In some cases, donor cells are coupled to recipient antigens and/or epitopes (*e.g.,* ECDI-induced coupling). For example, soluble donor antigen derived from genetically engineered and genotypically identical donor cells (*e.g.,* porcine cells) is coupled to recipient peripheral blood mononuclear cells with ECDI and the ECDI-coupled cells are administered via intravenous infusion.

[00382] In some cases, recipient cells are coupled to donor antigens and/or epitopes (*e.g.,* ECDI-induced coupling). In some cases, recipient cells are coupled to third party antigens and/or epitopes (*e.g.,* ECDI-induced coupling). In some cases, donor cells are coupled to recipient antigens and/or epitopes (*e.g.,* ECDI-induced coupling). In some cases, donor cells are coupled to third party antigens and/or epitopes (*e.g.,* ECDI-induced coupling). In some cases, third party cells are coupled to donor antigens and/or epitopes (*e.g.,* ECDI-induced coupling). In some cases, third party cells are coupled to recipient antigens and/or epitopes (*e.g.,* ECDI-induced

coupling). For example, soluble donor antigen derived from genetically engineered and genotypically identical donor cells (*e.g.,* porcine cells) is coupled to polystyrene nanoparticles with ECDI and the ECDI-coupled cells are administered via intravenous infusion.

[00383] Tolerogenic potency of any of these tolerizing cell vaccines can be further optimized by coupling to the surface of cells one or more of the following: IFN-g, NF-kB inhibitors (such as curcumin, triptolide, Bay-117085), vitamin D3, siCD40, cobalt protoporphyrin, insulin B9-23, or other immunomodulatory molecules that modify the function of host antigen-presenting cells and host lymphocytes.

[00384] These apoptotic cell vaccines can also be complemented by donor cells engineered to display on their surface molecules (such as FasL, PD-L1, galectin-9, CD8alpha) that trigger apoptotic death of donor-reactive cells.

[00385] Tolerizing vaccines dislosed herein can increase the duration of survival of a transplant (*e.g.,* a xenograft or an allograft transplant) in a recipient. Tolerizing vaccines disclosed herein can also reduce or eliminate need for immunosupression following transplantation. Xenograft or allograft transplant can be an organ, tissue, cell or cell line. Xenograft transplants and tolerizing vaccines can also be from different species. Alternatively, xenograft transplants and the tolerizing vaccines can be from the same species. For example, a xenograft transplant and a tolerizing vaccine can be from substantially genetically identical individuals (*e.g.,* the same individual).

[00386] In some cases a tolerizing vaccine or negative vaccine can produce synergistic effects in a subject administered a tolerizing or negative vaccine. In other cases, a tolerizing or negative vaccine can produce antagonistic effects in a subject administered a tolerizing or negative vaccine.

[00387] The ECDI fixed cells can be formulated into a pharmaceutical composition. For example, the ECDI fixed cells can be combined with a pharmaceutically acceptable excipient. An excipient that can be used is saline. An excipient that can be used is phosphate buffered saline (PBS). The pharmaceutical compositions can be then used to treat patients in need of transplantation.

IV. METHOD OF MAKING GENETICALLY MODIFIED NON-HUMAN ANIMALS

[00388] In order to make a genetically modified non-human animal as described above, various techniques can be used. Disclosed herein are a few examples to create genetically modified

animals. It is to be understood that the methods disclosed herein are simply examples, and are not meant to limiting in any way.

Gene disruption

[00389] Gene disruption can be performed by any methods described above, for example, by knockout, knockdown, RNA interference, dominant negative, etc. A detailed description of the methods is disclosed above in the section regarding genetically modified non-human animals.

CRISPR/Cas system

[00390] Methods described herein can take advantage of a CRISPR/Cas system. For example, double-strand breaks (DSBs) can be generated using a CRISPR/Cas system, *e.g.*, a type II CRISPR/Cas system. A Cas enzyme used in the methods disclosed herein can be Cas9, which catalyzes DNA cleavage. Enzymatic action by Cas9 derived from *Streptococcus pyogenes* or any closely related Cas9 can generate double stranded breaks at target site sequences which hybridize to 20 nucleotides of a guide sequence and that have a protospacer-adjacent motif (PAM) following the 20 nucleotides of the target sequence.

[00391] A vector can be operably linked to an enzyme-coding sequence encoding a CRISPR enzyme, such as a Cas protein. Cas proteins that can be used herein include class 1 and class 2. Non-limiting examples of Cas proteins include Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5d, Cas5t, Cas5h, Cas5a, Cas6, Cas7, Cas8, Cas9 (also known as Csn1 or Csx12), Cas10, Csy1 , Csy2, Csy3, Csy4, Cse1, Cse2, Cse3, Cse4, Cse5e, Csc1, Csc2, Csa5, Csn1, Csn2, Csm1, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx1S, Csf1, Csf2, CsO, Csf4, Csd1, Csd2, Cst1, Cst2, Csh1, Csh2, Csa1, Csa2, Csa3, Csa4, Csa5, C2c1, C2c2, C2c3, Cpf1, CARF, DinG, homologues thereof, or modified versions thereof. An unmodified CRISPR enzyme can have DNA cleavage activity, such as Cas9. A CRISPR enzyme can direct cleavage of one or both strands at a target sequence, such as within a target sequence and/or within a complement of a target sequence. For example, a CRISPR enzyme can direct cleavage of one or both strands within about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 100, 200, 500, or more base pairs from the first or last nucleotide of a target sequence. A vector that encodes a CRISPR enzyme that is mutated to with respect, to a corresponding wild-type enzyme such that the mutated CRISPR enzyme lacks the ability to cleave one or both strands of a target polynucleotide containing a target sequence can be used.

[00392] Cas9 can refer to a polypeptide with at least or at least about 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity and/or sequence homology to a wild type exemplary Cas9 polypeptide (*e.g.*, Cas9 from *S. pyogenes*).

Cas9 can refer to a polypeptide with at most or at most about 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity and/or sequence homology to a wild type exemplary Cas9 polypeptide (*e.g.*, from *S. pyogenes*). Cas9 can refer to the wild type or a modified form of the Cas9 protein that can comprise an amino acid change such as a deletion, insertion, substitution, variant, mutation, fusion, chimera, or any combination thereof.

[00393] *S. pyogenes* Cas9 (SpCas9) can be used as a CRISPR endonuclease for genome engineering. However, others can be used. In some cases, a different endonuclease may be used to target certain genomic targets. In some cases, synthetic SpCas9-derived variants with non-NGG PAM sequences may be used. Additionally, other Cas9 orthologues from various species have been identified and these "non-SpCas9s" can bind a variety of PAM sequences that could also be useful for the present invention. For example, the relatively large size of SpCas9 (approximately 4kb coding sequence) can lead to plasmids carrying the SpCas9 cDNA that may not be efficiently expressed in a cell. Conversely, the coding sequence for *Staphylococcus aureus* Cas9 (SaCas9) is approximately1 kilo base shorter than SpCas9, possibly allowing it to be efficiently expressed in a cell. Similar to SpCas9, the SaCas9 endonuclease is capable of modifying target genes in mammalian cells *in vitro* and in mice *in vivo*. In some cases, a Cas protein may target a different PAM sequence. In some cases, a target gene, such as NLRC5, may be adjacent to a Cas9 PAM, 5′-NGG, for example. In other cases, other Cas9 orthologs may have different PAM requirements. For example, other PAMs such as those of *S. thermophilus* (5′-NNAGAA for CRISPR1 and 5′-NGGNG for CRISPR3) and *Neisseria meningiditis* (5′-NNNNGATT) may also be found adjacent to a target gene, such as NLRC5. A transgene of the present invention may be inserted adjacent to any PAM sequence from any Cas, or Cas derivative, protein. In some cases, a PAM can be found every, or about every, 8 to 12 base pairs in a genome. A PAM can be found every 1 to 15 basepairs in a genome. A PAM can also be found every 5 to 20 basepairs in a genome. In some cases, a PAM can be found every 5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20, or more basepairs in a genome. A PAM can be found at or between every 5-100 base pairs in a genome.

[00394] For example, for a *S. pyogenes* system, a target gene sequence can precede (i.e., be 5′ to) a 5′-NGG PAM, and a 20-nt guide RNA sequence can base pair with an opposite strand to mediate a Cas9 cleavage adjacent to a PAM. In some cases, an adjacent cut may be or may be about 3 base pairs upstream of a PAM. In some cases, an adjacent cut may be or may be about 10 base pairs upstream of a PAM. In some cases, an adjacent cut may be or may be about 0-20 base pairs upstream of a PAM. For example, an adjacent cut can be next to,

1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28, 29,or 30 base pairs upstream of a PAM. An adjacent cut can also be downstream of a PAM by 1 to 30 base pairs.

[00395] Alternatives to *S. pyogenes* Cas9 may include RNA-guided endonucleases from the Cpf1 family that display cleavage activity in mammalian cells. Unlike Cas9 nucleases, the result of Cpf1-mediated DNA cleavage is a double-strand break with a short 3′ overhang. Cpf1's staggered cleavage pattern may open up the possibility of directional gene transfer, analogous to traditional restriction enzyme cloning, which may increase the efficiency of gene editing. Like the Cas9 variants and orthologues described above, Cpf1 may also expand the number of sites that can be targeted by CRISPR to AT-rich regions or AT-rich genomes that lack the NGG PAM sites favored by SpCas9.

[00396] A vector that encodes a CRISPR enzyme comprising one or more nuclear localization sequences (NLSs) can be used. For example, there can be or be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 NLSs used. A CRISPR enzyme can comprise the NLSs at or near the ammo-terminus, about or more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 NLSs at or near the carboxy-terminus, or any combination of these (*e.g.,* one or more NLS at the ammo-terminus and one or more NLS at the carboxy terminus). When more than one NLS is present, each can be selected independently of others, such that a single NLS can be present in more than one copy and/or in combination with one or more other NLSs present in one or more copies.

[00397] CRISPR enzymes used in the methods can comprise at most 6 NLSs. An NLS is considered near the N- or C-terminus when the nearest amino acid to the NLS is within about 50 amino acids along a polypeptide chain from the N- or C-terminus, *e.g.,* within 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, or 50 amino acids.

Guide RNA

[00398] As used herein, the term *"*guide RNA*"* and its grammatical equivalents can refer to an RNA which can be specific for a target DNA and can form a complex with Cas protein. An RNA/Cas complex can assist in "guiding" Cas protein to a target DNA.

[00399] A method disclosed herein also can comprise introducing into a cell or embryo at least one guide RNA or nucleic acid, *e.g.,* DNA encoding at least one guide RNA. A guide RNA can interact with a RNA-guided endonuclease to direct the endonuclease to a specific target site, at which site the 5' end of the guide RNA base pairs with a specific protospacer sequence in a chromosomal sequence.

[00400] A guide RNA can comprise two RNAs, *e.g.*, CRISPR RNA (crRNA) and transactivating crRNA (tracrRNA). A guide RNA can sometimes comprise a single-chain RNA, or single guide RNA (sgRNA) formed by fusion of a portion (*e.g.*, a functional portion) of crRNA and tracrRNA. A guide RNA can also be a dualRNA comprising a crRNA and a tracrRNA. Furthermore, a crRNA can hybridize with a target DNA.

[00401] As discussed above, a guide RNA can be an expression product. For example, a DNA that encodes a guide RNA can be a vector comprising a sequence coding for the guide RNA. A guide RNA can be transferred into a cell or organism by transfecting the cell or organism with an isolated guide RNA or plasmid DNA comprising a sequence coding for the guide RNA and a promoter. A guide RNA can also be transferred into a cell or organism in other way, such as using virus-mediated gene delivery.

[00402] A guide RNA can be isolated. For example, a guide RNA can be transfected in the form of an isolated RNA into a cell or organism. A guide RNA can be prepared by *in vitro* transcription using any *in vitro* transcription system known in the art. A guide RNA can be transferred to a cell in the form of isolated RNA rather than in the form of plasmid comprising encoding sequence for a guide RNA.

[00403] A guide RNA can comprise three regions: a first region at the 5' end that can be complementary to a target site in a chromosomal sequence, a second internal region that can form a stem loop structure, and a third 3' region that can be single-stranded. A first region of each guide RNA can also be different such that each guide RNA guides a fusion protein to a specific target site. Further, second and third regions of each guide RNA can be identical in all guide RNAs.

[00404] A first region of a guide RNA can be complementary to sequence at a target site in a chromosomal sequence such that the first region of the guide RNA can base pair with the target site. In some cases, a first region of a guide RNA can comprise from or from about 10 nucleotides to 25 nucleotides (*i.e.*, from 10 nts to 25nts; or from about 10nts to about 25 nts; or from 10 nts to about 25nts; or from about 10 nts to 25 nts) or more. For example, a region of base pairing between a first region of a guide RNA and a target site in a chromosomal sequence can be or can be about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, or more nucleotides in length. Sometimes, a first region of a guide RNA can be or can be about 19, 20, or 21 nucleotides in length.

[00405] A guide RNA can also comprises a second region that forms a secondary structure. For example, a secondary structure formed by a guide RNA can comprise a stem (or hairpin) and a

loop. A length of a loop and a stem can vary. For example, a loop can range from or from about 3 to 10 nucleotides in length, and a stem can range from or from about 6 to 20 base pairs in length. A stem can comprise one or more bulges of 1 to 10 or about 10 nucleotides. The overall length of a second region can range from or from about 16 to 60 nucleotides in length. For example, a loop can be or can be about 4 nucleotides in length and a stem can be or can be about 12 base pairs.

[00406] A guide RNA can also comprise a third region at the 3' end that can be essentially single-stranded. For example, a third region is sometimes not complementarity to any chromosomal sequence in a cell of interest and is sometimes not complementarity to the rest of a guide RNA. Further, the length of a third region can vary. A third region can be more than or more than about 4 nucleotides in length. For example, the length of a third region can range from or from about 5 to 60 nucleotides in length.

[00407] A guide RNA can target any exon or intron of a gene target. In some cases, a guide can target exon 1 or 2 of a gene, in other cases; a guide can target exon 3 or 4 of a gene. A composition can comprise multiple guide RNAs that all target the same exon or in some cases, multiple guide RNAs that can target different exons. An exon and an intron of a gene can be targeted.

[00408] A guide RNA can target a nucleic acid sequence of or of about 20 nucleotides. A target nucleic acid can be less than or less than about 20 nucleotides. A target nucleic acid can be at least or at least about 5, 10, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, or anywhere between 1-100 nucleotides in length. A target nucleic acid can be at most or at most about 5, 10, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40, 50, or anywhere between 1-100 nucleotides in length. A target nucleic acid sequence can be or can be about 20 bases immediately 5' of the first nucleotide of the PAM. A guide RNA can target a nucleic acid sequence. A target nucleic acid can be at least or at least about 1-10, 1-20, 1-30, 1-40, 1-50, 1-60, 1-70, 1-80, 1-90, or 1-100.

[00409] A guide nucleic acid, for example, a guide RNA, can refer to a nucleic acid that can hybridize to another nucleic acid, for example, the target nucleic acid or protospacer in a genome of a cell. A guide nucleic acid can be RNA. A guide nucleic acid can be DNA. The guide nucleic acid can be programmed or designed to bind to a sequence of nucleic acid site-specifically. A guide nucleic acid can comprise a polynucleotide chain and can be called a single guide nucleic acid. A guide nucleic acid can comprise two polynucleotide chains and can be called a double guide nucleic acid. A guide RNA can be introduced into a cell or embryo as an RNA molecule. For example, a RNA molecule can be transcribed *in vitro* and/or can be

chemically synthesized. An RNA can be transcribed from a synthetic DNA molecule, *e.g.*, a gBlocks® gene fragment. A guide RNA can then be introduced into a cell or embryo as an RNA molecule. A guide RNA can also be introduced into a cell or embryo in the form of a non-RNA nucleic acid molecule, *e.g.*, DNA molecule. For example, a DNA encoding a guide RNA can be operably linked to promoter control sequence for expression of the guide RNA in a cell or embryo of interest. A RNA coding sequence can be operably linked to a promoter sequence that is recognized by RNA polymerase III (Pol III). Plasmid vectors that can be used to express guide RNA include, but are not limited to, px330 vectors and px333 vectors (**FIG. 11** and **FIG. 89**). In some cases, a plasmid vector (*e.g.*, px333 vector) can comprise at least two guide RNA-encoding DNA sequences. A px333 vector can be used, for example, to introduce GGTA1-10 and Gal2-2, or GGTA1-10, Gal2-2, and NLRC5-6. In other cases, NLRC5-6 and Gal2-2 can be introduced with a px333 vector.

[00410] A DNA sequence encoding a guide RNA can also be part of a vector. Further, a vector can comprise additional expression control sequences (*e.g.*, enhancer sequences, Kozak sequences, polyadenylation sequences, transcriptional termination sequences, *etc.*), selectable marker sequences (*e.g.*, antibiotic resistance genes), origins of replication, and the like. A DNA molecule encoding a guide RNA can also be linear. A DNA molecule encoding a guide RNA can also be circular.

[00411] When DNA sequences encoding an RNA-guided endonuclease and a guide RNA are introduced into a cell, each DNA sequence can be part of a separate molecule (*e.g.*, one vector containing an RNA-guided endonuclease coding sequence and a second vector containing a guide RNA coding sequence) or both can be part of a same molecule (*e.g.*, one vector containing coding (and regulatory) sequence for both an RNA-guided endonuclease and a guide RNA).

[00412] Guide RNA can target a gene in a pig or a pig cell. In some cases, guide RNA can target a pig NLRC5 gene, *e.g.*, sequences listed in Table 4. In some cases, guide RNA can be designed to target pig NLRC5, GGTA1 or CMAH gene. Exemplary oligonucleotides for making the guide RNA are listed in Table 5. In some cases, at least two guide RNAs are introduced. At least two guide RNAs can each target two genes. For example, in some cases, a first guide RNA can target GGTA1 and a second guide RNA can target Gal2-2. In some cases, a first guide RNA can target NLRC5 and a second guide RNA can target Gal2-2. In other cases, a first guide RNA can target GGTA1-10 and a second guide RNA can target Gal2-2.

[00413] A guide nucleic acid can comprise one or more modifications to provide a nucleic acid with a new or enhanced feature. A guide nucleic acid can comprise a nucleic acid affinity tag. A

guide nucleic acid can comprise synthetic nucleotide, synthetic nucleotide analog, nucleotide derivatives, and/or modified nucleotides.

[00414] In some cases, a gRNA can comprise modifications. A modification can be made at any location of a gRNA. More than one modification can be made to a single gRNA. A gRNA can undergo quality control after a modification. In some cases, quality control may include PAGE, HPLC, MS, or any combination thereof.

[00415] A modification of a gRNA can be a substitution, insertion, deletion, chemical modification, physical modification, stabilization, purification, or any combination thereof.

[00416] A gRNA can also be modified by 5'adenylate, 5' guanosine-triphosphate cap, 5'N^7-Methylguanosine-triphosphate cap, 5'triphosphate cap, 3'phosphate, 3'thiophosphate, 5'phosphate, 5'thiophosphate, Cis-Syn thymidine dimer, trimers, C12 spacer, C3 spacer, C6 spacer, dSpacer, PC spacer, rSpacer, Spacer 18, Spacer 9,3'-3' modifications, 5'-5' modifications, abasic, acridine, azobenzene, biotin, biotin BB, biotin TEG, cholesteryl TEG, desthiobiotin TEG, DNP TEG, DNP-X, DOTA, dT-Biotin, dual biotin, PC biotin, psoralen C2, psoralen C6, TINA, 3'DABCYL, black hole quencher 1, black hole quencer 2, DABCYL SE, dT-DABCYL, IRDye QC-1, QSY-21, QSY-35, QSY-7, QSY-9, carboxyl linker, thiol linkers, 2'deoxyribonucleoside analog purine, 2'deoxyribonucleoside analog pyrimidine, ribonucleoside analog, 2'-0-methyl ribonucleoside analog, sugar modified analogs, wobble/universal bases, fluorescent dye label, 2'fluoro RNA, 2'O-methyl RNA, methylphosphonate, phosphodiester DNA, phosphodiester RNA, phosphothioate DNA, phosphorothioate RNA, UNA, pseudouridine-5'-triphosphate, 5-methylcytidine-5'-triphosphate, or any combination thereof.

[00417] In some cases, a modification is permanent. In other cases, a modification is transient. In some cases, multiple modifications are made to a gRNA. A gRNA modification may alter physio-chemical properties of a nucleotide, such as their conformation, polarity, hydrophobicity, chemical reactivity, base-pairing interactions, or any combination thereof.

[00418] A modification can also be a phosphorothioate substitute. In some cases, a natural phosphodiester bond may be susceptible to rapid degradation by cellular nucleases and; a modification of internucleotide linkage using phosphorothioate (PS) bond substitutes can be more stable towards hydrolysis by cellular degradation. A modification can increase stability in a gRNA. A modification can also enhance biological activity. In some cases, a phosphorothioate enhanced RNA gRNA can inhibit RNase A, RNase T1, calf serum nucleases, or any combinations thereof. These properties can allow the use of PS-RNA gRNAs to be used in applications where exposure to nucleases is of high probability *in vivo* or *in vitro*. For example,

phosphorothioate (PS) bonds can be introduced between the last 3-5 nucleotides at the 5'- or 3'-end of a gRNA which can inhibit exonuclease degradation. In some cases, phosphorothioate bonds can be added throughout an entire gRNA to reduce attack by endonucleases.

Table 4. Exemplary Sequences of the NLRC5 gene to be targeted by guide RNAs

SEQ ID No.	Sequence (5'-3')
61	ggggaggaagaacttcacct
62	gtaggacgaccctctgtgtg
63	gaccctctgtgtggggtctg
64	ggctcggttccattgcaaga
65	gctcggttccattgcaagat
66	ggttccattgcaagatgggc
67	gtcccctcctgagtgtcgaa
68	gcctcaggtacagatcaaaa
69	ggacctgggtgccaggaacg
70	gtacccagagtcagatcacc
71	gtacccagagtcagatcacc
72	gtgcccttcgacactcagga
73	gtgcccttcgacactcagga
74	gtgcccttcgacactcagga
75	gggggccccaaggcagaaga
76	ggcagtcttccagtacctgg

Table 5. Exemplary oligonucleotides for making guide RNA constructs

Gene	SEQ ID No.	Forward sequence (5' to 3')	SEQ ID No.	Reverse sequence (5' to 3')
NLRC5	77	acaccggggaggaagaacttcacctg	78	aaaacaggtgaagttcttcctccccg
NLRC5	79	acaccgtaggacgaccctctgtgtgg	80	aaaaccacacagagggtcgtcctacg
NLRC5	81	acaccgaccctctgtgtggggtctgg	82	aaaaccagaccccacacagagggtcg
NLRC5	83	acaccggctcggttccattgcaagag	84	aaaactcttgcaatggaaccgagccg
NLRC5	85	acaccgctcggttccattgcaagatg	86	aaaacatcttgcaatggaaccgagcg
NLRC5	87	acaccggttccattgcaagatgggcg	88	aaaacgcccatcttgcaatggaaccg
NLRC5	89	acaccgtcccctcctgagtgtcgaag	90	aaaacttcgacactcaggaggggacg
NLRC5	91	acaccgcctcaggtacagatcaaaag	92	aaaacttttgatctgtacctgaggcg
NLRC5	93	acaccggacctgggtgccaggaacgg	94	aaaaccgttcctggcacccaggtccg
NLRC5	95	acaccgtacccagagtcagatcaccg	96	aaaacggtgatctgactctgggtacg
NLRC5	97	acaccgtacccagagtcagatcaccg	98	aaaacggtgatctgactctgggtacg
NLRC5	99	acaccgtgcccttcgacactcaggag	100	aaaactcctgagtgtcgaagggcacg
NLRC5	101	acaccgtgcccttcgacactcaggag	102	aaaactcctgagtgtcgaagggcacg
NLRC5	103	acaccgtgcccttcgacactcaggag	104	aaaactcctgagtgtcgaagggcacg
NLRC5	105	acaccgggggccccaaggcagaagag	106	aaaactcttctgccttggggcccccg
NLRC5	107	acaccggcagtcttccagtacctggg	108	aaaacccaggtactggaagactgccg
GGTA1	109	caccgagaaaataatgaatgtcaa	110	aaacttgacattcattattttctc
CMAH	111	caccgagtaaggtacgtgatctgt	112	aaacacagatcacgtaccttactc

Homologous recombination

[00419] Homologous recombination can also be used for any of the relevant genetic modifications as disclosed herein. Homologous recombination can permit site-specific modifications in endogenous genes and thus novel modifications can be engineered into a genome. For example, the ability of homologous recombination (gene conversion and classical strand breakage/rejoining) to transfer genetic sequence information between DNA molecules can render targeted homologous recombination and can be a powerful method in genetic engineering and gene manipulation.

[00420] Cells that have undergone homologous recombination can be identified by a number of methods. For example, a selection method can detect an absence of an immune response against a cell, for example by a human anti-gal antibody. A selection method can also include assessing a level of clotting in human blood when exposed to a cell or tissue. Selection via antibiotic resistance can be used for screening.

Making transgenic non-human animals

Random insertion

[00421] One or more transgenes of the methods described herein can be inserted randomly to any locus in a genome of a cell. These transgenes can be functional if inserted anywhere in a genome. For instance, a transgene can encode its own promoter or can be inserted into a position where it is under the control of an endogenous promoter. Alternatively, a transgene can be inserted into a gene, such as an intron of a gene or an exon of a gene, a promoter, or a non-coding region. A transgene can be integrated into a first exon of a gene.

[00422] A DNA encoding a transgene sequences can be randomly inserted into a chromosome of a cell. A random integration can result from any method of introducing DNA into a cell known to one of skill in the art. This can include, but is not limited to, electroporation, sonoporation, use of a gene gun, lipotransfection, calcium phosphate transfection, use of dendrimers, microinjection, use of viral vectors including adenoviral, AAV, and retroviral vectors, and/or group II ribozymes.

[00423] A DNA encoding a transgene can also be designed to include a reporter gene so that the presence of the transgene or its expression product can be detected via activation of the reporter gene. Any reporter gene known in the art can be used, such as those disclosed above. By

selecting in cell culture those cells in which a reporter gene has been activated, cells can be selected that contain a transgene.

[00424] A DNA encoding a transgene can be introduced into a cell via electroporation (**FIG. 90**). A DNA can also be introduced into a cell via lipofection, infection, or transformation. Electroporation and/or lipofection can be used to transfect fibroblast cells.

[00425] Expression of a transgene can be verified by an expression assay, for example, qPCR or by measuring levels of RNA. Expression level can be indicative also of copy number. For example, if expression levels are extremely high, this can indicate that more than one copy of a transgene was integrated in a genome. Alternatively, high expression can indicate that a transgene was integrated in a highly transcribed area, for example, near a highly expressed promoter. Expression can also be verified by measuring protein levels, such as through Western blotting.

Site specific insertion

[00426] Inserting one or more transgenes in any of the methods disclosed herein can be site-specific. For example, one or more transgenes can be inserted adjacent to a promoter, for example, adjacent to or near a Rosa26 promoter.

[00427] Modification of a targeted locus of a cell can be produced by introducing DNA into cells, where the DNA has homology to the target locus. DNA can include a marker gene, allowing for selection of cells comprising the integrated construct. Homologous DNA in a target vector can recombine with a chromosomal DNA at a target locus. A marker gene can be flanked on both sides by homologous DNA sequences, a 3' recombination arm, and a 5' recombination arm.

[00428] A variety of enzymes can catalyze insertion of foreign DNA into a host genome. For example, site-specific recombinases can be clustered into two protein families with distinct biochemical properties, namely tyrosine recombinases (in which DNA is covalently attached to a tyrosine residue) and serine recombinases (where covalent attachment occurs at a serine residue). In some cases, recombinases can comprise Cre, fC31 integrase (a serine recombinase derived from Streptomyces phage fC31), or bacteriophage derived site-specific recombinases (including Flp, lambda integrase, bacteriophage HK022 recombinase, bacteriophage R4 integrase and phage TP901-1 integrase).

[00429] Expression control sequences can also be used in constructs. For example, an expression control sequence can comprise a constitutive promoter, which is expressed in a wide

variety of cell types. For example, among suitable strong constitutive promoters and/or enhancers are expression control sequences from DNA viruses (*e.g.*, SV40, polyoma virus, adenoviruses, adeno-associated virus, pox viruses, CMV, HSV, etc.) or from retroviral LTRs. Tissue-specific promoters can also be used and can be used to direct expression to specific cell lineages. While experiments discussed in the Examples below will be conducted using a Rosa26 gene promoter, other Rosa26-related promoters capable of directing gene expression can be used to yield similar results, as will be evident to those of skill in the art. Therefore, the description herein is not meant to be limiting, but rather disclose one of many possible examples. In some cases, a shorter Rosa26 5'-upstream sequences, which can nevertheless achieve the same degree of expression, can be used. Also useful are minor DNA sequence variants of a Rosa26 promoter, such as point mutations, partial deletions or chemical modifications.

[00430] A Rosa26 promoter is expressible in mammals. For example, sequences that are similar to the 5' flanking sequence of a pig Rosa26 gene, including, but not limited to, promoters of Rosa26 homologues of other species (such as human, cattle, mouse, sheep, goat, rabbit and rat), can also be used. A Rosa26 gene can be sufficiently conserved among different mammalian species and other mammalian Rosa26 promoters can also be used.

[00431] The CRISPR/Cas system can be used to perform site specific insertion. For example, a nick on an insertion site in the genome can be made by CRISPR/Cas to facilitate the insertion of a transgene at the insertion site.

[00432] The methods described herein, can utilize techniques which can be used to allow a DNA or RNA construct entry into a host cell include, but are not limited to, calcium phosphate/DNA coprecipitation, microinjection of DNA into a nucleus, electroporation, bacterial protoplast fusion with intact cells, transfection, lipofection, infection, particle bombardment, sperm mediated gene transfer, or any other technique known by one skilled in the art.

[00433] Certain aspects disclosed herein can utilize vectors. Any plasmids and vectors can be used as long as they are replicable and viable in a selected host. Vectors known in the art and those commercially available (and variants or derivatives thereof) can be engineered to include one or more recombination sites for use in the methods. Vectors that can be used include, but not limited to eukaryotic expression vectors such as pFastBac, pFastBacHT, pFastBacDUAL, pSFV, and pTet-Splice (Invitrogen), pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, and pYACneo (Clontech), pSVK3, pSVL, pMSG, pCH110, and pKK232-8 (Pharmacia, Inc.), p3'SS, pXT1, pSG5, pPbac, pMbac, pMClneo, and pOG44 (Stratagene, Inc.), and pYES2, pAC360, pBlueBa-cHis A, B, and C, pVL1392, pBlueBac111, pCDM8,

pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis (Invitrogen, Corp.), and variants or derivatives thereof.

[00434] These vectors can be used to express a gene, *e.g.,* a transgene, or portion of a gene of interest. A gene of portion or a gene can be inserted by using known methods, such as restriction enzyme-based techniques.

Making a similar genetically modified non-human animal using cell nuclear transfer

[00435] An alternative method of making a genetically modified non-human animal can be by cell nuclear transfer. A method of making genetically modified non-human animals can comprise a) producing a cell with reduced expression of one or more genes and/or comprise exogenous polynucleotides disclosed herein; b) providing a second cell and transferring a nucleus of the resulting cell from a) to the second cell to generate an embryo generating an embryo; c) growing the embryo into the genetically modified non-human animal. A cell in this method can be an enucleated cell. The cell of a) can be made using any methods, *e.g.,* gene disruption and/or insertion described herein or known in the art.

[00436] This method can be used to make a similar genetically modified non-human animal disclosed herein. For example, a method of making a genetically modified non-human animal can comprise: a) producing a cell with reduced expression of NLRC5, TAP1 and/or C3; b) providing a second cell and transferring a nucleus of the resulting cell from a) to the second cell to generate an embryo; and c) growing the embryo to the genetically modified non-human animal. A cell in this method can be an enucleated cell.

[00437] Cells used in this method can be from any disclosed genetically modified cells as described herein. For example, disrupted genes are not limited to NRLC5, TAP1, and/or C3. Other combinations of gene disruptions and transgenes can be found throughout disclosure herein. For example, a method can comprise providing a first cell from any non-human animal disclosed herein; providing a second cell; transferring a nucleus of the first cell of a) to the second cell of b); generating an embryo from the product of c); and growing the embryo to the genetically modified non-human animal.

[00438] A cell of a) in the methods disclosed herein can be a zygote. The zygote can be formed by joining: i) of a sperm of a wild-type non-human animal and an ovum of a wild-type non-human animal; ii) a sperm of a wild-type non-human animal and an ovum of a genetically modified non-human animal; iii) a sperm of a genetically modified non-human animal and an ovum of a wild-type non-human animal; and/or iv) a sperm of a genetically modified non-human

animal and an ovum of a genetically modified non-human animal. A non-human animal can be a pig.

[00439] One or more genes in a cell of a) in the methods disclosed herein can be disrupted by generating breaks at desired locations in the genome. For example, breaks can be double-stranded breaks (DSBs). DSBs can be generated using a nuclease comprising Cas (*e.g.,* Cas9), ZFN, TALEN, and maganuclease. Nuclease can be a naturally-existing or a modified nuclease. A nucleic acid encoding a nuclease can be delivered to a cell, where the nuclease is expressed. Cas9 and guide RNA targeting a gene in a cell can be delivered to the cell. In some cases, mRNA molecules encoding Cas9 and guide RNA can be injected into a cell. In some cases, a plasmid encoding Cas9 and a different plasmid encoding guide RNA can be delivered into a cell (*e.g.,* by infection). In some cases, a plasmid encoding both Cas9 and guide RNA can be delivered into a cell (*e.g.,* by infection).

[00440] As described above, following DSBs, one or more genes can be disrupted by DNA repairing mechanisms, such as homologous recombination (HR) and/or nonhomologous end-joining (NHEJ). A method can comprise inserting one or more transgenes to a genome of the cell of a). One or more transgenes can comprise ICP47, CD46, CD55, CD59, HLA-E, HLA-G (*e.g.,* HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7), B2M, any functional fragments thereof, and/or any combination thereof.

[00441] The methods provided herein can comprise inserting one or more transgenes where the one or more transgenes can be any transgene in any non-human animal or genetically modified cell disclosed herein.

[00442] Also disclosed herein are methods of making a non-human animal using a cell from a genetically modified non-human animal. A cell can be from any genetically modified non-human animal disclosed herein. A method can comprise: a) providing a cell from a genetically identified non-human animal; b) providing a cell; c) transferring a nucleus of the cell of a) to the cell of b); c) generating an embryo from the product of c); and d) growing the embryo to the genetically modified non-human animal. A cell of this method can be an enucleated cell.

[00443] Further, cells of a) in the methods can be any cell from a genetically modified non-human animal. For example, a cell of a) in methods disclosed herein can be a somatic cell, such as a fibroblast cell or a fetal fibroblast cell.

[00444] An enucleated cell in the methods can be any cell from an organism. For example, an enucleated cell is a porcine cell. An enucleated cell can be an ovum, for example, an enucleated unfertilized ovum.

[00445] Genetically modified non-human animal disclosed herein can be made using any suitable techniques known in the art. For example, these techniques include, but are not limited to, microinjection (*e.g.,* of pronuclei), sperm-mediated gene transfer, electroporation of ova or zygotes, and/or nuclear transplantation.

[00446] A method of making similar genetically modified non-human animals can comprise a) disrupting one or more genes in a cell, b) generating an embryo using the resulting cell of a); and c) growing the embryo into the genetically modified non-human animal.

[00447] A cell of a) in the methods disclosed herein can be a somatic cell. There is no limitation on a type or source of a somatic cell. For example, it can be from a pig or from cultured cell lines or any other viable cell. A cell can also be a dermal cell, a nerve cell, a cumulus cell, an oviduct epithelial cell, a fibroblast cell (*e.g.,* a fetal fibroblast cell), or hepatocyte. A cell of a) in the methods disclosed herein can be from a wild-type non-human animal, a genetically modified non-human animal, or a genetically modified cell. Furthermore, a cell of b) can be an enucleated ovum (*e.g.,* an enucleated unfertilized ovum).

[00448] Enucleation can also be performed by known methods. For example, metaphase II oocytes can be placed in either HECM, optionally containing or containing about 7-10 micrograms per milliliter cytochalasin B, for immediate enucleation, or can be placed in a suitable medium (*e.g.,* an embryo culture medium such as CRlaa, plus 10% estrus cow serum), and then enucleated later (*e.g.,* not more than 24 hours later or 16-18 hours later). Enucleation can also be accomplished microsurgically using a micropipette to remove the polar body and the adjacent cytoplasm. Oocytes can then be screened to identify those of which have been successfully enucleated. One way to screen oocytes can be to stain the oocytes with or with about 3-10 microgram per milliliter 33342 Hoechst dye in suitable holding medium, and then view the oocytes under ultraviolet irradiation for less than 10 seconds. Oocytes that have been successfully enucleated can then be placed in a suitable culture medium, for example, CRlaa plus 10% serum. The handling of oocytes can also be optimized for nuclear transfer.

[00449] The embryos generated herein can be transferred to surrogate non-human animals (*e.g.,* pigs) to produce offspring (*e.g.,* piglets). For example, the embryos can be transferred to the oviduct of recipient gilts on the day or 1 day after estrus *e.g.,* following mid-line laparotomy under general anesthesia. Pregnancy can be diagnosed, *e.g.,* by ultrasound. Pregnancy can be diagnosed after or after about 28 days from the transfer. The pregnancy can then checked at or at about 2-week intervals by ultrasound examination. All of the microinjected offspring (*e.g.,* piglets) can be delivered by natural birth. Information of the pregnancy and delivery (*e.g.,* time

of pregnancy, rates of pregnancy, number of offspring, survival rate, etc.) can be documented. The genotypes and phenotypes of the offspring can be measured using any methods described through the application such as sequencing (*e.g.*, next-generation sequencing). Sequencing can also be Zas 258 sequencing, as shown in **FIG. 109** and **FIG. 110 A**. Sequencing products can also be verified by electrophoresis of the amplification product, **FIG. 110 B**. For example, the CM1F sequencing is shown in **FIG. 111 A** and the electrophoresis product is shown in **FIG. 111 B**.

[00450] Cultured cells can be used immediately for nuclear transfer (*e.g.*, somatic cell nuclear transfer), embryo transfer, and/or inducing pregnancy, allowing embryos derived from stable genetic modifications give rise to offspring (*e.g.*, piglets). Such approach can reduce time and cost, *e.g.*, months of costly cell screening that may result in genetically modified cells fail to produce live and/or healthy piglets.

[00451] Embryo growing and transferring can be performed using standard procedures used in the embryo growing and transfer industry. For example, surrogate mothers can be used. Embryos can also be grown and transferred in culture, for example, by using incubators. In some cases, an embryo can be transferred to an animal, *e.g.*, a surrogate animal, to establish a pregnancy.

[00452] It can be desirable to replicate or generate a plurality of genetically modified non-human animals that have identical genotypes and/or phenotypes disclosed herein. For example, a genetically modified non-human animal can be replicated by breeding (*e.g.*, selective breeding). A genetically modified non-human animal can be replicated by nuclear transfer (*e.g.*, somatic cell nuclear transfer) or introduction of DNA into a cell (*e.g.*, oocytes, sperm, zygotes or embryonic stem cells). These methods can be reproduced a plurality of times to replicate or generate a plurality of a genetically modified non-human animal disclosed herein. In some cases, cells can be isolated from the fetuses of a pregnant genetically modified non-human animal. The isolated cells (*e.g.*, fetal cells) can be used for generating a plurality of genetically modified non-human animals similar or identical to the pregnant animal. For example, the isolated fetal cells can provide donor nuclei for generating genetically modified animals by nuclear transfer, (*e.g.*, somatic cell nuclear transfer).

V. METHODS OF USE

[00453] Cells, organs, and/or tissues can be extracted from a non-human animal as described herein. Cells, organs, and/or tissues can be genetically altered *ex vivo* and used accordingly. These cells, organs, and/or tissues can be used for cell-based therapies. These cells, organs,

and/or tissues can be used to treat or prevent disease in a recipient (*e.g.*, a human or non-human animal). Surprisingly, the genetic modifications as described herein can help prevent rejection. Additionally, cells, organs, and/or tissues can be made into tolerizing vaccines to also help tolerize the immune system to transplantation. Further, tolerizing vaccines can temper the immune system, including, abrogating autoimmune responses.

[00454] Disclosed herein are methods for treating a disease in a subject in need thereof can comprise administering a tolerizing vaccine to the subject; administering a pharmaceutical agent that inhibits T cell activation to the subject; and transplanting a genetically modified cell to the subject**.** The pharmaceutical agent that inhibits T cell activation can be an antibody. The antibody can be an anti-CD40 antibody disclosed herein. The anti-CD40 antibody can be an antagonistic antibody. The anti-CD40 antibody can be an anti-CD40 antibody that specifically binds to an epitope within the amino acid sequence: EPPTACREKQYLINSQCCSLCQPGQKLVSDCTEFTETECLPCGESEFLDTWNRETHCHQH KYCDPNLGLRVQQKGTSETDTICTCEEGWHCTSEACESCV (SEQ ID NO: 487). The anti-CD40 antibody can be an anti-CD40 antibody that specifically binds to an epitope within the amino acid sequence: EKQYLINSQCCSLCQPGQKLVSDCTEFTETECL (SEQ ID NO: 488). The anti-CD40 antibody can be a Fab' anti-CD40L monoclonal antibody fragment CDP7657. The anti-CD-40 antibody can be a FcR-engineered, Fc silent anti-CD40L monoclonal domain antibody. The cell transplanted to the subject can be any genetically modified cell described throughout the application. The tissue or organ transplanted to the subject can comprise one or more of the genetically modified cells. In some cases, the methods can further comprise administering one or more immunosuppression agent described in the application, such as further comprising providing to the recipient one or more of a B-cell depleting antibody, an mTOR inhibitor, a TNF-alpha inhibitor, a IL-6 inhibitor, a nitrogen mustard alkylating agent (*e.g.*, cyclophosphamide), and a complement C3 or C5 inhibitor.

[00455] Also disclosed herein are methods for treating a disease, comprising transplanting one or more cells to a subject in need thereof. The one or more cells can be any genetically modified cells disclosed herein. In some cases, the methods can comprise transplanting a tissue or organ comprising the one or more cells (*e.g.*, genetically modified cells) to the subject in need thereof.

[00456] Described herein are methods of treating or preventing a disease in a recipient (*e.g.*, a human or non-human animal) comprising transplanting to the recipient (*e.g.*, a human or non-human animal) one or more cells (including organs and/or tissues) derived from a genetically modified non-human animal comprising one or more genes with reduced expression. One or

more cells can be derived from a genetically modified non-human animal as described throughout.

[00457] The methods disclosed herein can be used for treating or preventing disease including, but not limited to, diabetes, cardiovascular diseases, lung diseases, liver diseases, skin diseases, or neurological disorders. For example, the methods can be used for treating or preventing Parkinson's disease or Alzheimer's disease. The methods can also be used for treating or preventing diabetes, including type 1, type 2, cystic fibrosis related, surgical diabetes, gestational diabetes, mitochondrial diabetes, or combination thereof. In some cases, the methods can be used for treating or preventing hereditary diabetes or a form of hereditary diabetes. Further, the methods can be used for treating or preventing type 1 diabetes. The methods can also be used for treating or preventing type 2 diabetes. The methods can be used for treating or preventing pre-diabetes.

[00458] For example, when treating diabetes, genetically modified splenocytes can be fixed with ECDI and given to a recipient. Further, genetically modified pancreatic islet cells can be grafted into the same recipient to produce insulin. Genetically modified splenocytes and pancreatic islet cells can be genetically identical and can also be derived from the same genetically modified non-human animal.

[00459] Provided herein include i) genetically modified cells, tissues or organs for use in administering to a subject in need thereof to treat a condition in the subject; ii) a tolerizing vaccine for use in immunotolerizing the subject to a graft, where the tolerizing vaccine comprise a genetically modified cell, tissue, or organ; iii) one or more pharmaceutical agents for use in inhibiting T cell activation, B cell activation, dendritic cell activation, or a combination thereof in the subject; or iv) any combination thereof.

[00460] Also provided herein include genetically modified cells, tissues or organs for use in administering to a subject in need thereof to treat a condition in the subject. The subject can have been or become tolerized to the genetically modified cell, tissue or organ by use of a tolerizing vaccine. Further, the subject can be administered one or more pharmaceutical agents that inhibit T cell activation, B cell activation, dendritic cell activation, or a combination thereof.

Transplantation

[00461] The methods disclosed herein can comprise transplanting. Transplanting can be autotransplanting, allotransplanting, xenotransplanting, or any other transplanting. For example, transplanting can be xenotransplanting. Transplanting can also be allotransplanting.

[00462] "Xenotransplantation" and its grammatical equivalents as used herein can encompass any procedure that involves transplantation, implantation, or infusion of cells, tissues, or organs into a recipient, where the recipient and donor are different species. Transplantation of the cells, organs, and/or tissues described herein can be used for xenotransplantation in into humans. Xenotransplantation includes but is not limited to vascularized xenotransplant, partially vascularized xenotransplant, unvascularized xenotransplant, xenodressings, xenobandages, and nanostructures.

[00463] "Allotransplantation" and its grammatical equivalents as used herein can encompass any procedure that involves transplantation, implantation, or infusion of cells, tissues, or organs into a recipient, where the recipient and donor are the same species. Transplantation of the cells, organs, and/or tissues described herein can be used for allotransplantation in into humans. Allotransplantation includes but is not limited to vascularized allotransplant, partially vascularized allotransplant, unvascularized allotransplant, allodressings, allobandages, and allostructures.

[00464] After treatment (*e.g.*, any of the treatment as disclosed herein), transplant rejection can be improved as compared to when one or more wild-type cells is transplanted into a recipient. For example, transplant rejection can be hyperacute rejection. Transplant rejection can also be acute rejection. Other types of rejection can include chronic rejection. Transplant rejection can also be cell-mediated rejection or T cell-mediated rejection. Transplant rejection can also be natural killer cell-mediated rejection.

[00465] In some cases, a subject is sensitized to major histocompatibility complex (MHC) or human leukocyte antigen (HLA). For example, a subject may have a positive result on a panel reactive antibody (PRA) screen. In some cases, a subject may have a calculated PRA (cPRA) score from 0.1 to 100%. A cPRA score can be or can be about from 0.1 to 10%, 5% to 30%, 10% to 50%, 20% to 80%, 40% to 90%, 50% to 100%. In some cases, a subject with a positive PRA screen may be transplanted with the genetically modified cells of the invention.

[00466] In some cases, a subject may have a quantification performed of their PRA level by a single antigen bead (SAB) test. An SAB test can identify MHC or HLA for which a subject has antibodies to.

[00467] "Improving" and its grammatical equivalents as used herein can mean any improvement recognized by one of skill in the art. For example, improving transplantation can mean lessening hyperacute rejection, which can encompass a decrease, lessening, or diminishing of an undesirable effect or symptom.

[00468] The disclosure describes methods of treatment or preventing diabetes or prediabetes. For example, the methods include but are not limited to, administering one or more pancreatic islet cell(s) from a donor non-human animal described herein to a recipient, or a recipient in need thereof. The methods can be transplantation or, in some cases, xenotransplantation. The donor animal can be a non-human animal. A recipient can be a primate, for example, a non-human primate including, but not limited to, a monkey. A recipient can be a human and in some cases, a human with diabetes or pre-diabetes. In some cases, whether a patient with diabetes or pre-diabetes can be treated with transplantation can be determined using an algorithm, *e.g.,* as described in *Diabetes Care* 2015;38:1016–1029, which is incorporated herein by reference in its entirety.

[00469] The methods can also include methods of xenotransplantation where the transgenic cells, tissues and/or organs, *e.g.,* pancreatic tissues or cells, provided herein are transplanted into a primate, *e.g.,* a human, and, after transplant, the primate requires less or no immunosuppressive therapy. Less or no immunosuppressive therapy includes, but is not limited to, a reduction (or complete elimination of) in dose of the immunosuppressive drug(s)/agent(s) compared to that required by other methods; a reduction (or complete elimination of) in the number of types of immunosuppressive drug(s)/agent(s) compared to that required by other methods; a reduction (or complete elimination of) in the duration of immunosuppression treatment compared to that required by other methods; and/or a reduction (or complete elimination of) in maintenance immunosuppression compared to that required by other methods.

[00470] The methods disclosed herein can be used for treating or preventing disease in a recipient (*e.g.,* a human or non-human animal). A recipient can be any non-human animal or a human. For example, a recipient can be a mammal. Other examples of recipient include but are not limited to primates, *e.g.,* a monkey, a chimpanzee, a bamboo, or a human. If a recipient is a human, the recipient can be a human in need thereof. The methods described herein can also be used in non-primate, non-human recipients, for example, a recipient can be a pet animal, including, but not limited to, a dog, a cat, a horse, a wolf, a rabbit, a ferret, a gerbil, a hamster, a chinchilla, a fancy rat, a guinea pig, a canary, a parakeet, or a parrot. If a recipient is a pet animal, the pet animal can be in need thereof. For example, a recipient can be a dog in need thereof or a cat in need thereof.

[00471] Transplanting can be by any transplanting known to the art. Graft can be transplanted to various sites in a recipient. Sites can include, but not limited to, liver subcapsular space, splenic subcapsular space, renal subcapsular space, omentum, bursa omentalis, gastric or intestinal

submucosa, vascular segment of small intestine, venous sac, testis, brain, spleen, or cornea. For example, transplanting can be subcapsular transplanting. Transplanting can also be intramuscular transplanting. Transplanting can be intraportal transplanting.

[00472] Transplanting can be of one or more cells, tissues, and/or organs from a human or non-human animal. For example, the tissue and/or organs can be, or the one or more cells can be from, a brain, heart, lungs, eye, stomach, pancreas, kidneys, liver, intestines, uterus, bladder, skin, hair, nails, ears, glands, nose, mouth, lips, spleen, gums, teeth, tongue, salivary glands, tonsils, pharynx, esophagus, large intestine, small intestine, rectum, anus, thyroid gland, thymus gland, bones, cartilage, tendons, ligaments, suprarenal capsule, skeletal muscles, smooth muscles, blood vessels, blood, spinal cord, trachea, ureters, urethra, hypothalamus, pituitary, pylorus, adrenal glands, ovaries, oviducts, uterus, vagina, mammary glands, testes, seminal vesicles, penis, lymph, lymph nodes or lymph vessels. The one or more cells can also be from a brain, heart, liver, skin, intestine, lung, kidney, eye, small bowel, or pancreas. The one or more cells are from a pancreas, kidney, eye, liver, small bowel, lung, or heart. The one or more cells can be from a pancreas. The one or more cells can be pancreatic islet cells, for example, pancreatic β cells. Further, the one or more cells can be pancreatic islet cells and/or cell clusters or the like, including, but not limited to pancreatic α cells, pancreatic β cells, pancreatic δ cells, pancreatic F cells (*e.g.,* PP cells), or pancreatic ε cells. In one instance, the one or more cells can be pancreatic α cells. In another instance, the one or more cells can be pancreatic β cells.

[00473] As discussed above, a genetically modified non-human animal can be used in xenograft (*e.g.,* cells, tissues and/or organ) donation. Solely for illustrative purposes, genetically modified non-human animals, *e.g.,* pigs, can be used as donors of pancreatic tissue, including but not limited to, pancreatic islets and/or islet cells. Pancreatic tissue or cells derived from such tissue can comprise pancreatic islet cells, or islets, or islet-cell clusters. For example, cells can be pancreatic islets which can be transplanted. More specifically, cells can be pancreatic β cells. Cells also can be insulin-producing. Alternatively, cells can be islet-like cells. Islet cell clusters can include any one or more of α, β, δ, PP or ε cells. A disease to be treated by methods and compositions herein can be diabetes. Transplantable grafts can be pancreatic islets and/or cells from pancreatic islets. A modification to a transgenic animal can be to the pancreatic islets or cells from pancreatic islets. In some cases, pancreatic islets or cells from a pancreatic islet can be porcine. In some cases, cells from a pancreatic islet include pancreatic β cells.

[00474] Donor non-human animals can be at any stage of development including, but not limited to, embryonic, fetal, neonatal, young and adult. For example, donor cells islet cells can be

isolated from adult non-human animals. Donor cells, *e.g.,* islet cells, can also be isolated from fetal or neonatal non-human animals. Donor non-human animals can be under the age of 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 year(s). For example, islet cells can be isolated from a non-human animal under the age of 6 years. Islet cells can also be isolated from a non-human animal under the age of 3 years. Donors can be non-human animals and can be any age from or from about 0 (including a fetus) to 2; 2 to 4; 4 to 6; 6 to 8; or 8 to 10 years. A non-human animal can be older than or than about 10 years. Donor cells can be from a human as well.

[00475] Islet cells can be isolated from non-human animals of varying ages. For example, islet cells can be isolated from or from about newborn to 2 year old non-human animals. Islets cells can also be isolated from or from about fetal to 2 year old non-human animals. Islets cells can be isolated from or from about 6 months old to 2 year old non-human animals. Islets cells can also be isolated from or from about 7 months old to 1 year old non-human animals. Islets cells can be isolated from or from about 2-3 year old non-human animals. In some cases, non-human animals can be less than 0 years (*e.g.,* a fetus or embryo). In some cases, neonatal islets can be more hearty and consistent post-isolation than adult islets, can be more resistant to oxidative stress, can exhibit significant growth potential (likely from a nascent islet stem cell subpopulation), such that they can have the ability to proliferate post-transplantation and engraftment in a transplantation site.

[00476] With regards to treating diabetes, neonatal islets can have the disadvantage that it can take them up to or up to about 4-6 weeks to mature enough such that they produce significant levels of insulin, but this can be overcome by treatment with exogenous insulin for a period sufficient for the maturation of the neonatal islets. In xenograft transplantation, survival and functional engraftment of neo-natal islets can be determined by measuring donor-specific c-peptide levels, which are easily distinguished from any recipient endogenous c-peptide.

[00477] As discussed above, adult cells can be isolated. For example, adult non-human animal islets, *e.g.,* adult porcine cells, can be isolated. Islets can then be cultured for or for about 1-3 days prior to transplantation in order to deplete the preparation of contaminating exocrine tissue. Prior to treatment, islets can be counted, and viability assessed by double fluorescent calcein-AM and propidium iodide staining. Islet cell viability >75% can be used. However, cell viability greater than or greater than about 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% can be used. For example, cells that exhibit viability from or from about 40% to 50%; 50% to 60%; 60% to 70%; 70% to 80%; 80% to 90%; 90% to 95%, or 90% to 100% can be used. Additionally, purity can be greater than or greater than about 80% islets/whole tissue. Purity can also be at least or at

least about 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% islets/whole tissue. For example, purity can be from or can be from about 40% to 50%; 50% to 60%; 60% to 70%; 70% to 80%; 80% to 90%; 90% to 100%; 90% to 95%, or 95% to 100%.

[00478] Functional properties of islets, including glucose-stimulated insulin secretion as assed by dynamic perifusion and viability, can be determined *in vitro* prior to treatment (Balamurugan, 2006). For example, non-human animal islet cells, *e.g.,* transgenic porcine islet cells can be cultured *in vitro* to expand, mature, and/or purify them so that they are suitable for grafting.

[00479] Islet cells can also be isolated by standard collagenase digestion of minced pancreas. For example, using aseptic techniques, glands can be distended with tissue dissociating enzymes (a mixture of purified enzymes formulated for rapid dissociation of a pancreas and maximal recovery of healthy, intact, and functional islets of Langerhans, where target substrates for these enzymes are not fully identified, but are presumed to be collagen and non-collagen proteins, which comprise intercellular matrix of pancreatic acinar tissue) (1.5 mg/ml), trimmed of excess fat, blood vessels and connective tissue, minced, and digested at 37 degree C in a shaking water bath for 15 minutes at 120 rpm. Digestion can be achieved using lignocaine mixed with tissue dissociating enzymes to avoid cell damage during digestion. Following digestion, the cells can be passed through a sterile 50mm to 1000mm mesh, *e.g.,* 100 mm, 200 mm, 300 mm, 400 mm, 500 mm, 600 mm, 700 mm, 800 mm, 900 mm, or 1000 mm mesh into a sterile beaker. Additionally, a second digestion process can be used for any undigested tissue.

[00480] Islets can also be isolated from the adult pig pancreas (Brandhorst *et al.*, 1999). The pancreas is retrieved from a suitable source pig, peri-pancreatic tissue is removed, the pancreas is divided into the splenic lobe and in the duodenal/connecting lobe, the ducts of each lobes are cannulated, and the lobes are distended with tissue dissociating enzymes. The pancreatic lobes are placed into a Ricordi chamber, the temperature is gradually increased to 28 to 32ºC, and the pancreatic lobes are dissociated by means of enzymatic activity and mechanical forces. Liberated islets are separated from acinar and ductal tissue using continuous density gradients. Purified pancreatic islets are cultured for or for about 2 to 7 days, subjected to characterization, and islet products meeting all specifications are released for transplantation (Korbutt *et al.*, 2009).

[00481] Donor cells, organs, and/or tissues before, after, and/or during transplantation can be functional. For example, transplanted cells, organs, and/or tissues can be functional for at least or at least about 1, 5, 10, 20, 30 days after transplantation. Transplanted cells, organs, and/or tissues can be functional for at least or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months

after transplantation. Transplanted cells, organs, and/or tissues can be functional for at least or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, or 30 years after transplantation. In some cases, transplanted cells, organs, and/or tissues can be functional for up to the lifetime of a recipient. This can indicate that transplantation was successful. This can also indicate that there is no rejection of the transplanted cells, tissues, and/or organs.

[00482] Further, transplanted cells, organs, and/or tissues can function at 100% of its normal intended operation. Transplanted cells, organs, and/or tissues can also function at least or at least about 50, 60, 65, 70, 75, 80, 85, 90, 95, 99, or 100% of its normal intended operation, *e.g.,* from or from about 50 to 60; 60 to 70; 70 to 80; 80 to 90; 90 to 100%. In certain instances, the transplanted cells, organs, and/or tissues can function at greater 100% of its normal intended operation (when compared to a normal functioning non-transplanted cell, organ, or tissue as determined by the American Medical Association). For example, the transplanted cells, organs, and/or tissues can function at or at about 110, 120, 130, 140, 150, 175, 200% or greater of its normal intended operation, *e.g.,* from or from about 100 to 125; 125 to 150; 150 to 175; 175 to 200%.

[00483] In certain instances, transplanted cells can be functional for at least or at least about 1 day. Transplanted cells can also functional for at least or at least about 7 days. Transplanted cells can be functional for at least or at least about 14 days. Transplanted cells can be functional for at least or at least about 21 days. Transplanted cells can be functional for at least or at least about 28 days. Transplanted cells can be functional for at least or at least about 60 days.

[00484] Another indication of successful transplantation can be the days a recipient does not require immunosuppressive therapy. For example, after treatment (*e.g.,* transplantation) provided herein, a recipient can require no immunosuppressive therapy for at least or at least about 1, 5, 10, 100, 365, 500, 800, 1000, 2000, 4000 or more days. This can indicate that transplantation was successful. This can also indicate that there is no rejection of the transplanted cells, tissues, and/or organs.

[00485] In some cases, a recipient can require no immunosuppressive therapy for at least or at least about 1 day. A recipient can also require no immunosuppressive therapy for at least or at least about 7 days. A recipient can require no immunosuppressive therapy for at least or at least about 14 days. A recipient can require no immunosuppressive therapy for at least or at least about 21 days. A recipient can require no immunosuppressive therapy for at least or at least about 28 days. A recipient can require no immunosuppressive therapy for at least or at least about 60 days. Furthermore, a recipient can require no immunosuppressive therapy for at least

or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, or 50 years, *e.g.,* for at least or at least about 1 to 2; 2 to 3; 3 to 4; 4 to 5; 1 to 5; 5 to 10; 10 to 15; 15 to 20; 20 to 25; 25 to 50 years.

[00486] Another indication of successful transplantation can be the days a recipient requires reduced immunosuppressive therapy. For example, after the treatment provided herein, a recipient can require reduced immunosuppressive therapy for at least or at least about 1, 5, 10, 50, 100, 200, 300, 365, 400, 500 days, *e.g.,* for at least or at least about 1 to 30; 30 to 120; 120 to 365; 365 to 500 days. This can indicate that transplantation was successful. This can also indicate that there is no or minimal rejection of the transplanted cells, tissues, and/or organs.

[00487] For example, a recipient can require reduced immunosuppressive therapy for at least or at least about 1 day. A recipient can also require reduced immunosuppressive therapy for at least 7 days. A recipient can require reduced immunosuppressive therapy for at least or at least about 14 days. A recipient can require reduced immunosuppressive therapy for at least or at least about 21 days. A recipient can require reduced immunosuppressive therapy for at least or at least about 28 days. A recipient can require reduced immunosuppressive therapy for at least or at least about 60 days. Furthermore, a recipient can require reduced immunosuppressive therapy for at least or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, or 50 years, *e.g.,* for at least or at least about 1 to 2; 2 to 3; 3 to 4; 4 to 5; 1 to 5; 5 to 10; 10 to 15; 15 to 20; 20 to 25; 25 to 50 years.

[00488] "Reduced" and its grammatical equivalents as used herein can refer to less immunosuppressive therapy compared to a required immunosuppressive therapy when one or more wild-type cells is transplanted into a recipient.

[00489] A donor (*e.g.,* a donor for a transplant graft and/or a cell in a tolerizing vaccine) can be a mammal. A donor of allografts can be an unmodified human cell, tissue, and/or organ, including but not limited to pluripotent stem cells. A donor of xenografts can be any cell, tissue, and/or organ from a non-human animal, such as a mammal. In some cases, the mammal can be a pig.

[00490] The methods herein can further comprise treating a disease by transplanting one or more donor cells to an immunotolerized recipient (*e.g.,* a human or a non-human animal).

EXAMPLES

Example 1: Generating plasmids expressing guide RNA for disrupting GGTA1, CMAH, NLRC5, B4GALNT2, and/or C3 genes in pigs

[00491] Genetically modified pigs will provide transplant grafts that induce low or no immuno-rejection in a recipient, and/or cells as tolerizing vaccines that enhance immuno-tolerization in the recipient. Such pigs will have reduced expression of any genes that regulate MHC molecules (*e.g.,* MHC I molecules and/or MHC II molecules) compared to a non-genetically modified counterpart animal. Reducing expression of such genes will result in reduced expression and/or function of MHC molecules. These genes will be one or more of the following: components of an MHC I-specific enhanceosome, transporters of a MHC I-binding peptide, natural killer group 2D ligands, CXCR 3 ligands, C3, and CIITA. Additionally or alternatively, such pigs will comprise reduced protein expression of an endogenous gene that is not expressed in human (*e.g.,* CMAH, GGTA1 and/or B4GALNT2). For example, the pigs will comprise reduced protein expression of one or more of the following: NLRC5, TAP1, C3, CXCL10, MICA, MICB, CIITA, CMAH, GGTA1 and/or B4GALNT2. In some cases, pigs will comprise reduced protein expression of NLRC5, C3, CXCL10, CMAH, GGTA1 and/or B4GALNT2.

[00492] This example shows exemplary methods for generating plasmids for disrupting GGTA1, CMAH, NLRC5, B4GALNT2, and/or C3 genes in pigs using the CRISPR/cas9 system. The plasmids were generated using the px330 vector, which simultaneously expressed a Cas9 DNA endonuclease and a guide RNA.

[00493] The px330-U6-Chimeric_BB-CBh-hSpCas9 (#42230) plasmid was obtained from Addgene in a bacterial stab culture format. The stab culture was streaked onto a pre-warmed LB agar with ampicillin plate and incubated at 37°C overnight. The next day, a single colony was selected and inoculated in a liquid LB overnight culture with ampicillin (5 mL for mini-prep, or 80-100 mL for maxi-prep). Mini-prep was performed using Qiagen kits according to manufacturer's instructions. Plasmid was eluted in nuclease free water and stocks were stored at -20°C. The oligonucleotides designed for targeting GGTA1, CMAH, NLRC5, C3, and B4GALNT2 are shown in **Table 6**. The oligonucleotides were synthesized by IDT. **FIGs. 7A-7E, 8A-8E, 9A-9E, 10A-10E, and 11A-11E,** show the cloning strategies for cloning plasmids targeting GGTA1 (*i.e.*, px330/Gal2-1) (**FIGs. 7A-7E**), CMAH (*i.e.*, px330/CM1F) (**FIGs. 8A-8E**), NLRC5 (*i.e.*, px330/NL1_First) (**FIGs. 9A-9E**), C3 (*i.e.*, px330/C3-5) (**FIGs. 10A-10E**), and B4GALNT2 (*i.e.*, px330/B41_second) (**FIGs. 11A-11E**). The constructed px330 plasmids were validated by sequencing using sequencing primers shown in **Table 7** and by sequencing as shown in **FIG. 109**. Oligonucleotides were re-suspended at 100μM with nuclease free water and stored in the -20°C freezer.

[00494] Vector digestion: The px330 vectors were digested in a reaction solution containing 5 µg px330 stock, 5 µL 10X FastDigest Reaction Buffer, 35 µL nuclease free water, and 5 µL FastDigest BbsI enzyme (Cutsite: GAAGAC). The reaction solution was incubated at 37°C for 15 minutes, the heat inactivated at 65°C for 15 minutes. To desphosphorylate the vector, 0.2 µL (2 U; 1 U/1 pmol DNA ends) CIP was added and the resulting mixture was incubated at 37°C for 60 minutes. The linearized plasmid was purified using Qiagen PCR Cleanup kit, and eluted with nuclease free water and stored at-20 °C until use.

[00495] Oligonucleotides Annealing and phosphorylation: a solution was made by mixing 1 µL 100uM Forward oligonucleotide, 1 µL 100uM Reverse oligonucleotide, 1 µL 10X T4 Ligase Buffer, 6 µL nuclease free water, 1 µL Polynucleotide Kinase (PNK). The resulting solution was incubated on a thermal cycler running the following program: 37°C for 30 min, 95°C for 5 min, ramp down to 25°C at 0.1°C/second.

[00496] Ligation Reaction: a solution was made by mixing diluted annealed oligonucleotides 1:250 with nuclease free water, 2 µL diluted annealed oligonucleotides, 100 ng linearized/dephosphorylated px330 vector, 5 µL 10X T4 Ligase Buffer, nuclease free water to bring to 50 µL final volume, and 2.5 µL T4 DNA Ligase. The solution was incubated at room temp for 4 hours, then heat inactivated at 65°C for 10 minutes.

[00497] Transformation: TOP10 E. coli vials were thawed from -80°C freezer on ice for 15 minutes prior to transformation. 2 µL of the ligation reaction product was added to the cells and mixed by gently flicking the tubes. The tubes were incubated on ice for 5 minutes, heat shocked in 42°C water bath for 30 seconds, and placed back on ice for additional 2 minutes after heat shock. 50 µL of transformed cells were plated onto an LB agar with ampicillin plate and spread with pipette tip. The plates were incubated at 37°C overnight.

[00498] Colony PCR screening for correctly inserted oligonucleotides: 3x colonies were selected from the plate and labeled 1-3 on bottom of plate. Master mix for PCR reaction was prepared by mixing 15 µL 10X Standard Taq Reaction Buffer, 3 µL 10mM dNTP mix, 0.5 µL 100uM px330-F1 primer (SEQ ID No. 161 in **Table 7**), 0.5 µL 100uM px330-R1 primer (SEQ ID No. 162 in **Table 7**), 130 µL nuclease free water, and 1 µL Standard Taq Polymerase. Master mix was vortexed briefly, then aliquotted 50 µL to 3x PCR tubes labeled 1-3. A pipette tip was dabbed into colony #1 on the agar plate and then pipetted up and down in PCR tube #1. Repeated for each colony being screened using a fresh tip for each colony. Tubes were placed in thermal cycler to run the following program: 95°C for 5 min, 95°C for 30 seconds, 52°C for 30 seconds, 68°C for 30 seconds, cycle step 2-4 for 30 cycles, 68°C for 5 min, hold at 4 °C until use. PCR

Cleanup was performed using Qiagen PCR Cleanup Kit and followed manufacturer's protocol. The product was eluted in nuclease free water.

[00499] Preparing samples for sequencing: a solution was made by mixing 120 ng PCR product, 6.4 pmols px330-F1 primer (1 µL of 6.4 µM stock), and nuclease free water that brought the final volume to 12 µL. After the sequence data was obtained, correct sequence inserts were identified. Glycerol stocks of colonies with correct inserts were prepared. On the LB agar plate labeled during colony PCR with #1-3, the correctly inserted colonies were inoculated in 5 mL LB medium with ampicillin by dabbing with a pipette tip and ejecting into the tube of medium. Liquid culture was grown out until an OD was reached between 1.0 and 1.4. 500 µL of bacterial culture was added to 500 µL of sterile 50% glycerol in a cryovial and placed immediately on dry ice until transfer to -80°C freezer.

Table 6. Exemplary oligonucleotides for making guide RNA constructs targeting GGTA1, CMAH, NLRC5, C3, GG1, and B4GALNT2

Gene	SEQ ID No.	Forward sequence (5' to 3')	SEQ ID No.	Reverse sequence (5' to 3')
C3	113	acaccgcaaggggatattcgggtttg	114	aaaacaaacccgaatatccccttgcg
c3	115	acaccggcgctctttgggaacgtccg	116	aaaacggacgttcccaaagagcgccg
c3	117	acaccgacgacaatggtctggcccag	118	aaaactgggccagaccattgtcgtcg
B4GALNT 2 (option1)	119	acaccgtgcttttggtcctgagcgtg	120	aaaacacgctcaggaccaaaagcacg
B4GALNT 2 (opition2)	121	acaccgtcgatcctcaagatattgag	122	aaaactcaatatcttgaggatcgacg
GGTA1	123	acaccggggagagaagcagaggatgg	124	aaaaccatcctctgcttctctccccg
GGTA1	125	acaccgctgcttgtctcaactgtaag	126	aaaacttacagttgagacaagcagcg
GGTA1	127	acaccgaatacatcaacagcccagag	128	aaaactctgggctgttgatgtattcg
GGTA1	129	acaccgcccagaaggttctttgttcg	130	aaaacgaacaaagaaccttctgggcg
GGTA1	131	acaccgttggcagcagtgctcagagg	132	aaaacctctgagcactgctgccaacg
GGTA1	133	acaccgggggccgggagccgaggtgg	134	aaaaccacctcggctcccggcccccg
GGTA1	135	acaccgcacccagcttctgccgatcg	136	aaaacgatcggcagaagctgggtgcg
GGTA1	137	acaccgagagggggctgatcactgtg	138	aaaacacagtgatcagccccctctcg
CMAH	139	acaccgtagaaaaggatgaagaaaag	140	aaaacttttcttcatccttttctacg

CMAH	141	acaccgccaaatcttcaggagatctg	142	aaaacagatctcctgaagatttggcg
CMAH	143	acaccgatctgggttctgaatcccag	144	aaaactgggattcagaacccagatcg
CMAH	145	acaccggttctgaatcccacgggttg	146	aaaacaacccgtgggattcagaaccg
NLRC5	147	acaccggcctcagaccccacacagag	148	aaaactctgtgtggggtctgaggccg
NLRC5	149	acaccgtactgctgctgagcacctgg	150	aaaaccaggtgctcagcagcagtacg
NLRC5	151	acaccgactgttgcaggggggccccag	152	aaaactggggccccctgcaacagtcg
GG1	159	gagaaaataatgaatgtcaa	160	ttgacattcattattttctc

Table 7. Exemplary sequencing primers for px330 plasmids

SEQ ID No.	Forward sequence (5' to 3')	SEQ ID No.	Reverse sequence (5' to 3')
161	gccttttgctggccttttgctc	162	cgggccatttaccgtaagttatgtaacg

Example 2: Generating a plasmid expressing guide RNA targeting the Rosa26 locus in pigs

[00500] Pigs with MHC deficiencies will provide transplant grafts that induce low or no immuno-rejection in a recipient. Exogenous proteins that inhibit MHC functions will be expressed in pigs to cause MHC deficiencies. Another goal of ours further along in the project is to insert one or more exogenous polynucleotides encoding one or more proteins under the control of a ubiquitous promoter that will direct ubiquitous expression of the one or more proteins. This example show generating a plasmid expressing guide RNA targeting one of such ubiquitous promoter, Rosa26. Rosa26 promoter will direct ubiquitous expression of a gene at the Rosa26 locus. Thus transgenic pigs will be generated by inserting transgenes encoding the exogenous proteins at the Rosa26 locus, so that the gene product will be expressed in all cells in the pig. A plasmid expressing guide RNA targeting Rosa26 will be used to facilitate insertion of a transgene into the Rosa26 locus. This example shows exemplary methods for generating plasmids for targeting the Rosa26 locus in pigs using the CRISPR/cas9 system. The plasmids were generated using the px330 vector, which was be used to simultaneously express a Cas9 DNA endonuclease and a guide RNA.

[00501] Sequencing Rosa26:

[00502] For designing guide RNA targeting Rosa26 locus in a pig, Rosa26 in the pig was sequenced to provide accurate sequence information.

[00503] Primer Design: The Rosa26 reference sequence utilized to generate primers was taken from Kong *et. al.*, *Rosa26 Locus Supports Tissue-Specific Promoter Driving Transgene*

Expression Specifically in Pig. PLoS ONE 2014;9(9):e107945, Li *et. al.*, *Rosa26-targeted swine models for stable gene over-expression and Cre-mediated lineage tracing*. Cell Research 2014;24(4):501-504, and Li *et. al.*, *Identification and cloning of the porcine ROSA26 promoter and its role in transgenesis*. Transplantation Technology 2014:2(1). The reference sequence was then expanded by searching the pig genome database (NCBI) and by using Ensembl Genome Browser. The base sequence was separated into four 1218 base pair regions to facilitate primer design. Primers were designed using Integrated DNA Technologies' PrimerQuest Tool and then searched against the *Sus scrofa* reference genomic sequences using Standard Nucleotide BLAST to check for specificity. Primer length was limited to 200-250 base pairs. Primer annealing temperature was calculated using the New England Tm Calculator for a primer concentration of 1000nM and the Taq DNA Polymerase Kit.

[00504] PCR: PCR was performed using Taq DNA Polymerase with Standard Taq Buffer (New England Biolabs). DNA template used for the PCR was extracted from cells isolated from the cloned pig. PCR conditions were 30 cycles of: 95°C, 30 seconds; 50°C, 30 seconds, 51°C 30 seconds, 52°C 30 seconds, 53°C 30 seconds, 54°C 30 seconds, 55°C 30 seconds; and an extension step at 68° for 30 seconds. PCR products were purified using the QIAquick PCR Purification Kit (Qiagen). Primers used for sequencing are listed in **Table 8**.

Table 8: Exemplary PCR primers for sequencing Rosa26

SEQ ID No.	**Primer Name**	**Sequence (from 5' to 3')**
163	R26F008	tctgattggctgctgaagtc
164	R26F013	gtagccagcaagtcatgaaatc
165	R26R013	gggagtattgctgaacctca
166	R26F014	tcttgactaccactgcgattg
167	R26R014	gttaggagccagtaatggagtt
168	R26F015	agtgtctctgtctccagtatct
169	R26R015	ttggtaaatagcaatcaactcagtg
170	R26F016	tttctgctcaagtcacactga
171	R26R016	caagcaatgacaacaacctgata
172	R26F017	ttgctttctcctgatcccatag
173	R26R017	cagtgctaatctagagcactacc
174	R26F018	cattctcctgaagagctcagaat

175	R26R018	tccattgggctttgtctatactt
176	R26F019	gacaaaggaaattagcagagaacc
177	R26R019	aactggtctttcccttggatatt
178	R26F020	ctggctgcagcatcaatatc
179	R26R020	gcctctattaattgcctttccc
180	R26F021	ccattcacttcgcatccct
181	R26F005	cgggaagtcgggagcata
182	R26R005	gaggagaagcggccaatc
183	R26F006	ctgctcttctcttgtcactgatt
184	R26R006	gcgggagccactttcac
185	R26F008	tctgattggctgctgaagtc
186	R26R008	cgagagcaggtagagctagt
187	R26F010	ggagtgccgcaataccttta
188	R26R010	cctggactcatttcccatctc
189	R26F011	gggtggagatgggaaatgag
190	R26F012	gctacaccaccaaagtatagca
191	R26R012	tggtggtggaacttatctgattt
192	R26F023	agggggtacacattctcctga
193	R26R023	gacctctgggttccattggg
194	R26F024	caaagcccaatggaacccag
195	R26F025	gaaggggctttcccaacagt
196	R26F026	gcccaagacagggaaaacga
197	R26R026	tgacaactctggtcgctctg
198	R26F028	cagagagcctcggctaggta
199	R26R028	aatggctccgtccgtattcc
200	R26F029	gggaagtcgggagcatatcg
201	R26R029	cactcccgaggctgtaactg
202	R26F030	atggcgtgttttggttggag

203	R26R030	ggagccactttcactgaccc
204	R26F031	gggagggtcagtgaaagtgg
205	R26R031	gagggccgtaccaaagacc
206	R26F032	ggtcccaaatgagcgaaacc
207	R26R032	gggtccgagagcaggtagag
208	R26F033	ccgcctgaaggacgagacta
209	R26R033	cagggcggtccttaggaaaa
210	R26F034	gggagtgccgcaataccttt
211	R26R034	gaaattgggctcgtcctcgt
212	R26F035	cgaggacgagcccaatttct
213	R26R035	agtgagggggcctaaggttt
214	R26F037	actaccactgcgattggacc
215	R26R037	aggagccagtaatggagttgt
216	R26F038	cacaactccattactggctcct
217	R26R038	ggagggtagcattccagagg
218	R26F021	ccattcacttcgcatccct
219	R26R021	ttgcagatgattgcttcctttc
220	R26F023	agggggtacacattctcctga
221	R26R023	gacctctgggttccattggg
222	R26F025	gaaggggctttcccaacagt
223	R26R025	gtggcgtatgccccagtatc

[00505] Sequencing Analysis: SnapGene software was used to align the DNA sequences. After DNA sequence results were received from the University of Minnesota Biogenomics Center, they were uploaded into the SnapGene software and aligned by the software for analysis. Base pair substitutions, deletions, and insertions were determined by referencing to the chromatograms and confirmed by comparing sequences of DNA fragments amplified using different primers. When all of the edits and confirmations were done, the resulting new DNA parent sequence was made by replacing the original parent DNA sequence with the aligned one (SEQ ID NO: 224, map shown in **FIG. 12**). The Rosa26 sequence was different from the

reference Rosa26 sequence. For example, there were base pair substitution, at positions 223, 420, 3927, 4029, and 4066, and base pair deletion between positions 2692 and 2693. Nucleotide substitutions and deletions make this sequence unique (**FIG. 12**). Thus the sequencing data provided more accurate sequence information for designing guide RNA targeting the Rosa26 locus.

Generating the plasmid expressing guide RNA targeting Rosa26

[00506] Oligonucleotides targeting Rosa26 was designed and synthesized by IDT. The sequences of the guide RNA are shown in **Table 9**. The px330 plasmid expressing guide RNA targeting Rosa26 was generated using methods described in Example 1. **FIGs. 13A-13E** show cloning strategies for cloning the plasmid targeting Rosa 26 (*i.e.*, px330/ROSA exon 1). The constructed px330 plasmid was validated by sequencing using sequencing primers shown in **Table** 7.

Table 9. Exemplary oligonucleotides for making guide RNA constructs targeting Rosa26

Gene	SEQ ID No.	Forward sequence (5' to 3')	SEQ ID No.	Reverse sequence (5' to 3')
Rosa26	225	acaccgccggggccgcctagagaagg	226	aaaaccttctctaggcggccccggcg

[00507] Example 3: Generating plasmids that simultaneously express two guide RNAs

[00508] An alternative vector (*e.g.*, px333) simultaneously expressing two guide RNAs will also be used for expressing guide RNA targeting two regions of a single gene. Targeting two regions of a single gene by CRISPR/Cas9 system will result in removal of the entire gene between the two cut sites when the DNA is repaired back together. Targeting two regions will increase the chance of producing a biallelic knockout, resulting in better sorts, more biallelic deletions, and overall a higher chance to produce pigs with a negative genotype, comparing to only targeting one locus in the gene.

The oligonucleotide pairs used in the px333 plasmid construction will contain higher G content, lower A content, and as many GGGG quadraplexes as possible, compared with the oligonucleotides used for the px330 plasmid. The GGTA1 targets will span nearly the entire GGTA1 gene, which will remove the entire gene from the genome. Furthermore, targeting multiple sites with this strategy will be used when inserting transgenes, which is another goal of ours further along in the project.

Example 4: Isolating, culturing and transfecting porcine fetal fibroblasts for making genetically modified pigs

[00509] To generate genetically modified pigs using a px330 plasmid expressing guide RNA targeting a gene, the px330 plasmid was transfected into porcine fetal fibroblasts. The transfected fibroblasts will express the guide RNA that causes disruption of one or more target genes. The resulting fibroblasts were used for making genetically modified pigs, *e.g.*, by somatic cell nuclear transfer. This example shows isolation and culturing porcine fetal fibroblasts, and transfection of the fibroblasts with a px330 plasmid.

[00510] Cell culture

[00511] Fetal fibroblasts cell lines used in the generation of genetically modified pigs included: Karoline Fetal (derived from female porcine ponor P1101, which provided a high islet yield after islet isolation), Marie Louise Fetal (derived from female porcine donor P1102, which provided a high islet yield after islet isolation), Slaughterhouse pig #41 (Male; showed a high number of islets in the native pancreas (as assessed by a very high dithizone (DTZ) score)), Slaughterhouse pig #53 (showed a high number of islets in the native pancreas as assessed by a high dithizone (DTZ) score).

[00512] Muscle and skin tissue samples taken from each of these pigs were dissected and cultured to grow out the fibroblast cells. The cells were then harvested and used for somatic cell nuclear transfer (SCNT) to produce clones. Multiple fetuses (up to 8) were harvested on day 30. Fetuses were separately dissected and plated on 150mm dishes to grow out the fetal fibroblast cells. Throughout culture, fetus cell lines were kept separate and labeled with the fetus number on each tube or culture vessel. When confluent, cells were harvested and frozen at about 1 million cells/mL in FBS with 10% DMSO for liquid nitrogen cryo-storage.

[00513] Culture medium preparation: 5 mL Glutamax, 5 mL pen/strep, and 25 mL HI-FBS (for standard 5% FBS medium; use 10% FBS for sorted cells) were added to a 500 mL bottle of DMEM, high glucose, no glutamine, no phenol red. Centrifuge settings for spinning down all fetal fibroblasts were 5 minutes at 0.4 rcf (1600rpm) at 4°C. Cells were thawed from liquid nitrogen storage by warming quickly to 37°C in water bath. The thawed cells were quickly transferred to about 25 mL fresh, pre-warmed culture medium (enough to dilute the DMSO sufficiently). The cells were then spun down, the supernatant was removed and the cells were re-suspended in 1-5 mL fresh culture medium for counting or plating. Cells received a medium change every 3-4 days with pre-warmed medium, and were passaged when 90-100% confluent using TrypLE Express Dissociation Reagent.

[00514] Harvesting Adherent Fibroblasts: The medium was aspirated off the cells. DPBS was added to wash the cells. Pre-warmed (37°C) TrypLE Express reagent was added to the cells. Minimum amount of the reagent was used to cover the cell layer thinly. The cells were incubated at 37°C for 10 minutes. A volume of culture medium containing FBS was added to the TrypLE cell suspension to neutralize the enzyme. The cell suspension was pipetted up and down to dislodge all cells from the culture surface. The cell suspension was transferred to a 15 or 50 mL conical tube on ice. The plate/flask was checked under a microscope to ensure all cells were collected. Sometimes a medium wash helped collect cells that were left behind. The cells were spun down, and then re-suspended with fresh culture medium (between 1-5 mL for counting). If counting, a 1:5 dilution of the cells suspension was prepared by adding 20 µL cell suspension to 80 µL 0.2% Trypan Blue. The suspension was mixed well by pipetting up and down. 12-14 µL of the dilution was added to a hemocytometer to count the 4 corners. The numbers were averaged. For example, counting 20, 24, 22, 22 for each corner yielded an average of 22. This number was multiplied by the dilution factor 5, yielding 110 x 10^4 cells/mL. The number was adjusted to 10^6 by moving the decimal two places to the left, 1.10 x 10^6 cells/mL. Finally, the numbers were multiplied by how many mL's the original sample was taken from to get the total number of cells.

Transfection of fetal fibroblasts

[00515] This experiment was to transfect fetal fibroblasts. The transfected fetal fibroblasts were used to generate genetically modified animal using the somatic cell nuclear transfer technique.

[00516] The GFP plasmid used (pSpCas9(BB)-2A-GFP) for transfection was an exact copy of the px330 plasmid, except that it contained a GFP expression region.

[00517] GFP transfected control cells: Transfections were done using the Neon Transfection System from Invitrogen. Kits came in 10 µL and 100 µL tip sizes. A day or two before the experiment, cells were plated in appropriate culture vessel depending on size of experiment and desired cell number and density. About 80% confluence was achieved on day of transfection.

[00518] On the day of the experiment, Neon module and pipette stand was set up in a biohood. A Neon tube was placed in the pipette stand and 3 mL of Buffer E (Neon Kit) was added to the Neon tube. The module was turned on and adjusted to desired settings (for fetal porcine fibroblasts: 1300 V, 30 ms, 1 pulse). Cells were harvested using TrypLE and counted to determine the experimental setup. Needed amount of cells were transferred to a new tube and remaining cells were re-plated. Cells were spun down after counting, and re-suspended in PBS

to wash. The cells were spun down and re-suspended in Buffer R (Neon Kit) according to **Table 10** for the number of cells and tip sizes.

Table 10: Exemplary Neon® plate formats, volumes, and recommended kits

Format	Cell Type	DNA (µg)	siRNA (nM)	Neon® Tip	Vol. plating medium	Cell no.	Buffer R or Buffer T
96-well	Adherent	0.25-0.5	10-200	10 µL	100 µL	1-2 x 10^4	10 µL/well
	Suspension	0.5-1		10 µL		2-5 x 10^4	10 µL/well
48-well	Adherent	0.25-1	10-200	10 µL	250 µL	2.5-5 x 10^4	10 µL/well
	Suspension	0.5-2		10 µL		5-12.5 x 10^4	10 µL/well
24-well	Adherent	0.5-2	10-200	10 µL	500 µL	0.5-1 x 10^5	10 µL/well
	Suspension	0.5-3		10 µL		1-2.5 x 10^5	10 µL/well
12-well	Adherent	0.5-3	10-200	10 µL	1 mL	1-2 x 10^5	10 µL/well
	Suspension	0.5-3		10 µL		2-5 x 10^5	10 µL/well
6-well	Adherent	0.5-3 (10 µL) 5-30 (100 µL)	10-200	10 µL/100 µL	2 mL	2-4 x 10^5	10 µL or 100 µL/well
	Suspension	0.5-3 (10 µL) 5-30 (100 µL)		10 µL/100 µL		0.4-1 x 10^6	10 µL or 100 µL/well
60 mm	Adherent	5-30	10-200	100 µL	5 mL	0.5-1 x 10^6	100 µL/well
	Suspension	5-30		100 µL		1-2.5 x 10^6	100 µL/well
10 cm	Adherent	5-30	10-200	100 µL	10 mL	1-2 x 10^6	100 µL/well
	Suspension	5-30		100 µL		2-5 x 10^6	100 µL/well

[00519] Appropriate amount of DNA according to **Table 10** was added to cell suspension and mixed by pipetting up and down. A Neon tip was applied from the kit to the Neon pipette to aspirate the volume of cell suspension into the Neon tip. The pipette was placed into the Neon tube in the pipette stand so that the Neon tip was submerged in the Buffer E. START was pressed on module interface until a "complete" message appeared. The pipette was removed

from the pipette stand to eject the cell suspension into a volume of pre-warmed culture medium without antibiotics in a well of appropriate size according to **Table 10**.

[00520] The above steps were repeated until the entire cell suspension was used. Neon tips were changed every 2 transfections, and Neon tubes were changed every 10 transfections. The cells were incubated at 37°C for 24 hours, and then the medium was changed with normal culture medium containing antibiotics. The resulting cells were cultured for about 5 days to allow for Cas9 cleavage, complete recycling of surface proteins after gene knockout, and proper cell division before sorting. The cells transfected with the GFP plasmid were shown in **FIG. 15.**

Example 5: Fluorescence *in situ* hybridization (FISH) to the GGTA1 gene

[00521] Gene disruption by CRISPR/cas9 was verified using FISH in a cell. This example shows exemplary methods for detecting GGTA1 gene using fluorescence in situ hybridization (FISH). The methods here were used to verify the presence or absence of a GGTA1 gene in a cell from an animal (*e.g.*, an animal with GGTA1 knocked out).

[00522] Preparation of FISH probes: GGTA1 DNA was extracted from an RP-44 pig BAC clone (RP44-324B21) using an Invitrogen PureLink kit. The DNA was labeled by nick translation reaction (Nick Translation Kit - Abbott Molecular) using Orange - 552 dUTP (Enzo Life Science). Sizes of the nick translated fragments were checked by electrophoresis on a 1% TBE gel. The labeled DNA was precipitated in COT-1 DNA, salmon sperm DNA, sodium acetate and 95% ethanol, then dried and re-suspended in 50% formamide hybridization buffer.

[00523] Hybridization of FISH probes: The probe/hybridization buffer mix and cytogenetic slides from pig fibroblasts (15AS27) were denatured. The probe was applied to the slides, and the slides were hybridized for 24 hours at 37°C in a humidified chamber.

[00524] FISH detection, visualization and image capture: After hybridization, the FISH slides were washed in a 2xSSC solution at 72°C for 15 seconds, and counterstained with DAPI stain. Fluorescent signals were visualized on an Olympus BX61 microscope workstation (Applied Spectral Imaging, Vista, CA) with DAPI and FITC filter sets. FISH images were captured using an interferometer-based CCD cooled camera (ASI) and FISHView ASI software. The FISH image is shown in **FIG. 16**.

Example 6: Phenotypic selection of cells with Cas9/guide RNA-mediated GGTA1 knockout

[00525] Disruption of GGTA1 gene by the Cas9/guide RNA system were verified by labeling GGTA1 gene products. The GGTA1 knockout will be used as a marker for phenotypic sorting in knockout experiments. The GGTA1 gene encoded for a glycoprotein found on the surface of

pig cells that if had been knocked out, would result in the glycoprotein being absent on the cell's surface. The lectin used to sort for GGTA1 negative cells was Isolectin GS-IB_4 Biotin-XX conjugate, which selectively bound terminal alpha-D-galactosyl residues, such as the glycoprotein produced by the GGTA1 gene.

[00526] Porcine fetal fibroblast cells were transfected with px330 plasmid expressing guide RNA targeting GGTA1 (generated in Example 1).

[00527] To select for negative cell after transfection, the cells were allowed to grow for about 5 days to recycle their surface proteins. The cells were then harvested, and labeled with the IB_4 lectin. The cells were then coated with DynaBeads Biotin-Binder, which were 2.8 micron supermagnetic beads that had a streptavidin tail that bound very tightly with the biotin-conjugated lectin on the surface of the cells. When placed in a magnet, the "positive" cells with lectin/beads bound on the surface stick to the sides of the tube, while the "negative" cells did not bind any beads and remained floating in suspension for an easy separation.

[00528] In detail, the cells were harvested from a plate using a TrypLE protocol and collected into a single tube. The cells were spun down, and re-suspended in 1 mL of sorting medium (DMEM, no supplements) to count. If less than 10 million cells, the cells were spun down and the supernatant was discarded. In a separate tube, IB_4 lectin (1 μg/μL) was diluted by 5 μL to 1 mL of sorting medium (final concentration 5 μg/mL). The cell pellet was re-suspended with the 1 mL of diluted lectin. The cell suspension was incubated on ice for about 15-20 minutes, with gentle sloshing every few minutes.

[00529] Biotin beads were prepared during incubation. A bottle of beads were vortexed for 30 seconds. 20 μL beads/1M cells were added to 5 mL of sorting medium in a 15 mL conical tube. The tube was vortexed, placed in DynaMag-15 magnet and let stand for 3 minutes. Medium were removed. 1 mL of fresh sorting medium was added and the tube was vortexed to wash the beads. The washed beads were placed on ice until use.

[00530] After cell incubation, cell suspension's volume was brought to 15 mL with sorting medium to dilute the lectin. The cells were spun and re-suspended with 1 mL of the washed biotin beads. The suspension was incubated on ice for 30 minutes in a shaking incubator at 125 rpm. The cell suspension was removed from shaking incubator and inspected. Small aggregates might be observed.

[00531] 5 mL of sorting medium was added to the cell suspension and the tube was placed in the DynaMag-15 for 3 minutes. The first fraction of "negatives" cells was collected and transferred to a new 15 mL conical tube. Another 5 mL sorting medium was added to wash the "positive"

tube that was still on the magnet. The magnet was inverted several times to mix the cell suspension again. The tube was let stand for 3 minutes to separate cells. The second "negative" fraction was then removed and combined with the first fraction. 10 mL sorting medium was added to the "positive" tube. The tube was removed from the magnet, and placed in an ice bath until ready to use.

[00532] The tube of "negative" fractions was placed onto the magnet to provide a secondary separation and remove any bead-bound cells that might have crossed over from the first tube. The tube was kept on the magnet for 3 minutes. The cells were pipetted away from the magnet and transferred into a new15 mL conical tube. The original "positive" tube and the double sorted "negative" tube were balanced and cells in them were spun down. The pellet of the "positives" appeared a dark, rusty red. The "negative" pellet was not visible, or appeared white.

[00533] Each pellet was re-suspended in 1 mL of fresh culture medium (10% FBS) and plated into separate wells on a 24-well plate. The wells were inspected under a microscope and diluted to more wells if necessary. The cells were cultured at 37°C. The genetically modified cells, *i.e.*, unlabeled cells were negatively selected by the magnet (**FIG. 17A**). The non-genetically modified cells, *i.e.*, the labeled cells had accumulated ferrous beads on the cell surface (**FIG. 17B**).

Example 7. Generation and characterization of GGTA1/NLRC5 knockout pigs

[00534] This example shows exemplary methods for generating knockout pigs. A knockout pig can have reduced protein expression of two or more of the following: NLRC5, TAP1, C3, CXCL10, MICA, MICB, CIITA, CMAH, GGTA1 and/or B4GALNT2. One of such knockout pig was a GGTA1/ CMAH/NLRC5 knockout pig using CRISPR/cas9 system. The pigs provided islets for transplantation. Porcine islets with disrupted GGTA1/ CMAH/NLRC5 had MHC class I deficiency and will induce low or no immuno-rejection when transplanted to a recipient.

Transfection of fetal fibroblasts

[00535] The px330 plasmids expressing guide RNA targeting GGTA1, CMAH, and NLRC5 generated in Example 1 were transected in porcine fetal fibroblasts. Pig fetal fibroblasts were cultured in DMEM containing 5-10% serum, glutamine and penicillin/streptomycin. The fibroblasts were co-transfected with two or three plasmids expressing Cas9 and sgRNA targeting the GGTA1, CMAH or NLRC5 genes using Lipofectamine 3000 system (Life Technologies, Grand Island, NY) according to the manufacturer's instructions.

Counter-selection of GGTA1 KO cells

[00536] Four days after transfection, the transfected cells were harvested and labeled with isolectin B4 (IB4)-biotin. Cells expressing αGal were labeled with biotin conjugated IB4 and depleted by streptavidin coated Dynabeads (Life Technologies) in a magnetic field (**FIG. 91**). The αGal deficient cells were selected from the supernatant. The cells were examined by microscopy. The cells containing no or very few bound beads after sorting were identified as negative cells.

DNA sequencing analysis of the CRISPR/Cas9 targeted GGTA1 and NLRC5 genes

[00537] Genomic DNA from the IB4 counter-selected cells and cloned pig fetuses were extracted using Qiagen DNeasy Miniprep Kit. PCR was performed with GGTA1 and NLRC5 specific primer pairs as shown in **Table 11**. DNA polymerase, dNTPack (New England Biolabs) was used and PCR conditions for GGTA1 were based on annealing and melting temperature ideal for those primers. The PCR products were separated on 1% agarose gel, purified by Qiagen Gel Extraction Kit and sequenced by the Sanger method (DNA Sequencing Core Facility, University of Minnesota) with the specific sequencing primers as shown in **Table 7**.

Table 11. Exemplary PCR primers for amplifying genomic DNA from genetically modified cells and animals

Gene	SEQ ID No.	Forward sequence (5' to 3')	SEQ ID No.	Reverse sequence (5' to 3')
GGTA1	227	cttcgtgaaaccgctgtttatt	228	gactggaggactttgtcttctt
CMAH	229	tgagttccttacgtggaatgtg	230	tcttcaggagatctgggttct
NLRC5	231	ctgctctgcaaacactcaga	232	tcagcagcagtacctcca

[00538] Somatic cell nuclear transfer (SCNT)

[00539] SCNT was performed as described by Whitworth *et al. Biology of Reproduction* 91(3):78, 1–13, (2014). The SCNT was performed using *in vitro* matured oocytes (DeSoto Biosciences Inc., St. Seymour, TN). Cumulus cells were removed from the oocytes by pipetting in 0.1% hyaluronidase. Only oocytes with normal morphology and a visible polar body were selected for SCNT. Oocytes were incubated in manipulation media (Ca-free NCSU-23 with 5% FBS) containing 5 µg/mL bisbenzimide and 7.5 µg/mL cytochalasin B for 15 min. Oocytes were enucleated by removing the first polar body plus metaphase II plate. A single cell was injected into each enucleated oocyte, fused, and activated simultaneously by two DC pulses of 180 V for 50 µsec (BTX cell electroporator, Harvard Apparatus, Hollison, MA, USA) in 280mM Mannitol,

0.1 mM $CaCl_2$, and 0.05 mM $MgCl_2$. Activated embryos were placed back in NCSU-23 medium with 0.4% bovine serum albumin (BSA) and cultured at 38.5 °C, 5% CO_2 in a humidified atmosphere for less than 1 hour, and transferred into the surrogate pigs.

Producing genetically modified pigs using embryos

[00540] Embryos for transferring to the surrogate pigs were added to a petri dish filled with embryo transferring media. A 0.25 ml sterile straw for cell cryopreservation was also used. Aspiration of embryos was performed at 25-35° C.

[00541] Aspiration of embryos was performed following this order: media layer-air layer-media layer-air layer-embryo layer-air layer-media layer-air layer-media layer. When the straw sterilized with EO gas was used, its interior was washed by repeating aspiration and dispensing of the medium for embryo transplantation 1-3 times, before aspiration of embryos. After the aspiration, the top end of straw was sealed by a plastic cap. To keep the aspirated and sealed straw sterile, a plastic pipette (Falcon, 2 ml) was cut in a slightly larger size than the straw, put therein, and sealed with a paraffin film. The temperature of the sealed straw was maintained using a portable incubator, until shortly before use.

[00542] Embryos and estrus-synchronized surrogate mothers were prepared. Transferring of embryos will be performed by exposing ovary through laparotomy of the surrogate mothers. After anesthetization, the mid-line of the abdominal region was incised to expose the uterus, ovary, oviduct, and fimbriae. The straw aspirating embryos were aseptically taken from the portable incubator, and inserted into the inlet of oviduct. The inserted straw was moved up to the ampullary-isthmic junction region. After the insertion procedure, the straw was cut at the air containing layer on the opposite using scissors. A 1 cc syringe was mounted on the cut end, and approximately 0.3 cc of air was injected to release the embryos and medium from the straw into the oviduct. At this time, 5 mm of the top end of a 0.2 ml yellow tip was cut off and used to connect the syringe and straw.

[00543] After the embryo transfer, the exposed uterus, ovary, oviduct, and fimbriae were put in the abdominal cavity, and the abdominal fascia was closed using an absorbable suture material. Then, the surgical site was cleaned with Betadine, and treated with antibiotics and anti-inflammatory and analgesic drugs. A pregnancy test of the surrogate mother transplanted with embryos was performed, followed by induction of delivery of non-human animals that successfully got pregnant.

Pregnancy and fetuses

[00544] Two litters of pig fetuses (7 from pregnancy 1 and 5 from pregnancy 2) were obtained. Fetuses were harvested at day 45 (pregnancy 1) or 43 (pregnancy 2) and processed for DNA and culture cell isolation. Tissue fragments and cells were plated in culture media for 2 days to allow fetal cells to adhere and grow. Wild type cells (fetal cells not genetically modified) and fetal cells from pregnancy 1 or 2 were removed from culture plates and labeled with IB4 lectin conjugated to alexa fluor 488 or anti-porcine MHC class I antibody conjugated to FITC. Flow cytometric analysis was performed and data shown in **FIG. 21A-C**: Pregnancy 1 or **FIG. 21D-E**: Pregnancy 2. The histogram for the WT cells is included in each panel to highlight the decrease in overall intensity of each group of fetal cells. Of specific interested is the decrease in alpha Gal and MHC class I labeling in pregnancy 1 indicated as a decrease in peak intensity. In pregnancy 2, fetus 1 and 3 have a large decrease in alpha gal labeling and significant reduction in MHC class 1 labeling as compared to WT fetal cells.

Genotypes of the fetuses

[00545] DNA from fetal cells was subjected to PCR amplification of the GGTA1 (compared to Sus scrofa breed mixed chromosome 1, Sscrofa10.2 NCBI Reference Sequence: NC_010443.4) or NLRC5 (consensus sequence) target regions and the resulting amplicons were separated on 1% agarose gels (**FIG. 18A, 18B, 19A, and 19B**). Amplicons were also analyzed by sanger sequencing using the forward primer alone from each reaction. The results are shown as Pregnancy 1 fetuses 1, 2, 4, 5, 6, and 7 truncated 6 nucleotides after the target site for GGTA1. Fetus 3 was truncated 17 nucleotides after the cut site followed by a 2,511 (668-3179) nucleotide deletion followed by a single base substitution. Truncation, deletion and substitution from a single sequencing experiment containing the alleles from both copies of the target gene can only suggest a gene modification has occurred but not reveal the exact sequence for each allele. From this analysis it appears that all 7 fetuses contained a single allele modification. Sequence analysis of the NLRC5 target site for fetuses from pregnancy 1 was unable to show consistent alignment suggesting an unknown complication in the sequencing reaction or varying DNA modifications between NLRC5 alleles that complicate the sanger sequencing reaction and analysis. Pregnancy 2 fetal DNA samples 1, 3, 4, and 5 were truncated 3 nucleotides from the GGTA1 gene target site. Fetus 2 had variability in sanger sequencing that suggests a complex variability in DNA mutations or poor sample quality. However, fetal DNA template quality was sufficient for the generation of the GGTA1 gene screening experiment described above. NLRC5 gene amplicons were all truncated 120 nucleotides downstream of the NLRC5 gene cut site.

[00546] Fetal DNA (from wild type (WT) controls, and fetuses 1-7 from pregnancy 1) was isolated from hind limb biopsies and the target genes NLRC5 and GGTA were amplified by PCR. PCR products were separated on 1% agarose gels and visualized by fluorescent DNA stain. The amplicon bands in the WT lane represent unmodified DNA sequence. An increase or decrease in size of an amplicon suggested an insertion or deletion within the amplicon, respectively. Variations in the DNA modification between alleles in one sample might make the band appear more diffuse. Minor variations in the DNA modification were possible to resolve by a 1% agarose gel. The results are shown in **FIGs. 20A-20B**. A lack of band as in the NLRC5 gel (fetuses 1, 3, and 4 of Pregnancy 1; **FIG. 20A bottom**) suggested that the modification to the target regions was disrupted the binding of DNA amplification primers. The presence of all bands in GGTA1 targeting experiment suggests that DNA quality was sufficient to generate DNA amplicons in the NLRC5 targeting PCR reactions. Fetuses 1, 2, 4, and 5 of Pregnancy 1 (**FIG. 20A, top**) had larger GGTA1 amplicons, suggesting an insertion within the targeted area. For fetus 3 of Pregnancy 1 (**FIG. 20A, top**), the GGTA1 amplicon migrated faster than the WT control, suggesting a deletion within the targeted area. For fetuses 6 and 7 of Pregnancy 1 (**FIG. 20A, bottom**), the NLRC5 amplicons migrated faster than the WT, suggesting a deletion with in the target area. Fetuses 1-5 of Pregnancy 2, (**FIG. 20B, top**) GGTA1 amplicons were difficult to interpret by size and were diffuse as compared to the WT control. Fetuses 1-5 (**FIG. 20B, bottom**) NLRC5 amplicons were uniform in size and density as compared to the wild type control.

[00547] Given the variation in phenotypic results for the alpha Gal and MHC class 1 flow cytometric labeling there is considerable variation in the bi-allelic mutations in the GGTA1 and NLRC5 genes. This observation is supported by differences in band size in the agarose gels, truncated gene products, and sequencing challenges (**FIGS. 18A-18B, 19A-19B, 20A-20B, and 21A-21E**). Cloning of individual alleles will be performed to fully decipher the sequence modifications. However, the phenotypic, DNA sequencing, and functional analysis of fetuses support the creation of biallelic GGTA1 and NLRC5 gene modifications in fetal pigs.

Impact of gene knockout on proliferation of human immune cells

[00548] Next, with cells from fetus 3 of pregnancy 1, co-culture assays were performed to evaluate the impact of decreased MHC class I expression on proliferation of human immune cells.

Mixed lymphocyte reaction (MLR)

[00549] Co-cultures were carried out in flat-bottom, 96-well plates. Human PBMCs labeled with Carboxyfluorescein succinimidyl ester (CFSE) (2.5μM/ml), were used as responders at 0.3-0.9 × 10^5 cells/well. Wild type or Porcine fibroblasts at 0.1-0.3 × 10^5 cells/well (from wild type pigs or the GGTA1/NLRC5 knockout fetuses) were used as stimulators at stimulator–responder ratios of 1:1, 1:5 and 1:10. MLR co-cultures were carried out for 4 days in all MLR assays. In another parallel experiment, total PBMCs cells were stimulated with phytohaemagglutinin (PHA) (2ug/ml) as positive control.

[00550] Cultured cells were washed and stained with anti-CD3 antibody, anti-CD4 antibody and anti-CD8 antibody followed by formaldehyde fixation and washed. BD FACS Canto II flow cytometer was used to assess the proliferative capacity of CD8+ and CD4+ T cells in response to fibroblasts from the GGTA1/NLRC5 knockout fetus compared to unmodified porcine fibroblast cells. Data were analyzed using FACS diva/Flow Jo software (Tri star, San Diego, CA, USA), and percentage CFSE dim/low was determined on pre gated CD8 T cells and CD4 T cells.

[00551] The proliferative response of human CD8+ cells and CD4+ T cells to wild type and GGTA1/NLRC5 knockout fetal cells are shown in **FIGs. 22A-22C**. Cells were gated as CD4+ or CD8+ before assessment of proliferation (**FIG. 22A**). CD8 T cell proliferation was reduced following treatments stimulation by fetal cells with GGTA1/NLRC5 knockout fibroblasts compared to wild type fetal cells. Almost 55% reduction in CD8+ T cells proliferation was observed when the human responders were treated with GGTA1/NLRC5 knockout fetal cells at 1:1 ratio (**FIG. 22B**). Wild type fetal cells elicited 17.2% proliferation in human CD8+ T cells whereas the GGTA1/NLRC5 knockout fetal cells from fetus 3 (pregnancy 1) induced only 7.6% proliferation (**FIG. 22B**). No differences were observed in CD8+ T cells proliferative response at 1:5 and 1:10 ratio compared to the wild type fetal cells (**FIG. 22B**). No changes were observed in CD4+ T cell proliferation in response to GGTA1/NLRC5 knockout compared to the wild type fetal cells (**FIG. 22C**).

Delivery of live piglets

[00552] One of the pregnancies obtained above was allowed to complete gestation. 7 live piglets were delivered by C-section at full term (**FIG. 23**). Ear clippings and tail skin samples were taken and analyzed for screening mutations at or near the GGTA1 and NLRC5 genes. The genotypes of the piglets were determined by PCR. Three PCR experiments using different primer pairs were performed to confirm the genotype of the piglets.

[00553] First PCR experiment: PCR was run using samples from piglets #6 and #7. The NLR amplification for piglet #6 produced one strong band, while #7 produced an array of bands when

run on a gel (**FIG. 24A**). The strongest bands were gel extracted from each piglet and yielded sufficient DNA for sequencing. The PCR product of piglet #6 showed robust band at predicted PCR product. The PCR product of piglet #7 showed a band at size different from the predicted PCR product. The results indicated that piglet #6 was a mono-allelic mutant while piglet #7 was a bi-allelic mutant at the NLRC5 gene site. Primer set used for GGTA1 genotyping were: Gal amp 1 forward: gagcagagctcactagaacttg (SEQ ID NO: 153), and Gal amp1 reverse: AAGAGACAAGCCTCAGACTAAAC (SEQ ID NO: 154) (644bp amplicon). Primer set used for NLRC5 genotyping were: NL1_First_screen Forward: ctgctctgcaaacactcaga (SEQ ID NO: 155), and NLRC5-678 Reverse: gtggtcttgcccatgcc (SEQ ID NO: 156 (630bp amplicon).

[00554] Second PCR experiment: PCR was run using samples from piglets #5, #6, and #7. Only NLRC5 gene was tested. The same PCR amplification as in the first PCR experiment was performed. The PCR product of piglets #5 and #6 showed a band at the expected size (**FIG. 24B**). The PCR product of piglet #5 showed a second faint band (**FIG. 24B**). The PCR product of piglet #7 showed an array of bands as in the first PCR experiment above. These results indicated that the NLRC5 gene had in piglets #5, #6, and #7 mono-allelic and bi-allelic mutations in these piglets.

[00555] Third PCR experiment: PCR was run using samples from piglets #1, #2, #4, #5, #6, and #7. Primer set used for GGTA1 genotyping were SEQ ID NOs. 193 and 194 in Table 11 (303bp amplicon). Primer set used for NLRC5 genotyping were SEQ ID NOs. 197 and 198 in Table 11 (217bp amplicon). The NLRC5 gene amplification for piglets #1 and #2 was not as robust as the rest and produced a fainter band (**FIG. 24C**). Piglet #5 produced a more smeared band than the rest as well (**FIG. 24C**). The GGTA1 screen produced consistent bands. The NLRC5 gene amplification product is smaller and different in this experiment and created a product that varied in piglets #1 and #2, #4 and #5, #6 and #7, indicating that different mutations were present that lead to the loss of MHC class 1 expression.

[00556] Genotyping the piglets by sequencing

[00557] The genotypes of the piglets were determined by sequencing. As shown in **FIGs. 25A-25F**, Piglets #1, #2, #4, #5, #6, and #7 had one or more mutations on the NLRC5 gene.

Example 8. Generation and characterization of GGTA1/NLRC5 knockout/HLA-G1 knockin cells for making genetically modified pig.

[00558] One strategy to enhance porcine xenografts survival when transplanted to a recipient (*e.g.*, a primate such as human) is to simultaneously suppress the level of Gal α-(1,3)Gal antigen (Gal antigen) and SLA1, and in the meantime, to suppress the graft-activated natural killer cell

(NK cells) proliferation in absence of SLA1. To this end, cells with GGTA1 knocked out (to suppress Gal antigen), NLRC5 knocked out (to suppress SLA1), and HLA-G1 knocked in (to suppress NK cell proliferation) were generated using CRISPR-Cas9-mediated gene editing technology.

[00559] To get the optimal expression of HLA-G1, HLA-G1 cDNA was integrated within the first exon of pig Rosa26. The accurate sequence of exon1 of Rosa26 was determined as described in Example 2 above. We first confirmed the 1000 bp DNA sequence to 5' and 3' sequence of the cut site on Rosa26. 1000 bp upstream of the cut site was designed as left homologous arm and 1000 bp downstream was designated as right homologous arm. The sequence of left homologous arm was adapted by Li et al., (Li P. et al., Identification and cloning of the porcine Rosa26 promoter and its role in transgenesis. Transplantation Technology 2014, doi: 10.7243/2053-6623-2-1) (**Fig. 26A**), which was later on confirmed by amplifying it using sequence specific primers. The primers for right homologous arm (including exon 1 and the cut site) were designed and amplified 1000 bp product based on the sequence available in database using Long Amp (NEB). Following were the primers for the amplification of left and right homologous arms: Left Rosa26 Forward: gcagccatctgagataggaaccctgaaaacgagagg (SEQ ID NO: 157), Left Rosa26 Reverse: acagcctcttctctaggcggcccc (SEQ ID NO: 158); Right Rosa26 Forward: cgcctagagaagaggctgtg (SEQ ID NO: 263) and Right Rosa26 Reverse: actcccataaaggtattg (SEQ ID NO: 264).

[00560] The sequences of the arms were validated by performing next generation sequencing. Amplicon of Rosa26 gene from pig obtained after long range PCR (Qiagen, USA) as per manufacturer's instructions. The amplified product was run of 0.8% of agarose gel (**FIG. 26B**, Lanes: Marker: 1 kb DNA ladder; 1 and 2 Rosa26 amplicons run in duplicates). The amplified fragments were eluted from gel using Gel extraction kit (Invitrogen, USA) following the manufacturer's instructions. The eluted fragment was quantitated by nano-drop and subjected to Next Gen Sequencing. The consensus sequence of amplicon based on paired read analysis is shown in **FIG. 26C**. Homology directed recombination constructs for inserting HLA-G1 at Rosa26 locus are shown in **FIGs. 26D, 26E, and 26F**; and **FIGs. 117-119**.

[00561] Generation of homology directing fragments containing HLAG1 for Rosa26 locus

[00562] Inserting HLA-G1 at the Rosa26 locus was performed using Gibson Assembly technology, which allowed for successful assembly of multiple DNA fragments, regardless of fragment length or end compatibility, in a single-tube isothermal reaction. The Gibson Assembly Master Mix included three different enzymatic activities that were adopted to perform

in a single reaction buffer: the exonuclease created single-stranded 3′ overhangs that facilitated the annealing of fragments that shared complementarity at one end (overlap region); the DNA polymerase filled in gaps within each annealed fragment; and the DNA ligase sealed nicks in the assembled DNA.

[00563] PCR was performed for generating homologous left and right arms (having appropriate base overlap with the HLA-G1 sequence). Chemical synthesized gBLOCK for HLA-G1 was re-suspended in nuclease free water at the concentration 10ng/mL. Since HLA-G1 was large enough to add on 50 bp as an overlapping mark further, we used left and right arms to add an extra 50 bp overlapping to HL-G1. We added the 50 bp overlap in the reverse primer of fragment 1 (Left arm for homology-directed repair (HDR)) and forward primer of fragment 2 (Right arm of HDR). So, left and right arm were 1050 bp in length.

[00564] The reaction for the left arm fragment was set up as follows: 2 µL of DNA (concentration 298 ng/ml), 1 µL of Forward Primer (GLF)(10 µM), 1 µL of Reverse Primer (GLR)(10 µM), and 21 µL of Nuclease Free Water (NFW) were mixed. The mixture was added to High Yield PCR EcoDry Premix (obtained from Clontech). PCR was performed. The predicted amplicon size was 1050 bp. The Tm was 61.5 ºC. The PCR product resulted multiple bands on an agarose gel. The 1050bp band was eluted from the agarose gel for assembly and for better representation of the image.

[00565] The reaction for the right arm fragment was set up as follows: 10 µL of 10x Long Range Buffer, 1 µL of dNTP, 2 µL of DNA (concentration 298 ng/ml), 1 µL of Forward Primer (10 uM), 1 µL of Reverse Primer (10 µM), 2 µL of Long Range Amp were mixed with nuclease free water to make up a total volume of 50 µL. The Tm was 67 ºC. The expected amplicon size was 987 bp.

[00566] The reaction for the middle fragment (HLA-G1) was set up as follows: 10 µL of 10x Buffer, 1 µL of dNTPs, 1 µL or 2 µL of gBlock concentration), 1 µL of Forward Primer (10 uM), 1 µL of Reverse Primer (10 uM), 2 µL of Long Range Amp were mixed with nuclease free water to make a total volume of 50 µL. The Tm was 67 ºC.

[00567] Purification of left, right and middle arms from the agarose gel was done as per instructions of PureLink® Quick Gel Extraction Kit (Invitrogen). The concentrations of all fragments were measured using nano-drop spectrophotomter. 23.5 ng/µL, 30 ng/µL and 28.3 ng/µL were the concentrations of left, middle and right fragments eluted from 1.2% agarose gel. Following the instructions for the Gibson assembly, 2 µL of each fragment was mixed with 10

μL of GA master mix (NEB) and 4 μL of nuclease free water to make the final volume 20 μL in a 0.2 ml of PCR tube and incubated in a thermal cycler at 50 ºC for an hour.

[00568] Then 2 μL of assembled product was subjected to Long range PCR using Long Amp (NEB) using forward primers of left arms and reverse primers of right arm. The reaction of the Long range PCR was set up as follows: 10 μL of 5x Long Range Buffer, 1 μL of dNTPs (100 μM; NEB), 2 μL of Amplified gblock HLA-G1, 1 μL of Forward Primer (10 μM), 1 μL of reverse Primer (10 μM), were mixed with nuclease free water to a final volume of 50 μL. The PCR was performed and the expected amplicon size was about 3000 bp.

[00569] Designing and cloning of gRNA to targeting the exon 1 of pig Rosa26 exon 1, GGTA1 and NLRC5 (for SLA1 knock out)

[00570] Specific oligonucleotides for making gRNAs that make cut in exon 1 of pig ROSA26 exon 1, in close proximity of first codon of GGTA1, or NLRC5 were designed using http://zifit.partners.org/ZiFiT/CSquare9Nuclease.aspx. The cDNA sequence of HLA-G1 is shown in Table 2, and the genomic sequence of HLA-G is shown as SEQ ID: No. 191. The maps of the genomic sequence and cDNA of HLA-G are shown in **FIGs. 14A-14B**.

[00571] Briefly, the oligonucleotides were synthesized and resuspended in respective amount of nuclease free water to get the concentration of 100 μM each. 1μL of each oligonucleotides (forward and reverse) were mixed with 1 μL of 10x T4 Polynucleotide Kinase Reaction Buffer, 0.5μL T4 Polynucleotide Kinase and 6.5μL of dH_2O to make up the total volume 10 μL in 0.2 μL tubes. The tubes with the reaction solution were placed in a thermocycler. The following program was run for the appropriate annealing of the forward and reverse oligos: 37 ºC for 30 min; 95 ºC for 5 min; Ramp down to 25 ºC at 0.1 ºC /sec. The annealed oligos were diluted by 1:100.

[00572] Plasmid pX330-U6-Chimeric_BB-CBh-hSpCas9 (Addgene) was used to clone the annealed oligonucleotides to generate gRNA for the CRISPR-associated Cas9 nuclease system. One microgram of plasmid pX330 was digested with BbsI (New England Biolabs, Ipswich, MA) for 15 min at 37 ºC using fast digest buffer and then kept for 15 min to inactivate BbsI. Then 0.2 μL of Calf-intestinal alkaline phosphatase (CIP) was added and incubated for 1 hour, to avoid the self-ligation of the digested vector. Digested pX330 was purified using Plasmid Extraction mini-prep kit (Qiagen). Digested vector was mixed with 300 μL of PB buffer and then added to purification column of this kit, which was then spun down at 8000 rpm x 1 min. The flow-through was discarded and the column was washed by PE buffer (containing absolute ethanol) and finally eluted in 50 μL of EB buffer. 1.3μL (50ng) of digested px330 vector was

mixed with 1.0 µL diluted oligonucleotides, 5 µL 10X T4 Ligase Buffer, and 2.5 µL T4 DNA Ligase, and the finally the volume was made to 50 µL by adding 39.9 µL of nuclease free water. Negative control was run without adding any oligo to the reaction mix. Ligase was then inactivated at 65 ºC for 5min before heading to transformation in TOP10 competent cells (Invitrogen), following the manufacturer's protocol. The DNA clones were sequence.

[00573] Evidence of ligation of Rosa26 oligos in px330 vector juxtaposed with gRNA was shown in **FIGs. 27A, 27B, and 27C**. The sequence of the correct clone was shown in **FIG. 27A** and the RNC1_E02_008 sequencing result of constructed plasmid was shown in **FIG. 27B**.

[00574] Restriction digestion of ligated products was also performed to verify the success of ligation. Two restriction enzymes (BsbI and AgeI) were used to digest the purified the ligated products. Since oligonucleotides were ligated in Bsbl sites, the BsbI site was disrupted in px300 vectors that harboring oligonucleotides (**FIG. 27C**, Lane 1: intact vector; Lane 2: ligated vector with disrupted BsbI site).

[00575] *In vitro* transcription (IVT) and *in vitro* Cas9-mediated cleavage of target DNA

[00576] To examine the cleavage potentials of gRNAs designed for Rosa26, GGTA1 and NLRC5 sites, Guide-it™ sgRNA *In Vitro* Transcription and Screening System was used for the *in vitro* transcription of guide RNAs following manufacturer's protocol. The respective cleavage potential of the guided RNAs was also examined. The gRNA for GGTA1 cleavage was performed using the GalMet oligos (Forward: acaccggagaaaataatgaatgtcaag (SEQ ID NO: 367); Reverse: aaaacttgacattcattattttctccg (SEQ ID NO: 368)) (**FIG. 28**). Gal(Met) targeted the first methionine of the GGTA1 cDNA transcript, but not any other regulatory methyl group outside in the promoter region.

[00577] A: Amplification of target (about 2000 kb) for gRNAs.

[00578] About 2kb long amplicon containing target sequence for gRNA for Rosa26, GGTA1 and NLRC5 were amplified using specific primers as per instructions of the kit. Pig DNA and primers were mixed with nuclease free water to a total volume of 25 µL. The mixture was later mixed with Dry PCR mix. The Tm of reactions for Rosa26, GGTA1 and NLRC5 were 61.5 ºC, 60 ºC, and 63 ºC, respectively. All the amplicons from agarose gel was eluted using of Purlink; Quick Gel Extraction kit (Invitrogen).

[00579] B: In-vitro transcription

[00580] Chemically synthesized DNA template that contained designed sgRNAs encoding sequence under the control of a T7 promoter and universal gRNA sequence were obtained from

IDT. The template was amplified by PCR with the d Guide-it Scaffold Template provided in the kit.

[00581] The IVT templates for Rosa26, NLRC5 and GGTA1 were as follows:
Rosa26: gccgcctctaatacgactcactatagggccgccggggccgcctagagagttttagagctagaaatagca (SEQ ID NO: 233); NLRC5: gccgcctctaatacgactcactatagggccggcctcagaccccacacagaggttttagagctagaaatagca (SEQ ID NO: 234);
GGTA1: gcggcctctaatacgactcactataggggagaaaataatgaatgtcaagttttagagctagaaatagca (SEQ ID NO: 235).

[00582] The 5 μl of Guide-it Scaffold Template (provided in kit) with 1 μl of the abovementioned templates were mixed at a concentration of 10 μM, and dilute with RNase-free water to a final volume of 25 μl. The solutions were mixed by gentle pipetting. The entire 25 μl mixture was added to one tube of High Yield PCR EcoDry Premix. Thermal cycling using the following program: 95°C for 1 min; 33 cycles of 95°C for 30 sec, 68 °C for 1 min, 68°C for 1 min.

[00583] The resulting PCR products were run on a 1.8 % agarose gel. A single band at about 140 bp was obtained for each of the three IVT templates. The bands were then purified by NucleoSpin Gel provided by the kit.

[00584] *In vitro* transcription was then performed by mixing 100 ng of the PCR products with Guide-it *In Vitro* Transcription Buffer and Guide-it T7 Polymerase Mix. The final volume was 20 μL by adding nuclease free water and incubated at 42 °C for 1 hour.

[00585] C: Purification and Quantification of In Vitro transcribed sgRNA

[00586] (1) 2 μl of RNase free DNase I was added to the entire 20 μl of the *in* vitro transcription reaction and incubate at 37°C for 0.5 hour.

[00587] (2) RNase free water was added to the reaction mixture to a final volume of 100 μl.

[00588] (3) 100 μl of phenol:chloroform: isoamyl alcohol (25:24:1), saturated with 10 mM Tris, pH 8.0, 1 mM EDTA was added to the diluted reaction mixture from Step (2) and vortex well.

[00589] (4) The solution was centrifuged at 12,000 rpm for 2 min at room temperature. The supernatant was transferred to a new tube, to which an equal volume of chloroform was added.

[00590] (5) The solution was vortexed well and then centrifuged at 12,000 rpm for 2 min at room temperature.

[00591] (6) The supernatant was transferred to a new tube, added 1/10 volume of 3M sodium acetate and an equal volume of isopropanol, and vortexed well.

[00592] (7) The solution from Step (6) was incubated for 5 min at room temperature, and then centrifuged at 15,000 rpm for 5 min at room temperature.

[00593] (8) The supernatant was removed carefully. The pellet was rinsed with 80% ethanol and centrifuged at 15,000 rpm for 5 min at room temperature.

[00594] (9) The pellet was air dried for about 15 min and resuspended in 20 µl of RNase free water and the concentration was checked using nano-drop.

[00595] D: Cas9 mediated cleavage of 2 kb template (section A) with purified gRNAs of Rosa26, NLRC5 and GGTA1

[00596] (1) Cleavage reactions containing above sgRNA (specific for a target) and the amplified experimental templates (about 2 kb long of each gene; Rosa26, NLRC5 (NL1) and GGTA1, containing target sequence) were set up.

[00597] (2) The experimental cleavage template (100 ng total) with experimental sgRNA sample (20 ng total from above), 1µL of Guide-it Recombinant Cas9 Nuclease, 1 µL of 10X Cas9 Reaction Buffer, 1µL of 10X BSA were mixed and made up to a final volume of 10 µL with nuclease free water. The mixture was incubated at 37°C for 1 hour. The reaction was stopped by incubating solution at 70 °C for 10 min. The entire 10 µl of reactions was analyzed on a 1% agarose gel alongside a negative control (100 ng of an uncleaved 2 kb control fragment) (**FIG. 29**).

[00598] Electroporation and flow sorting

[00599] Cryopreserved cells were seeded 1 x 10^6 cells per petri dish in 10 % complete DEMEM media. After that the cells were seeded, the media was changed after each 24h and allowed the petri dish to be confluent (>70%). Then the cells were harvested using PBS, TRYPLE Express and then resuspended in 100 µL of R buffer provided by Neon system for electroporation. 1.5 µg of px330 plasmids containing gRNAs (for Rosa26, GGTA1 or NLRC5) was added in the 1.5 ml tube and mixed by gentle tapping. Afterwards electroporation was performed in a 100 µL tube at 1300 V x 30 ms x 1 pulse. Cells were seeded in 15% complete DMEM media and monitored after each 12 h. After 12 h post electroporation, the signs of cells adherence were visible.

[00600] Pig fetus fibroblasts were electroporated with px330U6-gRNA (met, GGTA1); px330U6-gRNA (Rosa26) and px330U6-gRNA (NLRC5); and amplicon of Gibson assembled

HLA-G1 with Rosa26 homologous left and arms (designed for the insertion at the pig Rosa26 locus) were harvested at 5th day after the transfection using 1xPBS -/- and Triple Express.

[00601] We transfected in three different tubes of and recovered about 1 X 10^6 cells from each petri dish. These cells were stained with 1 μg of IB4-APC (Biolegend), 1 μg of anti-pig SLA1-FITC (Novus Biologicals), 5 μL of anti- HLA-G1-PE in 100 μL of flow buffer (PBS-1% BSA), and incubated at 4 °C for 30 min in dark. Negative unstained control was also kept at 4°C and was subjected to all treatments as we did in stained cells. Also, we made single stained tubes: IB4-APC and SLA1-FITC for the positive control of the respective fluorochromes. After that the pig fibroblasts were spun at 2000 rpm for 5 min in microfuge to remove extra antibodies. Next the cells were resuspended again in flow buffer (100 μL) and passed through flow tubes with strainer (BD). After staining, we capped all the tubes carefully to avoid the chances of contamination while traveling to Flow sorting facility (CCRB, University of Minnesota). The collection media was 2.5% complete DMEM (Pen-Step, Glutamax and FBS) per the instructions of the flow sort core facility. The sorting results are shown in **FIG. 30**.

Delivery of live piglets

[00602] FIG. 114 A-C shows pictures of live births of GGTA1/NLRC5 knockout/HLA-G1 knockin piglets.

Genotyping by sequencing

[00603] Next generation sequencing was performed to confirm the correct insertion of the HLA-G1 sequence into the ROSA site. The sequencing was performed on a skin sample taken from a live piglet. The confirmed sequence of the HLA-G1 knockin in the ROSA site is shown in **FIG 115** (SEQ ID NO: 499).

Example 9. Generation and characterization of GGTA1 knockout/CD47 knockin cells for making genetically modified pig

[00604] One strategy to enhance porcine xenografts survival when transplanted to a recipient (*e.g.,* a primate such as human) is to simultaneously suppress the level of Gal alpha-(1,3)Gal antigen (Gal antigen) and suppress activation of macrophages. To this end, cells with GGTA1 knocked out (to suppress Gal antigen) and human CD47 knocked in (to suppress macrophage activation) were generated using CRISPR-Cas9-mediated gene editing technology.

[00605] The GGTA1 Knockout/CD47 knockin cells were generated using similar methods as described in Example 26. GGTA1-targeting gRNA vector, in which GGTA1-specific gRNA (having binding site in exon 1) was cloned under U6 promoter in px330, was transfected with a

Gibson assembled GGTA1-CD47 gene hybrid. In the GGTA1-CD47 gene hybrid, CD47 gene was sandwiched between 1000 bp homologous arms (the 5' side and the 3' side of cut site) of GGTA1.

[00606] CD47 cDNA was assembled with a left arm and a right arm of GGTA1 locus.

[00607] The primers for the assembly were: CD47 assembly right forward primer: ttgagcctgtgcatcgcagcgt (SEQ ID NO: 236; CD47 assembly right reverse primer: ctacttttaatgcaagctggtgacttggctgataactagg (SEQ ID NO: 237); CD47 assembly left forward primer: aaattaaggtagaacgcactccttagcgctcgt (SEQ ID NO: 238); CD47 assembly left reverse primer: attttgggcttccatgttggtgacaaaacaaggg (SEQ ID NO: 239).

[00608] The sequence of resulting assembly construct comprising the left arm, CD47 coding sequence, and the right arm was shown in **FIG. 31** (left arm and right arm underlined). The CD47 sequence was optimized for pig codon usage and was made synthetically and assembled. This sequence was not derived from human cells. It was designed to express with the correct amino acid profile in pigs. The CD47 sequence (Table 12) was optimized for pig codon usage and was made synthetically and assembled.

Table 12. Synthetic CD47 for expressing in pig

SEQ ID NO 240	atgtggccccttgtcgctgcccttcttttgggctctgcatgttgcggctccgcacagctccttttcaacaaaacgaagtcagttg agttcaccttctgtaatgataccgttgtgatcccttgttttgtcaccaacatggaagcccaaaatacgactgaggtctacgtcaa gtggaaattcaaggggagggatatttatacgtttgatggtgctctgaataaatctacggttccgacggattttagttccgcaaa gattgaagtgtctcagctgttgaagggtgacgcttccctgaaaatggataaatccgatgccgttagccatacggggaattaca cctgcgaggttaccgaactcacccgcgagggggagacgataatagaacttaagtatagggtggttagctggttctctccaa acgagaacattctgatagttattttcccaatcttcgctatattgctgttctggggtcaattcggcattaaaacgcttaaatatagga gcggcgggatggacgagaaaacgatcgccttgcttgtcgcaggtttggttatcaccgtcattgtgattgtcggagccatcct gtttgtccctggtgagtatagcttgaaaaatgccactggcctcggtctgatcgtgacgtccactggcatccttatactccttcatt attatgtgttcagtactgccattggtcttacgtcttttgtgattgccatcctcgtcattcaggtcatcgcatacatactcgcagtcgt cggtttgagcctgtgcatcgcagcgtgcattcccatgcacggacctctcttgatctctggtctttctatattggcgctggcacaa cttcttggcttggtttacatgaagtttgtcgcctctaatcagaagacgatccaacccccgcgcaacaactga

[00609] The CD47 gene was targeted to the GGTA1 gene cut site with left and right arms that are homologous to the GGTA1 gene. The GGTA1 gene was inactive in adult islets but the promoter was turned on in blood cells and splenocytes of adult pigs. Therefore, a CD47 expressing pig (from the GGTA1 site) will be a great vaccine donor.

[00610] The assembly was confirmed by sequencing. The sequences of the assembled left arm and right arm are shown in **FIG. 32**.

[00611] The phenotypes of the cells were examined by cell sorting. Gal antigen was detected by IB4-APC staining. CD47 was detected by CD47-Brilliant Violet 421-A. The cells sorting results were shown in **FIGs. 33A-33C** (unstained), **FIGs. 34A-34C** (px330), **FIGs. 35A-35C** (IB4), and **FIGs. 36A-36C** (CD47/IB4). Cells with GGTA1 knocked out and cells with CD47 knocked in/GGTA1 knocked out were sorted and purified for somatic cell nuclear transfer. The cell sorting results for the sorted cells were shown in **FIGs. 37A-37C** (IB4) and **FIGs. 38A-38C** (CD47/IB4).

Example 10: The effect of MHC class I deficient porcine fibroblast cells (Fibroblast) on immune activation of human lymphocytes

A. Proliferation (CFSE): SLA-I/Gal-2 knockout

[00612] One strategy to determine the human immune response to xenotransplantation can be the co-culture of genetically modified, MHC class I deficient porcine fibroblast cells, with human PBMCs. Mixed lymphocyte reaction co-cultures were carried out in flat-bottom, 96-well plates. Human CFSE labeled (2.5μM/ml) PBMCs, were used as responders at 1-2 × 105 cells/well/200ul. Porcine fibroblast cells at 1000 to 1×10^5 cells/well (with or without SLA-I/Gal-2 knockout) were used as stimulators at stimulator–responder ratios of 100:1, 50:1, 10:1 and 1:10. MLR co-cultures were carried out for 24hrs for cytokines (Il-2, TNF-a and IFN-g) effector molecules (Perforin, Granzyme B LAMP-1/CD107a) expression and 5-6 days for measurement of T and B cells proliferation. **FIG. 39** and **FIG. 55** show the gating strategy used to analyze proliferation data. Results of one human donor are shown in **FIG. 40** and **FIG. 41- FIG. 44**. Results of additional donors are shown in **FIG. 56** to **FIG. 59**.

B. Proliferation (CFSE): NLRC5-6/Gal-2 -2 construct: SLA-I/Gal-2knockdown; NLRC5-6/Gal-2 construct and GGTA1-1/Gal2-2 construct SLA-I/Gal-2knockdown.

[00613] Human PBMCs: Pre labeled with CFSE, were cultured with following: Control: Porcine Fibroblast: Wild Type; Condition#3 MLF cells with NLRC5-6/Gal-2 -2construct: SLA-I/Gal-2knockdown; Condition#4 MLF cells with NLRC5-6/Gal-2 construct and GGTA1-1/Gal2-2 construct SLA-I/Gal-2knockdown; Culture cell density: MLF cells=4x10^4 cells/ml; Human PBMCs =1x10^6 cells/ml; Cells density of MLR culture: 2x10^5 to 1.4x10^5cells/200ul /well in 96 well plate flat bottom in duplicate or triplicates (Table 13).

Table 13. Testing plate configuration

	BLUE LASER (488nm)				RED LASER (633/640nm)		VIOLET LASER (405nm)	
	FL-1 530/30	FL-2 575/26	FL-3 670/14 695/40	FL-4 780/60	FL-5 660/20	FL-6 730/45 780/60	FL-7 450/40	FL-8 525/50
	FITC/ AF488 BDH B-Blue515	PE PI	PECy5 PerCP PerCP Cy5.5	PECy7 496/785	APC AF647 eF660	APC-Cy7 AF700 APC-H7	PacB(401/452) BV421/450 BDH450	BDHV500 AmCyan/PacO BV500/BV510
BS1	CFSE	x	CD20 PerCP, 20ul	CD8 PECy7 5ul	CD4 APC 5ul	X	L/D dye	CD3 V500 5ul
IC-1	Perfor in 5ul	IL-2 5ul	CD4 20ul	CD8 5ul	CD107a 5ul	Granzyme B 5ul	do	do
IC-2	CD8 20ul	IFN-g 5ul	CD4 20ul	TNF-a 5ul	CD56 5ul	Granzyme B CD20 10ul	do	do
FMO FMD	CD8 20ul		CD4 20ul		CD56 5ul	Granzyme B CD20 10ul	do	do

C. Intracellular Cytokine Staining (ICCS)

[00614] In a parallel experiment (Table 14) total PBMCs cells were stimulated with and without PHA (2ug/ml) as positive and unstimulated control respectively. Cultured cells were washed and stained with anti-CD3, anti-CD4 and anti-CD8 followed by formaldehyde fixation and washing and intracellular staining with anti-perforin, granzyme B, IL-2, TNF-a and IFN-g (**FIG. 45** to **FIG. 52**). BD FACS Canto II flow, were used to assessed the proliferative capacity of CD8 and CD4 T cells in response to SLA-I knockout porcine fibroblast (F3) compared to unmodified porcine fibroblast cells. Data were analyzed using FACS diva/Flow Jo software (Tri star, San Diego, CA, USA), and percentage CFSE dim/low was determined on pre gated CD8 T cells and CD4 T cells.

Table 14. ICCS Experimental Configuration

			Ratios of Human PBMCs vs FC

	PBMCs alone	PBMCs+ PHA	100:1	50:1	10:1	1;1
WT	2x10^5	2x10^5	1x10^5 + 1000MLF	1x10^5 + 2000MLF	1x10^5 + 10,000MLF	1x10^5 + 1x10^5 MLF
#3	2x10^5	2x10^5	do	do	do	do
#4	2x10^5	2x10^5	do	do	do	do

Example 11: Methodology for mixed cell cultures including PT85 antibody.

[00615] Mixed lymphocyte reaction co-cultures were carried out in flat-bottom, 96-well plates. Human CFSE labeled (2.5µM/ml) PBMCs, were used as responders at 1-2 × 10^5 cells/well/200ul. Porcine fibroblast cells/WT or HLA-G tranduced at 2000 to 1 × 10^5 cells/well (with or without PT85 Ab/blocking Abs, 10ug/ml) were used as stimulators at stimulator–responder ratios of 100:1, 50:1, 10:1 and 1:10. MLR co-cultures were carried out for 24hrs for cytokines (Il-2, TNF-a and IFN-g) effector molecules (Perforin, Granzyme B LAMP-1/CD107a) expression and 5-6 days for measurement of T and B cells proliferation. In another parallel experiment total PBMCs cells were stimulated with and without PHA (2ug/ml) as positive and unstimulated control respectively. Cultured cells were washed and stained with anti-CD3, anti-CD4 and anti-CD8 followed by formaldehyde fixation and washing and intracellular staining with anti-perforin, granzyme B, IL-2, TNF-a and IFN-g. BD FACS Canto II flow, were used to assessed the proliferative capacity of CD8 and CD4 T cells in response to SLA-I knockout porcine fibroblast (F3) compared to unmodified porcine fibroblast cells. Data were analyzed using FACS diva/Flow Jo software (Tri star, San Diego, CA, USA), (Table 15).

Table 15: Flow Cytometry Experimental Configuration

	BLUE LASER (488nm)				RED LASER (633/640nm)		VIOLET LASER (405nm)	
	FL-1 530/30	FL-2 575/26	FL-3 670/14 695/40	FL-4 780/60	FL-5 660/20	FL-6 730/45 780/60	FL-7 450/40	FL-8 525/50
	FITC/AF488 BDHB- BlueS15	PE PI	PECy5 PerCP PerCP Cy5.5	PECy7 496/785	APC AF647 eF660	APC-Cy7 AF700 APC-H7	Pac8(401/452) BV421/450 BDH450	BDHVS00 AmCyan/PacO BVS00/BVS10
BS1	CFSE	x	CD20 PerCP, 20ul	CD8 PECy7 5ul	CD4 APC 5ul	X	L/D dye	CD3 VS00 5ul
IC-1	Perforin 5ul	IL-2 5ul	CD4 20ul	CD8 5ul	CD107a 5ul	Granzyme B 5ul	do	do
IC-2	CD8 20ul	IFN-g 5ul	CD4 20ul	TNF-a 5ul	CD56 5ul	Granzyme B CD20 10ul	do	do
FMO FMD	CD8 20ul		CD4 20ul		CD56 5ul	Granzyme B CD20 10ul	do	do

Example 12: Blocking MHC class 1 molecule / TCR interaction PT-85 antibody.

[00616] Mixed lymphocyte reaction co-cultures were carried out in flat-bottom, 96-well plates. Human CFSE labeled (2.5μM/ml) PBMCs, were used as responders at 1-2 × 10^5 cells/well/200ul. Porcine fibroblast cells at 2000 to 1 × 10^5 cells/well (with or without SLA-blocking with PT85 10ug/ml) or with HLA-G transduced Porcine fibroblast /MLF cells were used as stimulators at stimulator–responder ratios of 100:1, 50:1, 10:1 and 1:10 (**FIG. 53** and **FIG. 54**). MLR co-cultures were carried out for 24hrs for cytokines (Il-2, TNF-a and IFN-g) effector molecules (Perforin, Granzyme B LAMP-1/CD107a) expression and 5-6 days for measurement of T and B cells proliferation. In another parallel experiment total PBMCs cells were stimulated with and without PHA (2ug/ml) as positive and unstimulated control respectively. Cultured cells were washed and stained with anti-CD3, anti-CD4 and anti-CD8 followed by formaldehyde fixation and washing and intracellular staining with anti perforin, granzyme B, IL-2, TNF-a and IFN-g (**FIG. 66** to **FIG. 74** and **FIG. 79** to **FIG. 86**). BD FACS Canto II flow, were used to assessed the proliferative capacity of CD8 and CD4 T cells in response to SLA-I knockout porcine fibroblast (F3) compared to unmodified porcine fibroblast cells (**FIG. 61** to **FIG. 65** and **FIG. 75** to **FIG. 78**). Data were analyzed using FACS diva/Flow Jo software (Tri star, San Diego, CA, USA), and percentage CFSE dim/low was determined on pre gated CD8 T cells and CD4 T cells, **FIG. 61** to **FIG. 65** . The gating strategy used to analyze data is shown in **FIG. 60**.

Example 13: testing HLA-G transgene expressing pig cells to inhibit the human T-cell proliferation response.

[00617] T cell proliferation was reduced following stimulation by porcine fibroblast treated with PT-85 blocking Abs compared to control unmodified porcine fibroblast/WT at ratios 10:1 of Human PBMCs and FC respectively. Substantial reduction in T cells (CD3/CD4/CD8)

proliferation was observed when human responder were treated with SLA-I blocking PT-85 Abs or HLA-G expressing at 10:1 and 1:1 ratio. No much difference were seen in T cells proliferative response at 100:1 and 50:1 ratio compared to unmodified/WT porcine fibroblast. No substantial reduction in B cells proliferation either with blocking SLA-I with PT-85 or HLA-G expression.

Example 14: Secreted cytokine profile after mixed lymphocyte assay measure by Luminex human cytokine panel (HSTCMAG-28SK human high sensitivity T cell).

[00618] To determine the cytokine profile of mixed lymphocytes to porcine genetically modified cells a co-culture assay was performed where the supernatant from day 24 mixed cell cultures and controls was collected and the luminex assay was performed. Following the manufacturers protocol, an aliquot of supernatant was removed and incubated with luminex bead for each cytokine, washed, and measured on a factory maintained luminex instrument. Double knock out (DKO) #3 and #4 are genetically and phenotypically GGTA1/NLRC5 knock out cells made separately. The HLAG1 transgenic cells were conducted in a separate experiment and therefore include matching unstimulated and wild type cell controls.

Example 15: Genetic Modifications of GGTA1-10, Gal2-2 and NLRC5-6

[00619] Primary porcine cells were transfected with: GGTA1-10/Gal2-2 (condition 2), NLRC5-6/Gal2-2 (condition 3), GGTA1-10/Gal2-2 and NLRC5-6/Gal2-2 (condition 4), or Condition 1: cells only (**FIG. 90**). Bead Selection of Negative cells by using magnetic bead sorting was performed using an IB4 lectin selective for terminal alpha-D-galactosyl residues (such as the product of GGTA1) (**FIG. 91**). The first bead selection was performed after 5 days followed by a second bead selection at day 8. Cell Sort Selection of Negative Cells using the sort machine from University of MN was done 7 days after transfection. Cells were stained with IB4 lectin Alexa Fluor 467 and SLA I FITC and analyzed by flow cytometry (**FIG. 92** to **FIG.102**). Confocal microscopy of the cultures is shown in **FIG. 103 A**. Additional data shows electrophoresis of sequencing confirmation is shown in **FIG 113A** to **113 I**.

Table 16. Exemplary sequencing primers for px333 plasmids

SEQ ID No.	Forward sequence (5' to 3')	SEQ ID No.	Reverse sequence (5' to 3')
241	cttcgtgaaaccgctgtttatt gagcagagctcactagaacttg	242	gactggaggactttgtcttctt aagagacaagcctcagactaaac
243	ttccactctgggtgtatttaatct	244	ccggatccttaagccaaaga
245	gctcagcctagggtttcaat	246	atgagcaaggcaggaatgt
247	agtttgggactgcctcattt	248	ggagcagggaaacctgataaa
249	gccactgttccctcagc	250	cgttgcctatagcgtcttctt

	gacccgctctgcacaaa		cagaggtaacgacgagaacaaa
251	gacccgctctgcacaaa	252	cagaggtaacgacgagaacaaa
253	ggagttacagggaatccgaatg	254	catgaagccaagatctaggaag
255	ctgctctgcaaacactcaga tgagtgccaaggtgaagttct gagtgccaaggtgaagttct	256	tcagcagcagtacctcca caaagcagtgcaggaagcag aagatggcacggatgtgag
257	ctgccaccgaacctacatc	258	gtggtcttgcccatgcc
259	catcagtcctggtgatgatcc	260	gatgagtgggaagatgacct

Table 17. Exemplary Sequences of the first exon of NLRC5 and/or B4GALNT2 gene to be targeted by guide RNA.

SEQ ID No.	Genomic Sequence (5' to 3')
261	caggaggggactgttgcagggggccccaaggcagaagatggcacggatgtgagcattcgggacctcttcagtg ccaaagccaacaagggcccgagagtcacggtgcttctgggaaaggcgggcatgggcaagacc
262	atgctgcttgtctcaactgtaatggttgtgttttgggaatacatcaacaggtaattatgaaacatgatgaaatgatgttg atgaaagtctcctctaatctcctagttatcagccaagtcaccagcttgcattaaa

[00620] Example 16: Generation and characterization of HLA-G knockin cells for making genetically modified animals of the *Laurasiatheria* super order

[00621] Cells of animals of the *Laurasiatheria* super order with HLA-G knocked in can be generated using CRISPR/Cas9-mediated gene editing technology. Knock in of HLA-G can include HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7. HLA-G can be inserted at a target locus. For example, HLA-G can be inserted into the Rosa26 locus of an animal of the *Laurasiatheria* super order. Alternatively, HLA-G can be inserted into another target locus such as a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), or a NOD-like receptor family CARD domain containing 5 (NLRC5). A knock-in of an HLA-G encoding sequence targeted to another gene can disrupt, or knock-out, that gene.

[00622] The target region for HLA-G insertion will be sequenced as described essentially in Example 2 above. Accurate sequence information will be used to design guide RNAs specific for

the target region as described in Example 2. A plasmid, such as px330, expressing guide RNAs specific for the target region will be generated using methods described in Example 1 and Example 2. Alternatively, a plasmid, such as px333, simultaneously expressing two guide RNAs specific for the target region can be generated as described in Example 3.

[00623] As described in Example 8, the DNA sequence 1000 bp upstream (5') and downstream (3') from the target locus cut site will be confirmed. The left homologous arm will be designated as 1000 bp upstream of the cut site, and the right homologous arm will be designed as 1000 bp downstream of the cute site. Generation of homology directing fragments containing HLA-G and insertion of HLA-G at the target locus will be performed as described for HLA-G1 insertion at the Rosa26 locus in Example 8. The HLA-G sequence used can be transcribed as an mRNA with modifications in a 5' and/or 3' untranslated region. Such modifications can increase mRNA stability.

[00624] Cells of animals of the *Laurasiatheria* super order can have knock out of genes in combination with HLA-G knock-in. For example, GGTA1 and/or NLRC5 can be knocked out, and HLA-G can be knocked in. Thus, a GGTA1/NLRC5 knockout/HLA-G knock-in animal of the *Laurasiatheria* super order can be generated using methods similar to those described in Example 8. As described, the knock-in of an HLA-G encoding sequence can disrupt, or knock out, another gene (e.g., GGTA1 and/or NLRC5).

[00625] Animals of the Laurasiatheria super order can include an ungulate, such as an even-toed ungulate (e.g., pigs, peccaries, hippopotamuses, camels, llamas, chevrotains (mouse deer), deer, giraffes, pronghorn, antelopes, goat-antelopes (which include sheep, goats and others), or cattle) or an odd-toed ungulate (e.g., horse, tapirs, and rhinoceroses), a non-human primate (e.g., a monkey, or a chimpanzee), a Canidae (e.g., a dog) or a cat. Members of the Laurasiatheria superorder can include Eulipotyphla (hedgehogs, shrews, and moles), Perissodactyla (rhinoceroses, horses, and tapirs), Carnivora (carnivores, such as cats, dogs, and bears), Cetartiodactyla (artiodactyls and cetaceans), Chiroptera (bats), and Pholidota (pangolins).

[00626] Table 18. Sequences for SEQ ID NOs: 5-60

SEQ ID NO: 5	NLRC5 Genomic Sequence
TGGAAACAACATGAACACTGTGAGCTCCCGGGAGTTCAGTCAGATCCACTGAGGTAGTGGCCGGGTCCAGCGGCCTT GCCTAACTTGGCAGTCCCCACCCGCTGCATCCTTAGATCTGGCTTTGTCCCTTACACAGGACAGCCCAGGCCTGTGA TCCCCAAGGTCAGGCTAACGCTACCTGGACCTGGGCTCTAAGACCTGGGAAGCTACAGGAGGGGTGAGCCAGTTCCC AGATTGGGAAAACTGAGGCTTGAGGCGAGAGGATAGTCATCCACAAGCCTCGTGGCTAAATCCCTGGCTTGGCCCAG GGCCCTGGACCTCAGGCCACTGGGCTGATCAGTGCTTGTATGCTTTCCTCATCGCACTTGTTTGGAAGACATTCCCT GGTTTAGCTGCTCTGGGATGGTAATCTATAAATACATACTTTGTTTAAAAAATTAATAAATTAAATCTTGGACCAGC	

ATGAGGGCATCTGGCCAGCCACATGGCATATGACATGGACATTTGCCACGTCTCAAATATGGACTGCCCATCACATG
TAGTGCTAGGACCCATGCCAACAACCCACAGGCCACACTGCAGGTTTCATGCAATGTCACATGGAACGCTGCCACGN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNTCACGCCACGACATCCTCACTGTGCTGCATATTCCCGACTGGTCATGCATGTCAT
GTGTGATGGAGGGTGGTCTGTTGGCCATANNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNTCTGAAGACCGTGCCTGGAAAACGG
CGTCTCTCCCTCCCGGAACAGTGTGCCGGGACAGCCAGCTGAGGCTCTTTTCCTGAGCCCTCTATCCTGGGGGATGG
AAGCGGACATCACTTGGCTGTATTGGAAGGGTCTTGCGGGGGCCGTCAAGCATCCCAGGGGACCTGTGGCTGATGGT
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CCACTGTGCCACGATGGGAACTCTGAAAGCTCCCCCTTTTTAGACACTTTATTTCTATCTTCTGAAACTGTCATACT
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TTTATAGAGCGAGACCCTTCACTACTACCAGAAACCTAACACGTCAACGGTGTGAACAGTGTCCTTTAGATGCAAGG
CCTTGGTACAGTGTGCAGCCTGTGCAACTGTACGTGGTGGCTGTGATTACAGTTATCATTTTAAGCACTTGCTATGT
GCCAGGCATTGTACTCAGTGCTTTGTAGAATCATTTAGTCTGCAGAGCGCCCATCTAAGGCTGATATGATCATTGTC
TCCAGTTTACAAATGAGGAAACCGAGGTTCAGGGAGGTTGAGTTACTGAGGCAAAGTTACACAGTCAGCAACCAGTA
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TCCAGGAGTTCCTGTTGTGGCGCAGCAGAAATGAATCCGACTAGTAACCATAAGGTTGCAGGTTCAATCCCTGGTCT
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CCCTAAAAAAAGCAATAAATAAGTAAATAGATAACCCTCAACCCAGGTCCTGCCTCCTCCTACAGAAAGTTCCTTTGC
ATTGTAGAGGCTGCTGTGGCCCCCACCTCCCACCATCCTCGCCCCTGCAAGTCCTGTTACCGAATGACTTGGATGCC
AGAGCCCTGAGCCAGCCCTTCAGCCAGGAGCCAGGCTCCATGAG

SEQ ID NO: 6	NLRC5 cDNA Sequence

GGGCCTGTCCTATGGAAAGAACCTGCAAGTCCAGCACAGGGGCTTGGCCGGGAACCCATGAGACCCCCTCTGGGGAC
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GAACCTGTGGGGATGGCTCGTGAGGCTGCTCTGCAAACACTCAGAATGGCTGAGTGCCAAGGTGAAGTTCTTCCTCC
CCAACATGGACCTGGGTGCCAGGAACGAGGCCTCAGACCCCACACAGAGGGTCGTCCTACAACTCAGAAAACTGCGT
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CTGCCAAGTTAGGCAAGGCCGCTGGACCCGGCCACTACCTCAGTGGATCTGACTGAACTCCCGGGAGCTCACAGTGT
TCATGTTGTTTCCAAGAAGGCCCAAGGATTGTGAGCCAAGTTTGATCAATAAATGTGAGTGATCTTCCGGCCTCTAA
AAAAAAAAAAAAAAA

SEQ ID NO: 7	NLRC5 Protein Sequence

MDPISRHLGTKNLWGWLVRLLCKHSEWLSAKVKFFLPNMDLGARNEASDPTQRVVLQLRKLRTQSQITWQAFIHCVC
MELDVPLDLEVLLLSTWGHGEGLPSQLEADEEHPPESQPHSGLKRPHQSCGPSPRPKQCRKQQRELAKRYLQLLRTF
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SEQ ID NO: 8	TAP1 Genomic Sequence

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SEQ ID NO: 9	TAP1 cDNA Sequence

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SEQ ID NO: 10	TAP1 Protein Sequence

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SEQ ID NO: 11	GGTA1 Genomic Sequence

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TGTAATCCTTGCCAGTGCTCTTATTTCGAACAAAATTGATTCCTTCCTTGAGATTGGCAGCTTCGGCAGGTGAGAGG
CACAACAGGATCTCCGTCGTTTGTTCGATG

SEQ ID NO: 15	CMAH cDNA Sequence

ATGAGCAGCATCGAACAAACGACGGAGATCCTGTTGTGCCTCTCACCTGCCGAAGCTGCCAATCTCAAGGAAGGAAT
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SEQ ID NO: 16	CMAH Protein Sequence

MSSIEQTTEILLCLSPAEAANLKEGINFVRNKSTGKDYILFKNKSRLKACKNMCKHQGGLFIKDIEDLNGRSVKCTK
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NQSGVQLTNINVVPFGIWQQVDKNLRFMILMDGVHPEMDTCIIVEYKGHKILHTVDCTRPNGGRLPMKVALMMSDFA
GGASGFPMTFSGGKFTEEWKAQFIKTERKKLLNYKARLVKDLQPRIYCPFAGYFVESHPADKYIKETNIKNDPNELN
NLIKKNSEVVTWTPRPGATLDLGRMLKDPTDSKGIVEPPEGTKIYKDSWDFGPYLNILNAAIGDEIFRHSSWIKEYF
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SEQ ID NO: 17	CXCL10 Genomic Sequence

CTTATAGTAACTTTATTACCTTTTTTGTCTGAACAGTTAGTCTTTCTTAATGTTTCTAGGAGAGAACATTAGTTTTA
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SEQ ID NO: 18	CXCL10 cDNA Sequence

ACGCGGGGGAGACACTCTTCAACTGCTCATTCTGAGCCTACTGCAGAAGAATCTTCAGCTGCAGCACCATGAACCAA AGTGCTGTTCTTATTTTCTGCCTTATTCTTCTGACTCTGAGTGGAACTCAAGGAATACCTCTCTCCAGAACTGTTCG CTGTACCTGCATCAAGATCAGTGACAGACCTGTTAATCCGAGGTCCTTAGAAAAACTTGAAATGATTCCTGCAAGTC AATCTTGCCCACATGTTGAGATCATTGCCACAATGAAAAAGAATGGGGAGAAAAGATGTCTGAATCCAGAGTCTAAG ACCATCAAGAATTTACTGAAAGCAATTAGCAAAGAAAGGTCTAAAAGATCTCCTCGAACACAGAGAGAAGCATAATC ACGGCACTACTGATAAGGATGGGCCGGAGAGAATCTACCTCTGCCATCATCTCTCTACATACACCATACATCAAGCC CTAACTGTCCATGGATTGCAGTCACCAAGTTAGCTGCTCCCACACTTGCAGGGCAGCAGATGGTTCATCATCCCGAG CTGTTGAGCAGTAACTCTGCCCAGGCACTATACTATAAGCTACACTGAGGTGCTACATTCTTAGTGAATGTGCCAAG TCCTGGCCCTGCTACTGACACTTTCCTCACCTTTCCTATCGTCTGGTTATTAAGGGATCATTCCACTTTGGGACTTA ATCGAAGTTCTTAGAATCTCAAATAACCAAGAGGTATTTAAAACAATAATAAAACCTGCTTTTTAAAGAAAGATCTT TACTCCGTGGGCTTCTACTGCTTTCCTTCCAAGGGGCCCATATTCTCTTGGTGATTACATACATAATTCTAAATACA CAGGAGAAGCTAGAAATCCCTGAAAATGTATATGAAAATAGTATTATTTAGTGAAAGACTATATAAAGTAGGATTCT TAGATGTATATGTTTCTTATAGTTTTCAGTGTTTATGGAATACCTTGTAAAAGTATGTACTACAATGAGATAAATTT TTAAATGTGGATACATGTTCTGCATGTTATGTAAGACAAATACGCTGAGTGGGTGCTCTTCAAAATAAAACTAATGT TCTCTCCTAGAAACATTAAGAAAGACTAACTGTTCAGACAAAAAAGGTAATAAAGTTACTATAAGCCAAAAAAAAAA AAAAAAAAAAAAAAAAAA

SEQ ID NO: 19	CXCL10 Protein Sequence

MNQSAVLIFCLILLTLSGTQGIPLSRTVRCTCIKISDRPVNPRSLEKLEMIPASQSCPHVEIIATMKKNGEKRCLNP ESKTIKNLLKAISKERSKRSPRTQREA

SEQ ID NO: 20	CIITA Genomic Sequence

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SEQ ID NO: 21	CIITA cDNA Sequence

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SEQ ID NO: 22	CIITA Protein Sequence

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SEQ ID NO: 23	B4GALNT2 Genomic Sequence

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SEQ ID NO: 25	B4GALNT2 Protein Sequence

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SEQ ID NO: 26	C3 Genomic Sequence

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SEQ ID NO: 27	C3 cDNA Sequence

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SEQ ID NO: 28	C3 Protein Sequence

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SEQ ID NO: 29	MICA Genomic Sequence

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SEQ ID NO: 30	MICA cDNA Sequence

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SEQ ID NO: 31	MICA Protein Sequence

MGLGPVFLLLAGIFPFAPPGAAAEPHSLRYNLTVLSWDGSVQSGFLTEVHLDGQPFLRCDRQKCRAKPQGQWAEDVL
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SEQ ID NO: 32	MICB Genomic Sequence

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SEQ ID NO: 33	MICB cDNA Sequence

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TGGCCACCAGGATTCGCCAAGGAGAGGAGCAGAGGTTCACCTGCTACATGGAACACAGCGGGAATCACGGCACTCAC
CCTGTGCCCTCTGGGAAGGCGCTGGTGCTTCAGAGTCAACGGACAGACTTTCCATATGTTTCTGCTGCTATGCCATG
TTTTGTTATTATTATTATTCTCTGTGTCCCTTGTTGCAAGAAGAAAACATCAGCGGCAGAGGGTCCAGAGCTTGTGA
GCCTGCAGGTCCTGGATCAACACCCAGTTGGGACAGGAGACCACAGGGATGCAGCACAGCTGGGATTTCAGCCTCTG
ATGTCAGCTACTGGGTCCACTGGTTCCACTGAGGGCACCTAGACTCTACAGCCAGGCGGCCAGGATTCAACTCCCTG
CCTGGATCTCACCAGCACTTTCCCTCTGTTTCCTGACCTATGAAACAGAGAAAATAACATCACTTATTTATTGTTGT
TGGATGCTGCAAAGTGTTAGTAGGTATGAGGTGTTTGCTGCTCTGCCACGTAGAGAGCCAGCAAAGGGATCATGACC
AACTCAACATTCCATTGGAGGCTATATGATCAAACAGCAAATTGTTTATCATGAATGCAGGATGTGGGCAAACTCAC
GACTGCTCCTGCCAACAGAAGGTTTGCTGAGGGCATTCACTCCATGGTGCTCATTGGAGTTATCTACTGGGTCATCT
AGAGCCTATTGTTTGAGGAATGCAGTCTTACAAGCCTACTCTGGACCCAGCAGCTGACTCCTTCTTCCACCCCTCTT
CTTGCTATCTCCTATACCAATAAATACGAAGGGCTGTGGAAGATCAGAGCCCTTGTTCACGAGAAGCAAGAAGCCCC
CTGACCCCTTGTTCCAAATATACTCTTTTGTCTTTCTCTTTATTCCCACGTTCGCCCTTTGTTCAGTCCAATACAGG
GTTGTGGGGCCCTTAACAGTGCCATATTAATTGGTATCATTATTTCTGTTGTTTTTGTTTTTGTTTTTGTTTTTGTT
TTTGAGACAGAGTCTCACTCTGTCACCCAGGCTGCAGTTCACTGGTGTGATCTCAGCTCACTGCAACCTCTGCCTCC
CAGGTTCAAGCACTTCTCGTACCTCAGACTCCCGAATAGCTGGGATTACAGACAGGCACCACCACACCCAGCTAATT
TTTGTATTTTTTGTAGAGACGGGGTTTCGCCAAGTTGACCAGCCCAGTTTCAAACTCCTGACCTCAGGTGATCTGCC
TGCCTTGGCATCCCAAAGTGCTGGGATTACAAGAATGAGCCACCGTGCCTGGCCTATTTTATTATATTGTAATATAT
TTTATTATATTAGCCACCATGCCTGTCCTATTTTCTTATGTTTTAATATATTTTAATATATTACATGTGCAGTAATT
AGATTATCATGGGTGAACTTTATGAGTGAGTATCTTGGTGATGACTCCTCCTGACCAGCCCAGGACCAGCTTTCTTG
TCACCTTGAGGTCCCCTCGCCCCGTCACACCGTTATGCATTACTCTGTGTCTACTATTATGTGTGCATAATTTATAC
CGTAAATGTTTACTCTTTAAATAGAAAAAAAAAAAAAAA

SEQ ID NO: 34	MICB Protein Sequence

MVLSQDGSVQSGFLAEGHLDGQPFLRYDRQKRRAKPQGQWAENVLGAKTWDTETEDLTENGQDLRRTLTHIKDQKGG
LHSLQEIRVCEIHEDSSTRGSRHFYYDGELFLSQNLETQESTVPQSSRAQTLAMNVTNFWKEDAMKTKTHYRAMQAD
CLQKLQRYLKSGVAIRRTVPPMVNVTCSEVSEGNITVTCRASSFYPRNITLTWRQDGVSLSHNTQQWGDVLPDGNGT
YQTWVATRIRQGEEQRFTCYMEHSGNHGTHPVPSGKALVLQSQRTDFPYVSAAMPCFVIIIILCVPCCKKKTSAAEG
PELVSLQVLDQHPVGTGDHRDAAQLGFQPLMSATGSTGSTEGT

SEQ ID NO: 37	CD46 cDNA Sequence

GGAACTCGGAGAGGTCTCCGCTAGGCTGGTGTCGGGTTACCTGCTCATCTTCCCGAAAATGATGGCGTTTTGCGCGC
TGCGCAAGGCACTTCCCTGCCGTCCCGAGAATCCCTTTTCTTCGAGGTGCTTCGTTGAGATTCTTTGGGTGTCGTTG
GCCCTAGTGTTCCTGCTTCCCATGCCCTCAGATGCCTGTGATGAGCCACCGAAGTTTGAAAGCATGCGGCCCCAATT
TTTGAATACCACTTACAGACCTGGAGACCGTGTAGAGTATGAATGTCGCCCCGGGTTCCAGCCCATGGTTCCTGCGC
TTCCCACCTTTTCCGTCTGTCAGGACGATAATACGTGGTCACCCCTCCAGGAGGCTTGTCGACGAAAAGCCTGTTCG
AATCTACCAGACCCGTTAAATGGCCAAGTTAGCTACCCAAATGGGGATATGCTGTTTGGTTCAAAGGCTCAGTTTAC

CTGTAACACTGGTTTTTACATAATTGGAGCCGAGACTGTGTATTGTCAGGTTTCTGGGAATGTTATGGCCTGGAGTG AGCCCTCCCCGCTATGTGAGAAGATTTTGTGTAAACCACCTGGCGAAATTCCAAATGGAAAATACACCAATAGCCAT AAGGATGTATTTGAATACAATGAAGTAGTAACTTACAGTTGTCTTTCTTCAACTGGACCGGATGAATTTTCACTTGT TGGAGAGAGCAGCCTTTTTTGTATTGGGAAGGACGAGTGGAGTAGTGACCCCCCTGAGTGTAAAGTGGTCAAATGTC CATATCCAGTAGTCCCAAATGGAGAAATTGTATCAGGATTTGGATCAAAATTTTACTACAAAGCAGAGGTTGTATTT AAATGCAATGCTGGTTTTACCCTTCATGGCAGAGACACAATTGTCTGCGGTGCAAACAGCACGTGGGAGCCTGAGAT GCCCCAATGTATCAAAGATTCCAAGCCTACTGATCCACCTGCAACCCCAGGACCAAGCCATCCAGGACCTCCCAGTC CCAGTGATGCATCACCACCTAAAGATGCTGAGAGTTTAGATGGAGGAATCATCGCTGCAATTGTTGTGGGCGTCTTA GCTGCCATTGCAGTAATTGCTGGTGGTGTATACTTTTTTCATCATAAATACAACAAGAAAAGGTCGAAGTAAAACTG ATGTGCTTAAAGTAAAAGTTGCTGAGAGGACGTGGAATCCAGCCCCTTCCCTCTCCTGTGCTGCTGCCTGGGTCCCG TTTTGCATGTCATGACTGTGTGCTTCCAAAAAATGCCTTTTGTTCGTATTTTTTTGCCTAAACGCATGATTTTGTCT CTACTTGAATTAAATCATCACTGAATCCACGC
SEQ ID NO: 38 CD55 cDNA Sequence
CGGCACGAGATTTCGTCTTAATCGCGGAGGTCGCAGAGTCCGGGAGCCGCTCGGGGTCCCCGTTCCCGCGCGCCATG AGTCCCCTGCCGCGGAGCGCCCCCGCGGTGAGGCGCCTAATGGGCGGACAGACGCCGCCGCCGCTGCTGCTGCTGCT GCTGCTGCTGTGTATCCCGGCTGCGCAGGGTGACTGCAGCCTTCCACCCGATGTACCTAATGCCCAACCAGATTTGC GAGGTCTTGCAAGTTTTCCTGAACAAACCACAATAACATACAAATGTAACAAAGGCTTTGTCAAAGTTCCTGGCATG GCAGACTCAGTGCTCTGTCTTAATGATAAATGGTCAGAAGTTGCAGAATTTTGTAATCGTAGCTGTGATGTTCCAAC CAGGCTACATTTTGCATCTCTTAAAAAGTCTTACAGCAAACAGAATTATTTCCCAGAGGGTTTCACCGTGGAATATG AGTGCCGTAAGGGCTATAAAAGGGATCTTACTCTATCAGAAAAACTAACTTGCCTTCAGAATTTTACGTGGTCCAAA CCTGATGAATTTTGCAAAAAAAAACAATGTCCGACTCCTGGAGAACTAAAAAATGGTCATGTCAATATAACAACTGA CTTGTTATTTGGCGCATCCATCTTTTTCTCATGTAACGCAGGGTACAGACTAGTTGGTGCAACTTCTAGTTACTGTT TTGCCATAGCAAATGATGTTGAGTGGAGTGATCCATTGCCAGAATGCCAAGAAATTTCTCCAACTGTCAAAGCCATA CCAGCTGTTGAGAAACCCATCACAGTAAATTTTCCAGCAACAAAGTATCCAGCTATTCCCAGGGCCACAACGAGTTT TCATTCAAGTACATCTAAAAATCGAGGAAACCCTTCTTCAGGCATGAGAATCATGTCGTCTGGTACCATGCTACTTA TTGCAGGAGGTGTTGCTGTTATTATAATAATTGTTGCCCTAATTCTAGCCAAAGGTTTCTGGCACTATGGAAAATCA GGCTCTTACCACACTCATGAGAACAACAAAGCCGTTAATGTTGCATTTTATAATTTACCTGCGACTGGCGATGCCGC AGATGTAAGACCTGGTAATTAACAAAAGGACGGTGCATGTGTAACACTGACAGTTTTGCTTATGGTGCTAGTAACCA TTGGCTAGCTGACTTAGCCAAAGAAGAGTTAAGAAGAAAGTGCACACAAGTACACAGAATATTTTCAGTTTCTTAGA ACTTTCAGGTGGAGTGGACATAGTTTGTGGATAGTGTTCTTCGTTTTGCATGTTTTCATTGTCTCTAAGGTACATAG GAATGTCACAGAACCAAAGAGAAACAAATCTATCCTGAAATTACATCCTCAACACTCCTAAGACTCTTGAAAATAGA ACAGCTCATAAGATTGAGAGCAATTACTTTCCAAAAAGGGTGAGAAAATGGAGAGATTTGTTCATGGTTAGAATATA AGAAAAAAGAAAACAAAAAGGTGATTTTTCCCACCAAATGTGTAATGTTATTTTTATTAATAAAGGAAAAAAAAAAA AAAAAA
SEQ ID NO: 39 CD59 cDNA Sequence
GAAAAGACGCGCAGGCCGGGCCGCTCTCCCGACGGGGAGTAGCGCTGCAGCCGGACGCAGGGTGCAGTTAGAATCCA TAGACGGTCACGATGGGAAGCAAAGGAGGGTTCATTTTGCTCTGGCTCCTGTCCATCCTGGCTGTTCTCTGCCACTT AGGTCACAGCCTGCAGTGCTATAACTGTATCAACCCAGCTGGTAGCTGCACTACGGCCATGAATTGTTCACATAATC AGGATGCCTGTATCTTCGTTGAAGCCGTGCCACCCAAAACTTACTACCAGTGTTGGAGGTTCGATGAATGCAATTTC GATTTCATTTCGAGAAACCTAGCGGAGAAGAAGCTGAAGTACAACTGCTGCCGGAAGGACCTGTGTAACAAGAGTGA TGCCACGATTTCATCAGGGAAAACCGCTCTGCTGGTGATCCTGCTGCTGGTAGCAACCTGGCACTTTTGTCTCTAAC

TGTACACCAGGAGAGTTTCTCCTCAACTTCCTCTGTCTCTCTGTTCCTATTTCCCATGCTGCGGTGTTCCAAAGGCT GTGTATGCTCCAGCTTCTTCCTGTTGGGAAGGACTAAACCTAGCTTGAGCACTTTGGATTAGAGAGAGAAACTTTGA GCGACTTTGAAGACCAGGCCTGTTGGCAGAGAAGACCTGTCAGAGGGGAAACGTTTTAAGAGTGAAGCACAGGTGAT TTGAGCGAGGCCTATGCGTCTTCCTCTGCTCTTGGCAGGACCAGCTTTGCGGTAACCATTCGATAGATTCCACAATC CTT
SEQ ID NO: 40 ICP47 cDNA Sequence
TCAAGGGGCCAGCACGCGATCCTGCCGCTCGTTCGATCTAGCACACCCACGGGTCTGCTGTGTGGGATTTCGACTCG CGGGATCCGATCGCACGTCCGGAGGACACAGCAGCGGGAGCTCCGGGTCGGTCACCGCAGTTCTGGCCGCCTCTCGG TCCTCCCGTTCCCTTTTATGGATCTCCGCGCAGACATCGCCATACGTCCGGTGTGTGCACCGCGAAGAATCCAGAAA CATGTCCGTCGTTTTCAGGGCCCAAGACAT
SEQ ID NO: 41 HLA-G1 cDNA Sequence
AGTGTGGTACTTTGTCTTGAGGAGATGTCCTGGACTCACACGGAAACTTAGGGCTACGGAATGAAGTTCTCACTCCC ATTAGGTGACAGGTTTTTAGAGAAGCCAATCAGCGTCGCCGCGGTCCTGGTTCTAAAGTCCTCGCTCACCCACCCGG ACTCATTCTCCCCAGACGCCAAGGATGGTGGTCATGGCGCCCCGAACCCTCTTCCTGCTGCTCTCGGGGGCCCTGAC CCTGACCGAGACCTGGGCGGGCTCCCACTCCATGAGGTATTTCAGCGCCGCCGTGTCCCGGCCCGGCCGCGGGGAGC CCCGCTTCATCGCCATGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGCGACTCGGCGTGTCCGAGGATG GAGCCGCGGGCGCCGTGGGTGGAGCAGGAGGGGCCGGAGTATTGGGAAGAGGAGACACGGAACACCAAGGCCCACGC ACAGACTGACAGAATGAACCTGCAGACCCTGCGCGGCTACTACAACCAGAGCGAGGCCAGTTCTCACACCCTCCAGT GGATGATTGGCTGCGACCTGGGGTCCGACGGACGCCTCCTCCGCGGGTATGAACAGTATGCCTACGATGGCAAGGAT TACCTCGCCCTGAACGAGGACCTGCGCTCCTGGACCGCAGCGGACACTGCGGCTCAGATCTCCAAGCGCAAGTGTGA GGCGGCCAATGTGGCTGAACAAAGGAGAGCCTACCTGGAGGGCACGTGCGTGGAGTGGCTCCACAGATACCTGGAGA ACGGGAAGGAGATGCTGCAGCGCGCGGACCCCCCCAAGACACACGTGACCCACCACCCTGTCTTTGACTATGAGGCC ACCCTGAGGTGCTGGGCCCTGGGCTTCTACCCTGCGGAGATCATACTGACCTGGCAGCGGGATGGGGAGGACCAGAC CCAGGACGTGGAGCTCGTGGAGACCAGGCCTGCAGGGGATGGAACCTTCCAGAAGTGGGCAGCTGTGGTGGTGCCTT CTGGAGAGGAGCAGAGATACACGTGCCATGTGCAGCATGAGGGGCTGCCGGAGCCCCTCATGCTGAGATGGAAGCAG TCTTCCCTGCCCACCATCCCCATCATGGGTATCGTTGCTGGCCTGGTTGTCCTTGCAGCTGTAGTCACTGGAGCTGC GGTCGCTGCTGTGCTGTGGAGAAAGAAGAGCTCAGATTGAAAAGGAGGGAGCTACTCTCAGGCTGCAATGTGAAACA GCTGCCCTGTGTGGGACTGAGTGGCAAGTCCCTTTGTGACTTCAAGAACCCTGACTCCTCTTTGTGCAGAGACCAGC CCACCCCTGTGCCCACCATGACCCTCTTCCTCATGCTGAACTGCATTCCTTCCCCAATCACCTTTCCTGTTCCAGAA AAGGGGCTGGGATGTCTCCGTCTCTGTCTCAAATTTGTGGTCCACTGAGCTATAACTTACTTCTGTATTAAAATTAG AATCTGAGTATAAATTTACTTTTTCAAATTATTTCCAAGAGAGATTGATGGGTTAATTAAAGGAGAAGATTCCTGAA ATTTGAGAGACAAAATAAATGGAAGACATGAGAACTTT
SEQ ID NO: 42 HLA-E cDNA Sequence
GCAGACTCAGTTCTCATTCCCAATGGGTGTCGGGTTTCTAGAGAAGCCAATCAGCGTCGCCACGACTCCCGACTATA AAGTCCCCATCCGGACTCAAGAAGTTCTCAGGACTCAGAGGCTGGGATCATGGTAGATGGAACCCTCCTTTTACTCC TCTCGGAGGCCCTGGCCCTTACCCAGACCTGGGCGGGCTCCCACTCCTTGAAGTATTTCCACACTTCCGTGTCCCGG CCCGGCCGCGGGGAGCCCCGCTTCATCTCTGTGGGCTACGTGGACGACACCCAGTTCGTGCGCTTCGACAACGACGC CGCGAGTCCGAGGATGGTGCCGCGGGCGCCGTGGATGGAGCAGGAGGGGTCAGAGTATTGGGACCGGGAGACACGGA GCGCCAGGGACACCGCACAGATTTTCCGAGTGAATCTGCGGACGCTGCGCGGCTACTACAATCAGAGCGAGGCCGGG TCTCACACCCTGCAGTGGATGCATGGCTGCGAGCTGGGGCCCGACGGGCGCTTCCTCCGCGGGTATGAACAGTTCGC CTACGACGGCAAGGATTATCTCACCCTGAATGAGGACCTGCGCTCCTGGACCGCGGTGGACACGGCGGCTCAGATCT

CCGAGCAAAAGTCAAATGATGCCTCTGAGGCGGAGCACCAGAGAGCCTACCTGGAAGACACATGCGTGGAGTGGCTC
CACAAATACCTGGAGAAGGGGAAGGAGACGCTGCTTCACCTGGAGCCCCCAAAGACACACGTGACTCACCACCCCAT
CTCTGACCATGAGGCCACCCTGAGGTGCTGGGCCCTGGGCTTCTACCCTGCGGAGATCACACTGACCTGGCAGCAGG
ATGGGGAGGGCCATACCCAGGACACGGAGCTCGTGGAGACCAGGCCTGCAGGGGATGGAACCTTCCAGAAGTGGGCA
GCTGTGGTGGTGCCTTCTGGAGAGGAGCAGAGATACACGTGCCATGTGCAGCATGAGGGGCTACCCGAGCCCGTCAC
CCTGAGATGGAAGCCGGCTTCCCAGCCCACCATCCCCATCGTGGGCATCATTGCTGGCCTGGTTCTCCTTGGATCTG
TGGTCTCTGGAGCTGTGGTTGCTGCTGTGATATGGAGGAAGAAGAGCTCAGGTGGAAAAGGAGGGAGCTACTCTAAG
GCTGAGTGGAGCGACAGTGCCCAGGGGTCTGAGTCTCACAGCTTGTAAAGCCTGAGACAGCTGCCTTGTGTGCGACT
GAGATGCACAGCTGCCTTGTGTGCGACTGAGATGCAGGATTTCCTCACGCCTCCCCTATGTGTCTTAGGGGACTCTG
GCTTCTCTTTTTGCAAGGGCCTCTGAATCTGTCTGTGTCCCTGTTAGCACAATGTGAGGAGGTAGAGAAACAGTCCA
CCTCTGTGTCTACCATGACCCCCTTCCTCACACTGACCTGTGTTCCTTCCCTGTTCTCTTTTCTATTAAAAATAAGA
ACCTGGGCAGAGTGCGGCAGCTCATGCCTGTAATCCCAGCACTTAGGGAGGCCGAGGAGGGCAGATCACGAGGTCAG
GAGATCGAAACCATCCTGGCTAACACGGTGAAACCCCGTCTCTACTAAAAAATACAAAAAATTAGCTGGGCGCAGAG
GCACGGGCCTGTAGTCCCAGCTACTCAGGAGGCGGAGGCAGGAGAATGGCGTCAACCCGGGAGGCGGAGGTTGCAGT
GAGCCAGGATTGTGCGACTGCACTCCAGCCTGGGTGACAGGGTGAAACGCCATCTCAAAAAATAAAAATTGAAAAAT
AAAAAAAGAACCTGGATCTCAATTTAATTTTTCATATTCTTGCAATGAAATGGACTTGAGGAAGCTAAGATCATAGC
TAGAAATACAGATAATTCCACAGCACATCTCTAGCAAATTTAGCCTATTCCTATTCTCTAGCCTATTCCTTACCACC
TGTAATCTTGACCATATACCTTGGAGTTGAATATTGTTTTCATACTGCTGTGGTTTGAATGTTCCCTCCAACACTCA
TGTTGAGACTTAATCCCTAATGTGGCAATACTGAAAGGTGGGGCCTTTGAGATGTGATTGGATCGTAAGGCTGTGCC
TTCATTCATGGGTTAATGGATTAATGGGTTATCACAGGAATGGGACTGGTGGCTTTATAAGAAGAGGAAAAGAGAAC
TGAGCTAGCATGCCCAGCCCACAGAGAGCCTCCACTAGAGTGATGCTAAGTGGAAATGTGAGGTGCAGCTGCCACAG
AGGGCCCCCACCAGGGAAATGTCTAGTGTCTAGTGGATCCAGGCCACAGGAGAGAGTGCCTTGTGGAGCGCTGGGAG
CAGGACCTGACCACCACCAGGACCCCAGAACTGTGGAGTCAGTGGCAGCATGCAGCGCCCCCTTGGGAAAGCTTTAG
GCACCAGCCTGCAACCCATTCGAGCAGCCACGTAGGCTGCACCCAGCAAAGCCACAGGCACGGGGCTACCTGAGGCC
TTGGGGGCCCAATCCCTGCTCCAGTGTGTCCGTGAGGCAGCACACGAAGTCAAAAGAGATTATTCTCTTCCCACAGA
TACCTTTTCTCTCCCATGACCCTTTAACAGCATCTGCTTCATTCCCCTCACCTTCCCAGGCTGATCTGAGGTAAACT
TTGAAGTAAAATAAAAGCTGTGTTTGAGCATCATTTGTATTTCAAAAAAAAAAAAAAAAAA

SEQ ID NO: 43	Human β-2-microglobulin cDNA Sequence

AATATAAGTGGAGGCGTCGCGCTGGCGGGCATTCCTGAAGCTGACAGCATTCGGGCCGAGATGTCTCGCTCCGTGGC
CTTAGCTGTGCTCGCGCTACTCTCTCTTTCTGGCCTGGAGGCTATCCAGCGTACTCCAAAGATTCAGGTTTACTCAC
GTCATCCAGCAGAGAATGGAAAGTCAAATTTCCTGAATTGCTATGTGTCTGGGTTTCATCCATCCGACATTGAAGTT
GACTTACTGAAGAATGGAGAGAGAATTGAAAAAGTGGAGCATTCAGACTTGTCTTTCAGCAAGGACTGGTCTTTCTA
TCTCTTGTACTACACTGAATTCACCCCCACTGAAAAAGATGAGTATGCCTGCCGTGTGAACCATGTGACTTTGTCAC
AGCCCAAGATAGTTAAGTGGGATCGAGACATGTAAGCAGCATCATGGAGGTTTGAAGATGCCGCATTTGGATTGGAT
GAATTCCAAATTCTGCTTGCTTGCTTTTTAATATTGATATGCTTATACACTTACACTTTATGCACAAAATGTAGGGT
TATAATAATGTTAACATGGACATGATCTTCTTTATAATTCTACTTTGAGTGCTGTCTCCATGTTTGATGTATCTGAG
CAGGTTGCTCCACAGGTAGCTCTAGGAGGGCTGGCAACTTAGAGGTGGGGAGCAGAGAATTCTCTTATCCAACATCA
ACATCTTGGTCAGATTTGAACTCTTCAATCTCTTGCACTCAAAGCTTGTTAAGATAGTTAAGCGTGCATAAGTTAAC
TTCCAATTTACATACTCTGCTTAGAATTTGGGGGAAAATTTAGAAATATAATTGACAGGATTATTGGAAATTTGTTA
TAATGAATGAAACATTTTGTCATATAAGATTCATATTTACTTCTTATACATTTGATAAAGTAAGGCATGGTTGTGGT
TAATCTGGTTTATTTTTGTTCCACAAGTTAAATAAATCATAAAACTTGATGTGTTATCTCTTA

SEQ ID NO: 44	Human PD-L1 cDNA Sequence

GGCGCAACGCTGAGCAGCTGGCGCGTCCCGCGCGGCCCCAGTTCTGCGCAGCTTCCCGAGGCTCCGCACCAGCCGCG
CTTCTGTCCGCCTGCAGGGCATTCCAGAAAGATGAGGATATTTGCTGTCTTTATATTCATGACCTACTGGCATTTGC
TGAACGCCCCATACAACAAAATCAACCAAAGAATTTTGGTTGTGGATCCAGTCACCTCTGAACATGAACTGACATGT
CAGGCTGAGGGCTACCCCAAGGCCGAAGTCATCTGGACAAGCAGTGACCATCAAGTCCTGAGTGGTAAGACCACCAC
CACCAATTCCAAGAGAGAGGAGAAGCTTTTCAATGTGACCAGCACACTGAGAATCAACACAACAACTAATGAGATTT
TCTACTGCACTTTTAGGAGATTAGATCCTGAGGAAAACCATACAGCTGAATTGGTCATCCCAGAACTACCTCTGGCA
CATCCTCCAAATGAAAGGACTCACTTGGTAATTCTGGGAGCCATCTTATTATGCCTTGGTGTAGCACTGACATTCAT
CTTCCGTTTAAGAAAAGGGAGAATGATGGATGTGAAAAAATGTGGCATCCAAGATACAAACTCAAAGAAGCAAAGTG
ATACACATTTGGAGGAGACGTAATCCAGCATTGGAACTTCTGATCTTCAAGCAGGGATTCTCAACCTGTGGTTTAGG
GGTTCATCGGGGCTGAGCGTGACAAGAGGAAGGAATGGGCCCGTGGGATGCAGGCAATGTGGGACTTAAAAGGCCCA
AGCACTGAAAATGGAACCTGGCGAAAGCAGAGGAGGAGAATGAAGAAAGATGGAGTCAAACAGGGAGCCTGGAGGGA
GACCTTGATACTTTCAAATGCCTGAGGGGCTCATCGACGCCTGTGACAGGGAGAAAGGATACTTCTGAACAAGGAGC
CTCCAAGCAAATCATCCATTGCTCATCCTAGGAAGACGGGTTGAGAATCCCTAATTTGAGGGTCAGTTCCTGCAGAA
GTGCCCTTTGCCTCCACTCAATGCCTCAATTTGTTTTCTGCATGACTGAGAGTCTCAGTGTTGGAACGGGACAGTAT
TTATGTATGAGTTTTTCCTATTTATTTTGAGTCTGTGAGGTCTTCTTGTCATGTGAGTGTGGTTGTGAATGATTTCT
TTTGAAGATATATTGTAGTAGATGTTACAATTTTGTCGCCAAACTAAACTTGCTGCTTAATGATTTGCTCACATCTA
GTAAAACATGGAGTATTTGTAAGGTGCTTGGTCTCCTCTATAACTACAAGTATACATTGGAAGCATAAAGATCAAAC
CGTTGGTTGCATAGGATGTCACCTTTATTTAACCCATTAATACTCTGGTTGACCTAATCTTATTCTCAGACCTCAAG
TGTCTGTGCAGTATCTGTTCCATTTAAATATCAGCTTTACAATTATGTGGTAGCCTACACACATAATCTCATTTCAT
CGCTGTAACCACCCTGTTGTGATAACCACTATTATTTTACCCATCGTACAGCTGAGGAAGCAAACAGATTAAGTAAC
TTGCCCAAACCAGTAAATAGCAGACCTCAGACTGCCACCCACTGTCCTTTTATAATACAATTTACAGCTATATTTTA
CTTTAAGCAATTCTTTTATTCAAAAACCATTTATTAAGTGCCCTTGCAATATCAATCGCTGTGCCAGGCATTGAATC
TACAGATGTGAGCAAGACAAAGTACCTGTCCTCAAGGAGCTCATAGTATAATGAGGAGATTAACAAGAAAATGTATT
ATTACAATTTAGTCCAGTGTCATAGCATAAGGATGATGCGAGGGGAAAACCCGAGCAGTGTTGCCAAGAGGAGGAAA
TAGGCCAATGTGGTCTGGGACGGTTGGATATACTTAAACATCTTAATAATCAGAGTAATTTTCATTTACAAAGAGAG
GTCGGTACTTAAAATAACCCTGAAAAATAACACTGGAATTCCTTTTCTAGCATTATATTTATTCCTGATTTGCCTTT
GCCATATAATCTAATGCTTGTTTATATAGTGTCTGGTATTGTTTAACAGTTCTGTCTTTTCTATTTAAATGCCACTA
AATTTTAAATTCATACCTTTCCATGATTCAAAATTCAAAAGATCCCATGGGAGATGGTTGGAAAATCTCCACTTCAT
CCTCCAAGCCATTCAAGTTTCCTTTCCAGAAGCAACTGCTACTGCCTTTCATTCATATGTTCTTCTAAAGATAGTCT
ACATTTGGAAATGTATGTTAAAAGCACGTATTTTTAAAATTTTTTTCCTAAATAGTAACACATTGTATGTCTGCTGT
GTACTTTGCTATTTTTATTTATTTTAGTGTTTCTTATATAGCAGATGGAATGAATTTGAAGTTCCCAGGGCTGAGGA
TCCATGCCTTCTTTGTTTCTAAGTTATCTTTCCCATAGCTTTTCATTATCTTTCATATGATCCAGTATATGTTAAAT
ATGTCCTACATATACATTTAGACAACCACCATTTGTTAAGTATTTGCTCTAGGACAGAGTTTGGATTTGTTTATGTT
TGCTCAAAAGGAGACCCATGGGCTCTCCAGGGTGCACTGAGTCAATCTAGTCCTAAAAAGCAATCTTATTATTAACT
CTGTATGACAGAATCATGTCTGGAACTTTTGTTTTCTGCTTTCTGTCAAGTATAAACTTCACTTTGATGCTGTACTT
GCAAAATCACATTTTCTTTCTGGAAATTCCGGCAGTGTACCTTGACTGCTAGCTACCCTGTGCCAGAAAAGCCTCAT
TCGTTGTGCTTGAACCCTTGAATGCCACCAGCTGTCATCACTACACAGCCCTCCTAAGAGGCTTCCTGGAGGTTTCG
AGATTCAGATGCCCTGGGAGATCCCAGAGTTTCCTTTCCCTCTTGGCCATATTCTGGTGTCAATGACAAGGAGTACC
TTGGCTTTGCCACATGTCAAGGCTGAAGAAACAGTGTCTCCAACAGAGCTCCTTGTGTTATCTGTTTGTACATGTGC
ATTTGTACAGTAATTGGTGTGACAGTGTTCTTTGTGTGAATTACAGGCAAGAATTGTGGCTGAGCAAGGCACATAGT

CTACTCAGTCTATTCCTAAGTCCTAACTCCTCCTTGTGGTGTTGGATTTGTAAGGCACTTTATCCCTTTTGTCTCAT GTTTCATCGTAAATGGCATAGGCAGAGATGATACCTAATTCTGCATTTGATTGTCACTTTTTGTACCTGCATTAATT TAATAAAATATTCTTATTTATTTTGTTACTTGGTACACCAGCATGTCCATTTTCTTGTTTATTTTGTGTTTAATAAA ATGTTCAGTTTAACATCCCAGTGGAGAAAGTTAAAAAA

SEQ ID NO: 45	Human PD-L2 cDNA Sequence

GCAAACCTTAAGCTGAATGAACAACTTTTCTTCTCTTGAATATATCTTAACGCCAAATTTTGAGTGCTTTTTTGTTA CCCATCCTCATATGTCCCAGCTAGAAAGAATCCTGGGTTGGAGCTACTGCATGTTGATTGTTTTGTTTTTCCTTTTG GCTGTTCATTTTGGTGGCTACTATAAGGAAATCTAACACAAACAGCAACTGTTTTTTGTTGTTTACTTTTGCATCTT TACTTGTGGAGCTGTGGCAAGTCCTCATATCAAATACAGAACATGATCTTCCTCCTGCTAATGTTGAGCCTGGAATT GCAGCTTCACCAGATAGCAGCTTTATTCACAGTGACAGTCCCTAAGGAACTGTACATAATAGAGCATGGCAGCAATG TGACCCTGGAATGCAACTTTGACACTGGAAGTCATGTGAACCTTGGAGCAATAACAGCCAGTTTGCAAAAGGTGGAA AATGATACATCCCCACACCGTGAAAGAGCCACTTTGCTGGAGGAGCAGCTGCCCCTAGGGAAGGCCTCGTTCCACAT ACCTCAAGTCCAAGTGAGGGACGAAGGACAGTACCAATGCATAATCATCTATGGGGTCGCCTGGGACTACAAGTACC TGACTCTGAAAGTCAAAGCTTCCTACAGGAAAATAAACACTCACATCCTAAAGGTTCCAGAAACAGATGAGGTAGAG CTCACCTGCCAGGCTACAGGTTATCCTCTGGCAGAAGTATCCTGGCCAAACGTCAGCGTTCCTGCCAACACCAGCCA CTCCAGGACCCCTGAAGGCCTCTACCAGGTCACCAGTGTTCTGCGCCTAAAGCCACCCCCTGGCAGAAACTTCAGCT GTGTGTTCTGGAATACTCACGTGAGGGAACTTACTTTGGCCAGCATTGACCTTCAAAGTCAGATGGAACCCAGGACC CATCCAACTTGGCTGCTTCACATTTTCATCCCCTTCTGCATCATTGCTTTCATTTTCATAGCCACAGTGATAGCCCT AAGAAAACAACTCTGTCAAAAGCTGTATTCTTCAAAAGACACAACAAAAAGACCTGTCACCACAACAAAGAGGGAAG TGAACAGTGCTATCTGAACCTGTGGTCTTGGGAGCCAGGGTGACCTGATATGACATCTAAAGAAGCTTCTGGACTCT GAACAAGAATTCGGTGGCCTGCAGAGCTTGCCATTTGCACTTTTCAAATGCCTTTGGATGACCCAGCACTTTAATCT GAAACCTGCAACAAGACTAGCCAACACCTGGCCATGAAACTTGCCCCTTCACTGATCTGGACTCACCTCTGGAGCCT ATGGCTTTAAGCAAGCACTACTGCACTTTACAGAATTACCCCACTGGATCCTGGACCCACAGAATTCCTTCAGGATC CTTCTTGCTGCCAGACTGAAAGCAAAAGGAATTATTTCCCCTCAAGTTTTCTAAGTGATTTCCAAAAGCAGAGGTGT GTGGAAATTTCCAGTAACAGAAACAGATGGGTTGCCAATAGAGTTATTTTTTATCTATAGCTTCCTCTGGGTACTAG AAGAGGCTATTGAGACTATGAGCTCACAGACAGGGCTTCGCACAAACTCAAATCATAATTGACATGTTTTATGGATT ACTGGAATCTTGATAGCATAATGAAGTTGTTCTAATTAACAGAGAGCATTTAAATATACACTAAGTGCACAAATTGT GGAGTAAAGTCATCAAGCTCTGTTTTTGAGGTCTAAGTCACAAAGCATTTGTTTTAACCTGTAATGGCACCATGTTT AATGGTGGTTTTTTTTTTGAACTACATCTTTCCTTTAAAAATTATTGGTTTCTTTTTATTTGTTTTTACCTTAGAAA TCAATTATATACAGTCAAAAATATTTGATATGCTCATACGTTGTATCTGCAGCAATTTCAGATAAGTAGCTAAAATG GCCAAAGCCCCAAACTAAGCCTCCTTTTCTGGCCCTCAATATGACTTTAAATTTGACTTTTCAGTGCCTCAGTTTGC ACATCTGTAATACAGCAATGCTAAGTAGTCAAGGCCTTTGATAATTGGCACTATGGAAATCCTGCAAGATCCCACTA CATATGTGTGGAGCAGAAGGGTAACTCGGCTACAGTAACAGCTTAATTTTGTTAAATTTGTTCTTTATACTGGAGCC ATGAAGCTCAGAGCATTAGCTGACCCTTGAACTATTCAAATGGGCACATTAGCTAGTATAACAGACTTACATAGGTG GGCCTAAAGCAAGCTCCTTAACTGAGCAAAATTTGGGGCTTATGAGAATGAAAGGGTGTGAAATTGACTAACAGACA AATCATACATCTCAGTTTCTCAATTCTCATGTAAATCAGAGAATGCCTTTAAAGAATAAAACTCAATTGTTATTCTT CAACGTTCTTTATATATTCTACTTTTGGGTA

SEQ ID NO: 46	Human Spi9 cDNA Sequence

AGCGGGAGTCCGCGGCGAGCGCAGCAGCAGGGCCGGGTCCTGCGCCTCGGGGGTCGGCGTCCAGGCTCGGAGCGCGG CACGGAGACGGCGGCAGCGCTGGACTAGGTGGCAGGCCCTGCATCATGGAAACTCTTTCTAATGCAAGTGGTACTTT TGCCATACGCCTTTTAAAGATACTGTGTCAAGATAACCCTTCGCACAACGTGTTCTGTTCTCCTGTGAGCATCTCCT

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GGCCAACAGGCTCTTTGGAGAGAAAACTTGTCAGTTCCTCTCAACGTTTAAGGAATCCTGTCTTCAATTCTACCATG
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ACCCACCATCACACCCAGCTAATTTTGTATTTTTCAGTAGAGACGGGGTTTCGCCACATTGGCCGTGTTGGTCTTGA
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ACTTTTCTGCTTCGTTTTTACATATGTCTTTGCCTATTAAAGATATTATCCCTCTGTTTTATATTTTCTCTCATTCT
TGTATTGCCTTTTAAATTTTGTTATGATGTTTCATTAATAAACAGTGTTTTGTTTTCCTCTATAATCAAAAAAAAAA
AAAAAAAAA

SEQ ID NO: 47	Human CD47 cDNA Sequence

GGGGAGCAGGCGGGGGAGCGGGCGGGAAGCAGTGGGAGCGCGCGTGCGCGCGGCCGTGCAGCCTGGGCAGTGGGTCC
TGCCTGTGACGCGCGGCGGCGGTCGGTCCTGCCTGTAACGGCGGCGGCGGCTGCTGCTCCAGACACCTGCGGCGGCG
GCGGCGACCCCGCGGCGGGCGCGGAGATGTGGCCCCTGGTAGCGGCGCTGTTGCTGGGCTCGGCGTGCTGCGGATCA
GCTCAGCTACTATTTAATAAAACAAAATCTGTAGAATTCACGTTTTGTAATGACACTGTCGTCATTCCATGCTTTGT
TACTAATATGGAGGCACAAAACACTACTGAAGTATACGTAAAGTGGAAATTTAAAGGAAGAGATATTTACACCTTTG
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CAGTGTTTCTTCACTTCTTTTCTGATCTGGGGCATGAAAAAAGCAAGATTGAAATTTGAACTATGAGTCTCCTGCAT
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AGCAGAGTTTTAATTAAAAGTTTTAAATCAGTC

SEQ ID NO: 48	Human galectin-9 cDNA Sequence
TCCCCATTGAATAACAGCCAAGTTGCTTTGGTTTCTATTTCTTTGTTAAGTCGTTCCCTCTACAAAGGACTTCCTAG TGGGTGTGAAAGGCAGCGGTGGCCACAGAGGCGGCGGAGAGATGGCCTTCAGCGGTTCCCAGGCTCCCTACCTGAGT CCAGCTGTCCCCTTTTCTGGGACTATTCAAGGAGGTCTCCAGGACGGACTTCAGATCACTGTCAATGGGACCGTTCT CAGCTCCAGTGGAACCAGGTTTGCTGTGAACTTTCAGACTGGCTTCAGTGGAAATGACATTGCCTTCCACTTCAACC CTCGGTTTGAAGATGGAGGGTACGTGGTGTGCAACACGAGGCAGAACGGAAGCTGGGGGCCCGAGGAGAGGAAGACA CACATGCCTTTCCAGAAGGGGATGCCCTTTGACCTCTGCTTCCTGGTGCAGAGCTCAGATTTCAAGGTGATGGTGAA CGGGATCCTCTTCGTGCAGTACTTCCACCGCGTGCCCTTCCACCGTGTGGACACCATCTCCGTCAATGGCTCTGTGC AGCTGTCCTACATCAGCTTCCAGAACCCCCGCACAGTCCCTGTTCAGCCTGCCTTCTCCACGGTGCCGTTCTCCCAG CCTGTCTGTTTCCCACCCAGGCCCAGGGGGCGCAGACAAAAACCTCCCGGCGTGTGGCCTGCCAACCCGGCTCCCAT TACCCAGACAGTCATCCACACAGTGCAGAGCGCCCCTGGACAGATGTTCTCTACTCCCGCCATCCCACCTATGATGT ACCCCCACCCCGCCTATCCGATGCCTTTCATCACCACCATTCTGGGAGGGCTGTACCCATCCAAGTCCATCCTCCTG TCAGGCACTGTCCTGCCCAGTGCTCAGAGGTTCCACATCAACCTGTGCTCTGGGAACCACATCGCCTTCCACCTGAA CCCCCGTTTTGATGAGAATGCTGTGGTCCGCAACACCCAGATCGACAACTCCTGGGGGGTCTGAGGAGCGAAGTCTGC CCCGAAAAATGCCCTTCGTCCGTGGCCAGAGCTTCTCAGTGTGGATCTTGTGTGAAGCTCACTGCCTCAAGGTGGCC GTGGATGGTCAGCACCTGTTTGAATACTACCATCGCCTGAGGAACCTGCCCACCATCAACAGACTGGAAGTGGGGGG CGACATCCAGCTGACCCATGTGCAGACATAGGCGGCTTCCTGGCCCTGGGGCCGGGGGCTGGGGTGTGGGGCAGTCT GGGTCCTCTCATCATCCCCACTTCCCAGGCCCAGCCTTTCCAACCCTGCCTGGGATCTGGGCTTTAATGCAGAGGCC ATGTCCTTGTCTGGTCCTGCTTCTGGCTACAGCCACCCTGGAACGGAGAAGGCAGCTGACGGGGATTGCCTTCCTCA GCCGCAGCAGCACCTGGGGCTCCAGCTGCTGGAATCCTACCATCCCAGGAGGCAGGCACAGCCAGGGAGAGGGGAGG AGTGGGCAGTGAAGATGAAGCCCCATGCTCAGTCCCCTCCCATCCCCCACGCAGCTCCACCCCAGTCCCAAGCCACC AGCTGTCTGCTCCTGGTGGGAGGTGGCCTCCTCAGCCCCTCCTCTCTGACCTTTAACCTCACTCTCACCTTGCACCG TGCACCAACCCTTCACCCCTCCTGGAAAGCAGGCCTGATGGCTTCCCACTGGCCTCCACCACCTGACCAGAGTGTTC TCTTCAGAGGACTGGCTCCTTTCCCAGTGTCCTTAAAATAAAGAAATGAAAATGCTTGTTGGCACATTCAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
SEQ ID NO: 49	CD46 Protein Sequence
MMAFCALRKALPCRPENPFSSRCFVEILWVSLALVFLLPMPSDACDEPPKFESMRPQFLNTTYRPGDRVEYECRPGF QPMVPALPTFSVCQDDNTWSPLQEACRRKACSNLPDPLNGQVSYPNGDMLFGSKAQFTCNTGFYIIGAETVYCQVSG NVMAWSEPSPLCEKILCKPPGEIPNGKYTNSHKDVFEYNEVVTYSCLSSTGPDEFSLVGESSLFCIGKDEWSSDPPE CKVVKCPYPVVPNGEIVSGFGSKFYYKAEVVFKCNAGFTLHGRDTIVCGANSTWEPEMPQCIKDSKPTDPPATPGPS HPGPPSPSDASPPKDAESLDGGIIAAIVVGVLAAIAVIAGGVYFFHHKYNKKRSK	
SEQ ID NO: 50	CD55 Protein Sequence
MSPLPRSAPAVRRLMGGQTPPPLLLLLLLLCIPAAQGDCSLPPDVPNAQPDLRGLASFPEQTTITYKCNKGFVKVPG MADSVLCLNDKWSEVAEFCNRSCDVPTRLHFASLKKSYSKQNYFPEGFTVEYECRKGYKRDLTLSEKLTCLQNFTWS KPDEFCKKKQCPTPGELKNGHVNITTDLLFGASIFFSCNAGYRLVGATSSYCFAIANDVEWSDPLPECQEISPTVKA IPAVEKPITVNFPATKYPAIPRATTSFHSSTSKNRGNPSSGMRIMSSGTMLLIAGGVAVIIIIVALILAKGFWHYGK SGSYHTHENNKAVNVAFYNLPATGDAADVRPGN	
SEQ ID NO: 51	CD59 Protein Sequence
MGSKGGFILLWLLSILAVLCHLGHSLQCYNCINPAGSCTTAMNCSHNQDACIFVEAVPPKTYYQCWRFDECNFDFIS RNLAEKKLKYNCCRKDLCNKSDATISSGKTALLVILLLVATWHFCL	
SEQ ID NO: 52	ICP47 Protein Sequence

MSWALKTTDMFLDSSRCTHRTYGDVCAEIHKREREDREAARTAVTDPELPLLCPPDVRSDPASRNPTQQTRGCARSN ERQDRVLAP	
SEQ ID NO: 53	HLA-G1 Protein Sequence
MVVMAPRTLFLLLSGALTLTETWAGSHSMRYFSAAVSRPGRGEPRFIAMGYVDDTQFVRFDSDSACPRMEPRAPWVE QEGPEYWEEETRNTKAHAQTDRMNLQTLRGYYNQSEASSHTLQWMIGCDLGSDGRLLRGYEQYAYDGKDYLALNEDL RSWTAADTAAQISKRKCEAANVAEQRRAYLEGTCVEWLHRYLENGKEMLQRADPPKTHVTHHPVFDYEATLRCWALG FYPAEIILTWQRDGEDQTQDVELVETRPAGDGTFQKWAAVVVPSGEEQRYTCHVQHEGLPEPLMLRWKQSSLPTIPI MGIVAGLVVLAAVVTGAAVAAVLWRKKSSD	
SEQ ID NO: 54	HLA-E Protein Sequence
MVDGTLLLLLSEALALTQTWAGSHSLKYFHTSVSRPGRGEPRFISVGYVDDTQFVRFDNDAASPRMVPRAPWMEQEG SEYWDRETRSARDTAQIFRVNLRTLRGYYNQSEAGSHTLQWMHGCELGPDGRFLRGYEQFAYDGKDYLTLNEDLRSW TAVDTAAQISEQKSNDASEAEHQRAYLEDTCVEWLHKYLEKGKETLLHLEPPKTHVTHHPISDHEATLRCWALGFYP AEITLTWQQDGEGHTQDTELVETRPAGDGTFQKWAAVVVPSGEEQRYTCHVQHEGLPEPVTLRWKPASQPTIPIVGI IAGLVLLGSVVSGAVVAAVIWRKKSSGGKGGSYSKAEWSDSAQGSESHSL	
SEQ ID NO: 55	Human β-2-microglobulin Protein Sequence
MSRSVALAVLALLSLSGLEAIQRTPKIQVYSRHPAENGKSNFLNCYVSGFHPSDIEVDLLKNGERIEKVEHSDLSFS KDWSFYLLYYTEFTPTEKDEYACRVNHVTLSQPKIVKWDRDM	
SEQ ID NO: 56	Human PD-L1 Protein Sequence
MRIFAVFIFMTYWHLLNAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLF NVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMD VKKCGIQDTNSKKQSDTHLEET	
SEQ ID NO: 57	Human PD-L2 Protein Sequence
MIFLLLMLSLELQLHQIAALFTVTVPKELYIIEHGSNVTLECNFDTGSHVNLGAITASLQKVENDTSPHRERATLLE EQLPLGKASFHIPQVQVRDEGQYQCIIIYGVAWDYKYLTLKVKASYRKINTHILKVPETDEVELTCQATGYPLAEVS WPNVSVPANTSHSRTPEGLYQVTSVLRLKPPPGRNFSCVFWNTHVRELTLASIDLQSQMEPRTHPTWLLHIFIPFCI IAFIFIATVIALRKQLCQKLYSSKDTTKRPVTTTKREVNSAI	
SEQ ID NO: 58	Human Spi9 Protein Sequence
METLSNASGTFAIRLLKILCQDNPSHNVFCSPVSISSALAMVLLGAKGNTATQMAQALSLNTEEDIHRAFQSLLTEV NKAGTQYLLRTANRLFGEKTCQFLSTFKESCLQFYHAELKELSFIRAAEESRKHINTWVSKKTEGKIEELLPGSSID AETRLVLVNAIYFKGKWNEPFDETYTREMPFKINQEEQRPVQMMYQEATFKLAHVGEVRAQLLELPYARKELSLLVL LPDDGVELSTVEKSLTFEKLTAWTKPDCMKSTEVEVLLPKFKLQEDYDMESVLRHLGIVDAFQQGKADLSAMSAERD LCLSKFVHKSFVEVNEEGTEAAAASSCFVVAECCMESGPRFCADHPFLFFIRHNRANSILFCGRFSSP	
SEQ ID NO: 59	Human CD47 Protein Sequence
MWPLVAALLLGSACCGSAQLLFNKTKSVEFTFCNDTVVIPCFVTNMEAQNTTEVYVKWKFKGRDIYTFDGALNKSTV PTDFSSAKIEVSQLLKGDASLKMDKSDAVSHTGNYTCEVTELTREGETIIELKYRVVSWFSPNENILIVIFPIFAIL LFWGQFGIKTLKYRSGGMDEKTIALLVAGLVITVIVIVGAILFVPGEYSLKNATGLGLIVTSTGILILLHYYVFSTA IGLTSFVIAILVIQVIAYILAVVGLSLCIAACIPMHGPLLISGLSILALAQLLGLVYMKFVASNQKTIQPPRKAVEE PLNAFKESKGMMNDE	
SEQ ID NO: 60	Human galectin-9 Protein Sequence
MAFSGSQAPYLSPAVPFSGTIQGGLQDGLQITVNGTVLSSSGTRFAVNFQTGFSGNDIAFHFNPRFEDGGYVVCNTR QNGSWGPEERKTHMPFQKGMPFDLCFLVQSSDFKVMVNGILFVQYFHRVPFHRVDTISVNGSVQLSYISFQNPRTVP	

VQPAFSTVPFSQPVCFPPRPRGRRQKPPGVWPANPAPITQTVIHTVQSAPGQMFSTPAIPPMMYPHPAYPMPFITTI
LGGLYPSKSILLSGTVLPSAQRFHINLCSGNHIAFHLNPRFDENAVVRNTQIDNSWGSEERSLPRKMPFVRGQSFSV
WILCEAHCLKVAVDGQHLFEYYHRLRNLPTINRLEVGGDIQLTHVQT

[00627] While some embodiments have been shown and described herein, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein will be employed in practicing the invention.

WHAT IS CLAIMED IS:

1. A genetically modified non-human animal comprising an exogenous nucleic acid sequence at least 95% identical to SEQ ID NO: 359.
2. The genetically modified non-human animal of claim 1, wherein the exogenous nucleic acid is at least 96% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
3. The genetically modified non-human animal of claim 1, wherein the exogenous nucleic acid is at least 97% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
4. The genetically modified non-human animal of claim 1, wherein the exogenous nucleic acid is at least 98% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
5. The genetically modified non-human animal of claim 1, wherein the exogenous nucleic acid is at least 99% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
6. The genetically modified non-human animal of claim 1, wherein the exogenous nucleic acid is 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
7. A genetically modified non-human animal comprising an exogenous nucleic acid that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region.
8. The genetically modified non-human animal of claim 7, wherein the modified 3' untranslated region comprises one or more deletions.
9. The genetically modified non-human animal of claim 7 or 8, wherein the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA.
10. The genetically modified non-human animal of any one of claims 7-9, wherein the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7.
11. The genetically modified non-human animal of any one of claims 7-9, wherein the HLA-G is HLA-G1.
12. The genetically modified non-human animal of any one of claims 7-9, wherein the HLA-G is HLA-G2.
13. The genetically modified non-human animal of any one of claims 1-12, wherein at least one cell of the genetically modified non-human animal expresses a HLA-G protein.
14. The genetically modified non-human animal of claim 13, wherein the HLA-G protein is HLA-G1.
15. The genetically modified non-human animal of any one of claims 1-14, further comprising a second exogenous nucleic acid that encodes for a β-2-microglobulin (B2M) protein.

16. The genetically modified non-human animal of claim 15, wherein the B2M protein is a human B2M protein.
17. A genetically modified non-human animal comprising an exogenous nucleic acid sequence at least 75% identical to SEQ ID NO: 240.
18. The genetically modified non-human animal of claim 17, wherein the exogenous nucleic acid sequence is at least 80% identical to SEQ ID NO: 240.
19. The genetically modified non-human animal of claim 17, wherein the exogenous nucleic acid sequence is at least 85% identical to SEQ ID NO: 240.
20. The genetically modified non-human animal of claim 17, wherein the exogenous nucleic acid sequence is at least 90% identical to SEQ ID NO: 240.
21. The genetically modified non-human animal of claim 17, wherein the exogenous nucleic acid sequence is at least 95% identical to SEQ ID NO: 240.
22. The genetically modified non-human animal of claim 17, wherein the exogenous nucleic acid sequence is identical to SEQ ID NO: 240.
23. The genetically modified non-human animal of any one of claims 17-22, wherein at least one cell of the genetically modified non-human animal expresses a human CD47 protein.
24. The genetically modified non-human animal of any one of claims 17-23, further comprising a second exogenous nucleic acid sequence that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region.
25. The genetically modified non-human animal of claim 24, wherein the modified 3' untranslated region comprises one or more deletions.
26. The genetically modified non-human animal of claim 24 or 25, wherein the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA.
27. The genetically modified non-human animal of any one of claims 24-26, wherein the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7.
28. The genetically modified non-human animal of any one of claims 24-26, wherein the HLA-G is HLA-G1.
29. The genetically modified non-human animal of any one of claims 24-26, wherein the HLA-G is HLA-G2.
30. The genetically modified non-human animal of any one of claims 24-26, wherein the second exogenous nucleic acid sequence is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.

31. The genetically modified non-human animal of any one of claims 1-30, wherein the exogenous nucleic acid sequence is operatively linked to a constitutively active endogenous promoter.
32. The genetically modified non-human animal of any one of claims 1-31, wherein the exogenous nucleic acid sequence is inserted in the genetically modified non-human animal's genome at a ROSA 26 gene site.
33. The genetically modified non-human animal of any one of claims 1-31, wherein the exogenous nucleic acid sequence is inserted in the genetically modified non-human animal's genome at a site effective to reduce expression of a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a NOD-like receptor family CARD domain containing 5 (NLRC5), or a combination thereof in comparison to: an animal of the same species without the exogenous nucleic acid sequence or an animal of the same species with the exogenous nucleic acid inserted in a different site.
34. The genetically modified non-human animal of any one of claims 1-31, wherein the exogenous nucleic acid sequence is inserted in the genetically modified non-human animal's genome at the site effective to reduce expression of the glycoprotein galactosyltransferase alpha 1,3 (GGTA1).
35. The genetically modified non-human animal of any one of claims 1-34, wherein the genetically modified non-human animal further comprises a genomic disruption in one or more genes selected from the list consisting of: a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a NOD-like receptor family CARD domain containing 5 (NLRC5), and any combination thereof.
36. The genetically modified non-human animal of any one of claims 1-34, wherein the genetically modified non-human animal further comprises a genomic disruption in one or more genes selected from the list consisting of: a component of an MHC I-specific

enhanceosome, a transporter of an MHC I-binding peptide, a natural killer (NK) group 2D ligand, a CXC chemokine receptor (CXCR)3 ligand, MHC II transactivator (CIITA), C3, an endogenous gene not expressed in a human, and any combination thereof.

37. The genetically modified non-human animal of claim 36, comprising the genomic disruption of the component of a MHC I-specific enhanceosome, wherein the component of a MHC I-specific enhanceosome is NOD-like receptor family CARD domain containing 5 (NLRC5).
38. The genetically modified non-human animal of claim 36 or 37, comprising the genomic disruption of the transporter of a MHC I-binding peptide, wherein the transporter is transporter associated with antigen processing 1 (TAP1).
39. The genetically modified non-human animal of any one of claim 36-38, comprising the genomic disruption of C3.
40. The genetically modified non-human animal of any one of claim 36-39, comprising the genomic disruption of the NK group 2D ligand, wherein the NK group 2D ligand is MHC class I polypeptide-related sequence A (MICA) or MHC class I polypeptide-related sequence B (MICB).
41. The genetically modified non-human animal of any one of claim 36-40, comprising the genomic disruption of the endogenous gene not expressed in a human, wherein the endogenous gene not expressed in a human is glycoprotein galactosyltransferase alpha 1,3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), or β1,4 N-acetylgalactosaminyltransferase (B4GALNT2).
42. The genetically modified non-human animal of any one of claim 36-41, comprising the genomic disruption of the CXCR3 ligand, wherein the CXCR3 ligand is C-X-C motif chemokine 10 (CXCL10).
43. The genetically modified non-human animal of any one of claims 35-42, wherein the genomic disruption reduces expression of the disrupted gene in comparison to an animal of the same species without the genomic disruption.
44. The genetically modified non-human animal of any one of claims 35-42, wherein the genomic disruption reduces protein expression from the disrupted gene in comparison to an animal of the same species without the genomic disruption.
45. The genetically modified non-human animal of any one of claims 1-44, further comprising an additional exogenous nucleic acid sequence encoding an infected cell protein 47 (ICP47).

46. The genetically modified non-human animal of any one of claims 1-45, wherein the genetically modified non-human animal is a member of the *Laurasiatheria* superorder.
47. The genetically modified non-human animal of any one of claims 1-45, wherein the genetically modified non-human animal is an ungulate.
48. The genetically modified non-human animal of any one of claims 1-45, wherein the genetically modified non-human animal is a pig.
49. The genetically modified non-human animal of any one of claims 1-45, wherein the genetically modified non-human animal is a non- human primate.
50. The genetically modified non-human animal of any one of claims 1-49, wherein the genetically modified non-human animal is fetus.
51. A cell isolated from the genetically modified non-human animal of any one of claims 1-50.
52. The cell of claim 51, wherein the cell is an islet cell.
53. The cell of claim 51, wherein the cell is a stem cell.
54. A tissue isolated from the genetically modified non-human animal of any one of claims 1-50.
55. The tissue of claim 54, wherein the tissue is a solid organ transplant.
56. The tissue of claim 54, wherein the tissue is all or a portion of a liver.
57. The tissue of claim 54, wherein the tissue is all or a portion of a kidney.
58. A non-human cell comprising an exogenous nucleic acid sequence at least 95% identical to SEQ ID NO: 359.
59. The non-human cell of claim 58, wherein the exogenous nucleic acid is at least 96% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
60. The non-human cell of claim 58, wherein the exogenous nucleic acid is at least 97% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
61. The non-human cell of claim 58, wherein the exogenous nucleic acid is at least 98% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
62. The non-human cell of claim 58, wherein the exogenous nucleic acid is at least 90% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
63. The non-human cell claim 58, wherein the exogenous nucleic acid is 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
64. The non-human cell of any one of claims 58-63, wherein the non-human cell expresses human leukocyte antigen G1 (HLA-G1) on the cell surface.

65. A non-human cell comprising an exogenous nucleic acid that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region.
66. The non-human cell of claim 65, wherein the modified 3' untranslated region comprises one or more deletions.
67. The non-human cell of claim 65 or 66, wherein the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA.
68. The non-human cell of any one of claims 65-67, wherein the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7.
69. The non-human cell of any one of claims 65-67, wherein the HLA-G is HLA-G1.
70. The non-human cell of any one of claims 65-67, wherein the HLA-G is HLA-G2.
71. The non-human cell of any one of claims 58-70, wherein the non-human cell further comprises a second exogenous nucleic acid that encodes for a β-2-microglobulin (B2M) protein.
72. The non-human cell of claim 71, wherein the B2M protein is a human B2M protein.
73. A non-human cell comprising an exogenous nucleic acid at least 75% identical to SEQ ID NO: 240.
74. The non-human cell of claim 73, wherein the exogenous nucleic acid sequence is at least 80% identical to SEQ ID NO: 240.
75. The non-human cell of claim 73, wherein the exogenous nucleic acid sequence is at least 85% identical to SEQ ID NO: 240.
76. The non-human cell of claim 73, wherein the exogenous nucleic acid sequence is at least 90% identical to SEQ ID NO: 240.
77. The non-human cell of claim 73, wherein the exogenous nucleic acid sequence is at least 95% identical to SEQ ID NO: 240.
78. The non-human cell of claim 73, wherein the exogenous nucleic acid sequence is 100% identical to SEQ ID NO: 240.
79. The non-human cell of any one of claims 73-78, wherein the at least one non-human cell expresses a human CD47 protein.
80. The non-human cell of any one of claims 73-79, wherein the non-human cell further comprises a second exogenous nucleic acid sequence that is transcribed as a human leukocyte antigen G (HLA-G) mRNA with a modified 3' untranslated region.
81. The non-human cell of claim 80, wherein the modified 3' untranslated region comprises one or more deletions.

82. The non-human cell of claim 80 or 81, wherein the modified 3' untranslated region increases stability of the mRNA in comparison to an unmodified HLA-G mRNA.
83. The non-human cell of any one of claims 80-82, wherein the HLA-G is HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G6, or HLA-G7.
84. The non-human cell of any one of claims 80-82, wherein the HLA-G is HLA-G1.
85. The non-human cell of any one of claims 80-82, wherein the HLA-G is HLA-G2.
86. The non-human cell of any one of claims 80-82, wherein the second exogenous nucleic acid sequence is at least 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 359 or SEQ ID NO: 502.
87. The non-human cell of any one of claims 58-86, wherein the exogenous nucleic acid sequence is operatively linked to a constitutively active endogenous promoter.
88. The non-human cell of any one of claims 58--87, wherein the exogenous nucleic acid sequence is inserted in the non-human cell's genome at a ROSA 26 gene site.
89. The non-human cell of any one of claims 58--87, wherein the exogenous nucleic acid sequence is inserted in the non-human cell's genome at a site effective to reduce expression of a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a NOD-like receptor family CARD domain containing 5 (NLRC5), or a combination thereof in comparison to: a cell of the same species without the exogenous nucleic acid sequence or a cell of the same species wherein the exogenous nucleic acid is inserted in a different site.
90. The non-human cell of any one of claims 58-87, wherein the exogenous nucleic acid sequence is inserted in the non-human cell's genome at a site that reduces expression of a glycoprotein galactosyltransferase alpha 1,3 (GGTA1).
91. The non-human cell of any one of claims 58-87, wherein the non-human cell further comprises a genomic disruption in one or more genes selected from the list consisting of: a glycoprotein galactosyltransferase alpha 1,3 (GGTA1), a putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), a β1,4 N-acetylgalactosaminyltransferase (B4GALNT2), a C-X-C motif chemokine 10 (CXCL10), a MHC class I polypeptide-related sequence A (MICA), a MHC class I polypeptide-related sequence B (MICB), a transporter associated with antigen processing 1 (TAP1), a

NOD-like receptor family CARD domain containing 5 (NLRC5), and any combination thereof.

92. The non-human cell of any one of claims 58-87, wherein the non-human cell further comprises a genomic disruption in one or more genes selected from the list consisting of: a component of an MHC I-specific enhanceosome, a transporter of an MHC I-binding peptide, a natural killer (NK) group 2D ligand, a CXC chemokine receptor (CXCR)3 ligand, MHC II transactivator (CIITA), C3, an endogenous gene not expressed in a human, and any combination thereof.
93. The non-human cell of claim 92, wherein the non-human cell comprises the genomic disruption of the component of a MHC I-specific enhanceosome, wherein the component of a MHC I-specific enhanceosome is NOD-like receptor family CARD domain containing 5 (NLRC5).
94. The non-human cell of claim 92 or 93, wherein the non-human cell comprises the genomic disruption of the transporter of a MHC I-binding peptide, wherein the transporter is transporter associated with antigen processing 1 (TAP1).
95. The non-human cell of any one of claim 92 -94, wherein the non-human cell comprises the genomic disruption of C3.
96. The non-human cell of any one of claim 92 -95, wherein the non-human cell comprises the genomic disruption of the NK group 2D ligand, wherein the NK group 2D ligand is MHC class I polypeptide-related sequence A (MICA) or MHC class I polypeptide-related sequence B (MICB).
97. The non-human cell of any one of claim 92-96, wherein the non-human cell comprises the genomic disruption of the endogenous gene not expressed in a human, wherein the endogenous gene not expressed in a human is glycoprotein galactosyltransferase alpha 1,3 (GGTA1), putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein (CMAH), or β1,4 N-acetylgalactosaminyltransferase (B4GALNT2).
98. The non-human cell of any one of claim 92-97, wherein the non-human cell comprises the genomic disruption of a CXCR3 ligand, wherein the CXCR3 ligand is C-X-C motif chemokine 10 (CXCL10).
99. The non-human cell of any one of claim 91-98, wherein the genomic disruption reduces expression of the disrupted gene in comparison to a cell from the same species without the genomic disruption.

100. The non-human cell of any one of claim 91-98, wherein the genomic disruption reduces protein expression from the disrupted gene in comparison to a cell from the same species without the genomic disruption.

101. The non-human cell of any one of claims 58-100, further comprising an additional exogenous nucleic acid sequence encoding an infected cell protein 47 (ICP47).

102. The non-human cell of any one of claims 58-101, wherein the non-human cell is a *Laurasiatheria* superorder cell.

103. The non-human cell of any one of claims 58-101, wherein the non-human cell is an ungulate cell.

104. The non-human cell of any one of claims 58-101, wherein the non-human cell is a pig cell.

105. The non-human cell of any one of claims 58-101, wherein the non-human cell is a non- human primate cell.

106. The non-human cell of any one of claims 58-105, wherein the non-human cell is a fetal cell.

107. The non-human cell of any one of claims 58-106, wherein the non-human cell is a stem cell.

108. The method of any one of claims 58-106, wherein the non-human cell is an islet cell.

109. A solid organ transplant comprising the non-human cell of any one of claims 58-106.

110. An embryo comprising the non-human cell of any one of claims 58-106.

111. A method comprising providing to a subject, at least one non-human cell of any one of claims 58-106.

112. The method of claim 111, wherein the at least one non-human cell is a solid organ transplant.

113. The method of claim 111, wherein the at least one non-human cell is a stem cell transplant.

114. The method of claim 111, wherein the at least one non-human cell is an islet cell transplant.

115. The method of any one of claims 111-114, further comprising providing to the subject a tolerizing vaccine.

116. The method of claim 115, wherein the tolerizing vaccine is provided prior to, concurrently with, or after the at least one non-human cell is provided to the subject.

117. The method of claim 115 or 116, wherein the tolerizing vaccine comprises apoptotic cells.

118. The method of any one of claims 115-117, wherein the tolerizing vaccine comprises cells from the same species as the at least one non-human cell provided to the subject.

119. The method of any one of claims 115-118, wherein the tolerizing vaccine comprises cells that are genetically identical to the at least one non-human cell provided to the subject.

120. The method of any one of claims 111-119, further comprising providing an anti-CD40 antibody to the subject.

121. The method of claim 120, wherein the anti-CD40 antibody is provided prior to, concurrently with, or after the at least one non-human cell is provided to the subject.

122. The method of claim 120 or 121, wherein the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 487.

123. The method of claim 120 or 121, wherein the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 488.

124. A system for xenotransplantation comprising:

a) at least one cell isolated from the genetically modified non-human animal of any one of claims 1-50; and

b) a tolerizing vaccine, anti-CD40 antibody, or a combination thereof.

125. The system of claim 124, wherein the at least one cell comprises an islet cell, a stem cell, or a combination thereof.

126. The system of claim 124, wherein the at least one cell is a solid organ transplant.

127. The system of claim 124, wherein the at least one cell is all or a portion of a liver.

128. The system of claim 124, wherein the at least one cell is all or a portion of a kidney.

129. The system of any one of claims 124-128, comprising the tolerizing vaccine.

130. The system of claim 129, wherein the tolerizing vaccine comprises apoptotic cells.

131. The system of claim 129 or 130, wherein the tolerizing vaccine comprises cells from the same species as the at least one cell.

132. The system of any one of claims 129 -131, wherein the tolerizing vaccine comprises cells that are genetically identical to the at least one cell.

133. The system of any one of claims 129 -132, comprising the anti-CD40 antibody.

134. The system of claim 133, wherein the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 487.

135. The system of claim 133, wherein the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 488.

136. A system for xenotransplantation comprising:

a) at least one non-human cell of any one of claims 58-108; and

b) a tolerizing vaccine, an anti-CD40 antibody, or a combination thereof.

137. The system of claim 136, wherein the at least one non-human cell comprises an islet cell, a stem cell, or a combination thereof.

138. The system of claim 136, wherein the at least one non-human cell is a solid organ transplant.

139. The system of claim 136, wherein the at least one non-human cell is all or a portion of a liver.

140. The system of claim 136, wherein the at least one non-human cell is all or a portion of a kidney.

141. The system of any one of claims 136-140, comprising the tolerizing vaccine.

142. The system of claim 141, wherein the tolerizing vaccine comprises apoptotic cells.

143. The system of claim 141 or 142, wherein the tolerizing vaccine comprises cells from the same species as the at least one cell.

144. The system of any one of claims 141-143, wherein the tolerizing vaccine comprises cells that are genetically identical to the at least one cell.

145. The system of any one of claims 141-144, comprising the anti-CD40 antibody.

146. The system of claim 145, wherein the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 487.

147. The system of claim 145, wherein the anti-CD40 antibody specifically binds to an epitope within amino acid sequence SEQ ID NO: 488.

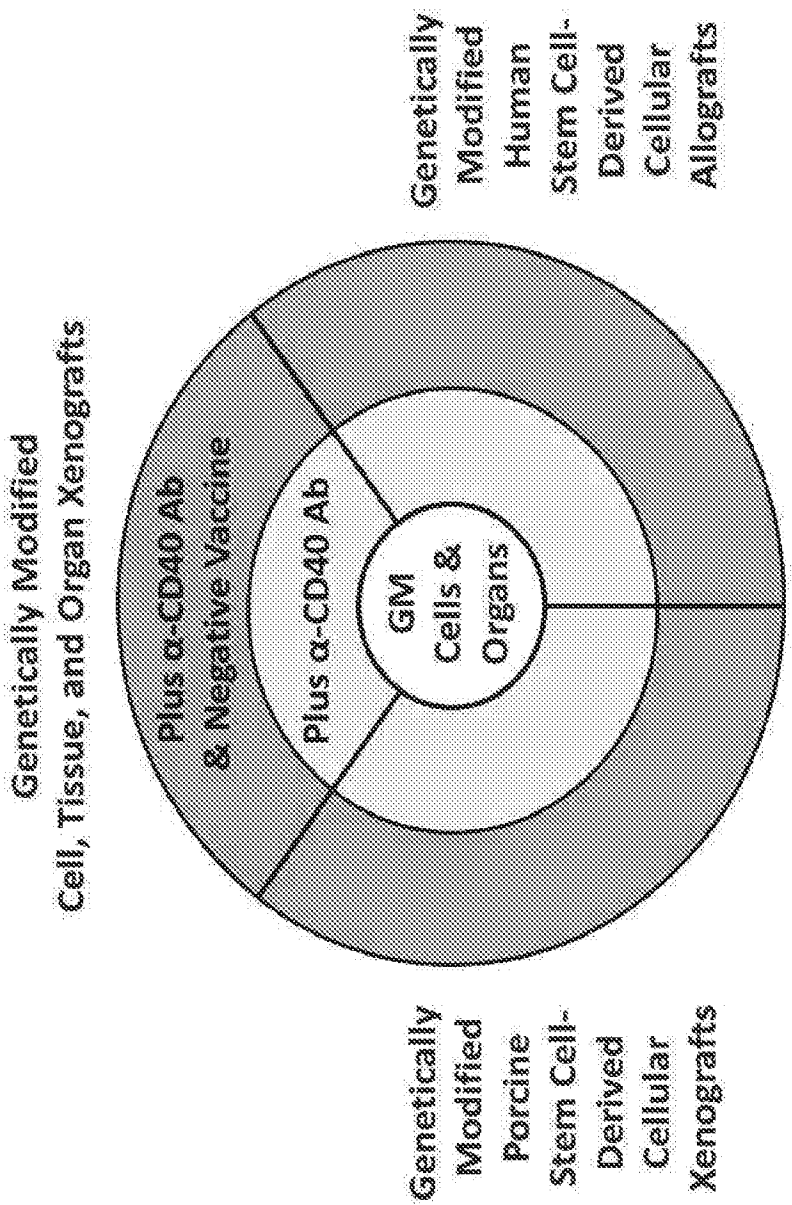

Genetically Modified
Cell, Tissue, and Organ Xenografts
Plus α-CD40 Ab
& Negative Vaccine
Plus α-CD40 Ab
GM
Cells &
Organs
Genetically
Modified
Porcine
Stem Cell-
Derived
Cellular
Xenografts
Genetically
Modified
Human
Stem Cell-
Derived
Cellular
Allografts

FIG. 1

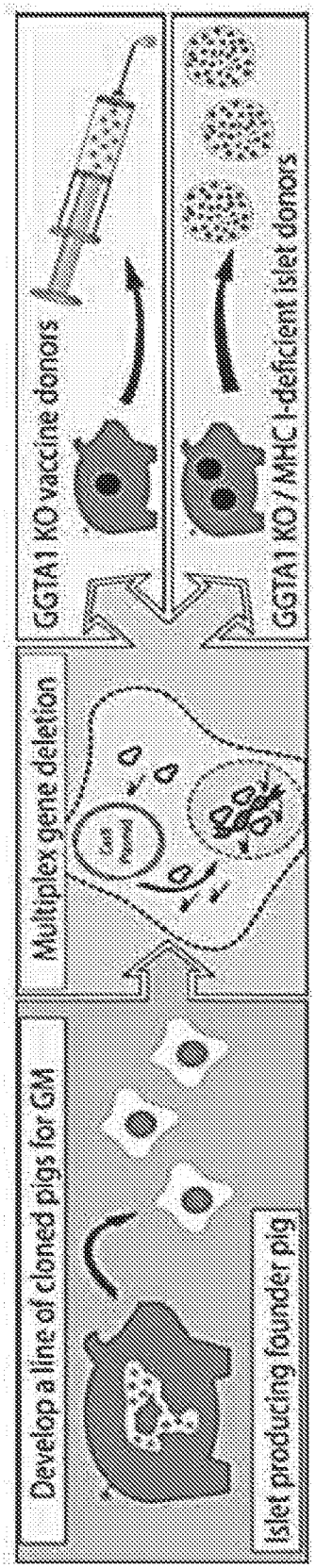

Develop a line of cloned pigs for GM
Multiplex gene deletion
GGTA1 KO vaccine donors
Islet producing founder pig
GGTA1 KO / MHC I-deficient islet donors

FIG. 2

Use of Positive and Negative Vaccines
E.g., inactivated virus
with adjuvant
injected under the skin
(positive vaccine)
Immunity
Inactivated donor cells
without adjuvant
injected intravenously
(negative vaccine)
Tolerance

FIG. 3

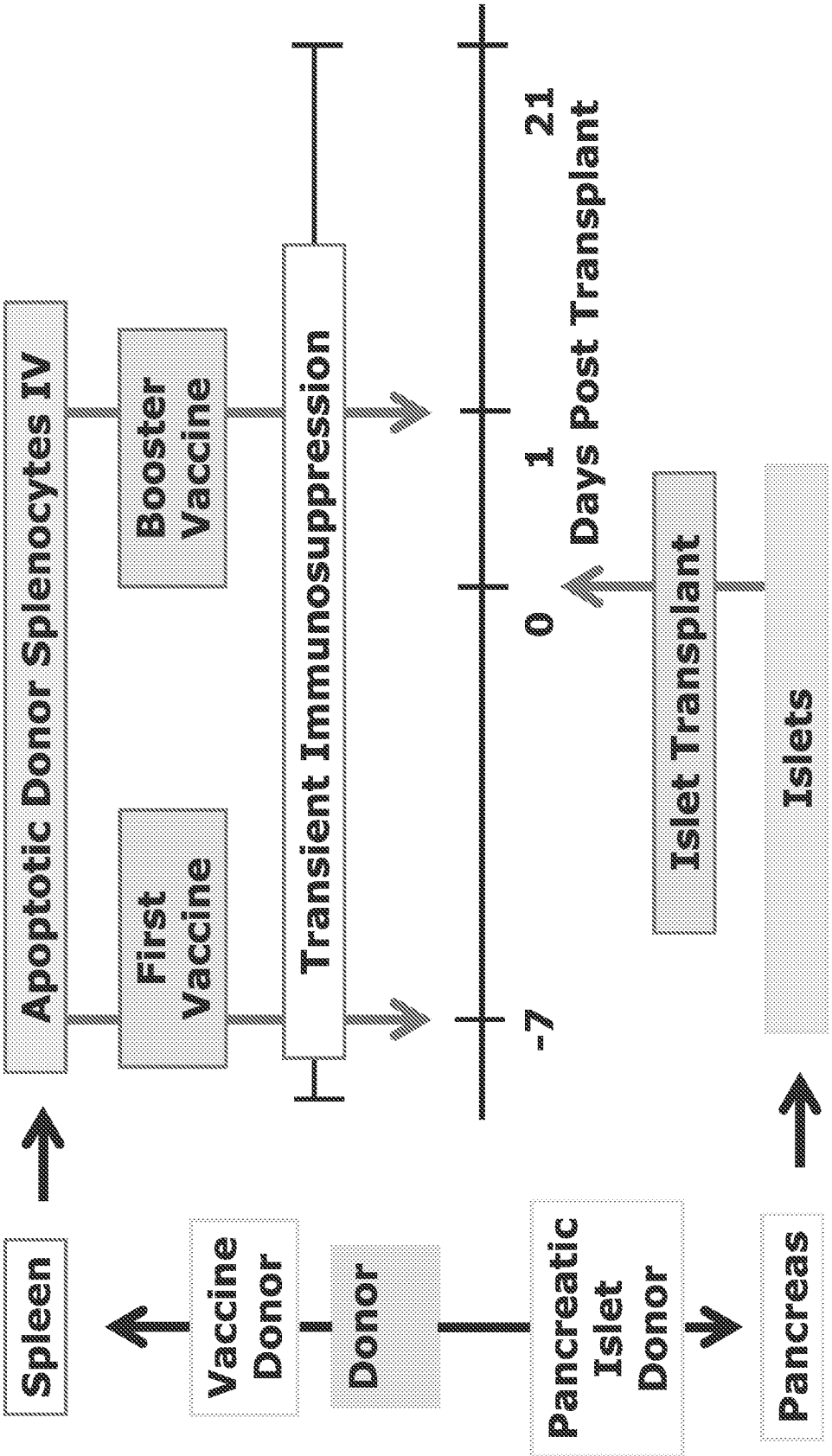

Spleen
Vaccine Donor
Donor
Pancreatic Islet Donor
Pancreas
Apoptotic Donor Splenocytes IV
First Vaccine
Booster Vaccine
Transient Immunosuppression
Islet Transplant
Islets
-7
0
1
21
Days Post Transplant

FIG. 4

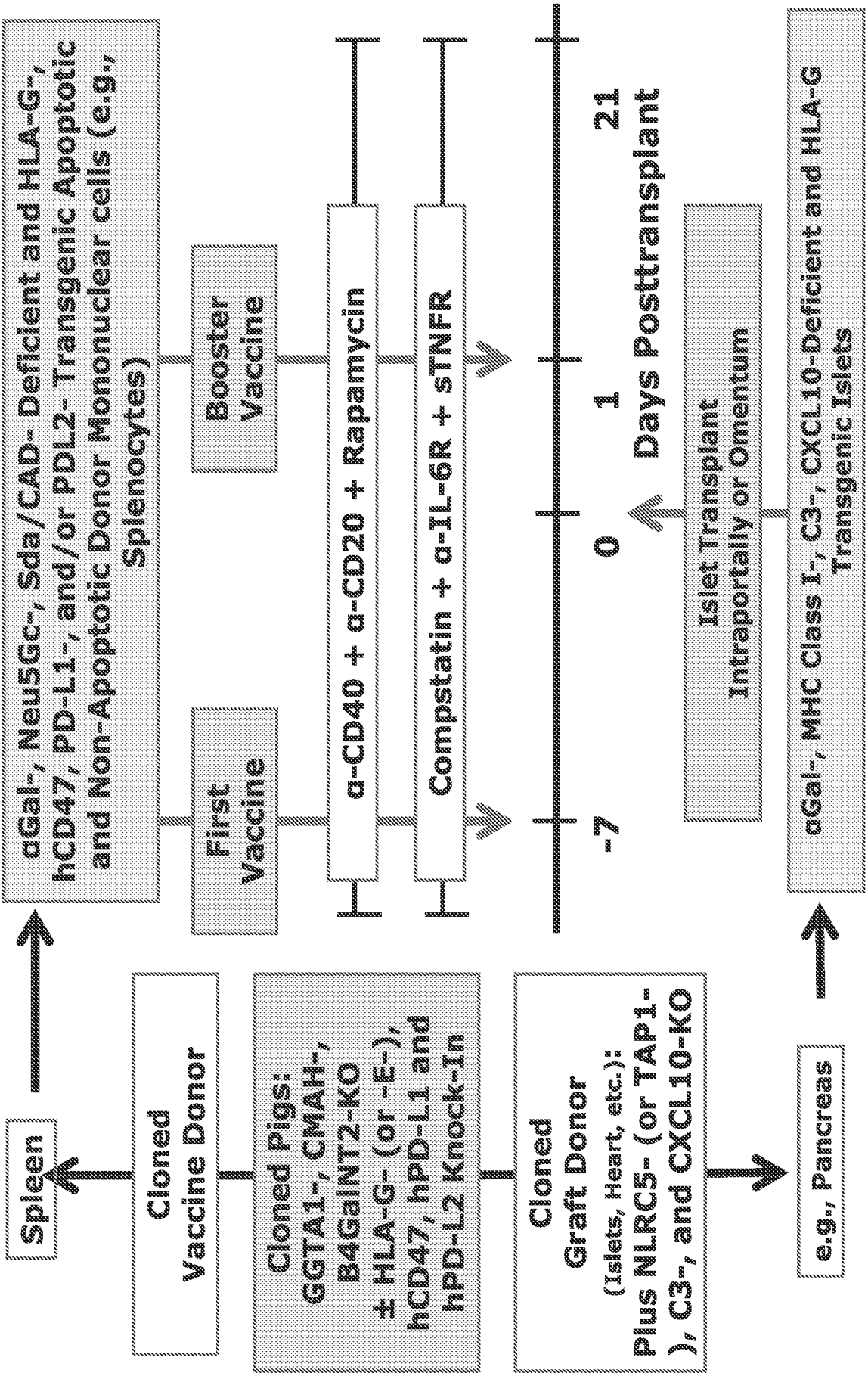

αGal-, Neu5Gc-, Sda/CAD- Deficient and HLA-G-, hCD47, PD-L1-, and/or PDL2- Transgenic Apoptotic and Non-Apoptotic Donor Mononuclear cells (e.g., Splenocytes)
Booster Vaccine
First Vaccine
α-CD40 + α-CD20 + Rapamycin
Compstatin + α-IL-6R + sTNFR
-7
0
1
21
Days Posttransplant
Islet Transplant Intraportally or Omentum
αGal-, MHC Class I-, C3-, CXCL10-Deficient and HLA-G Transgenic Islets
Spleen
Cloned Vaccine Donor
Cloned Pigs: GGTA1-, CMAH-, B4GalNT2-KO ± HLA-G- (or -E-), hCD47, hPD-L1 and hPD-L2 Knock-In
Cloned Graft Donor (Islets, Heart, etc.): Plus NLRC5- (or TAP1-), C3-, and CXCL10-KO
e.g., Pancreas

FIG. 5

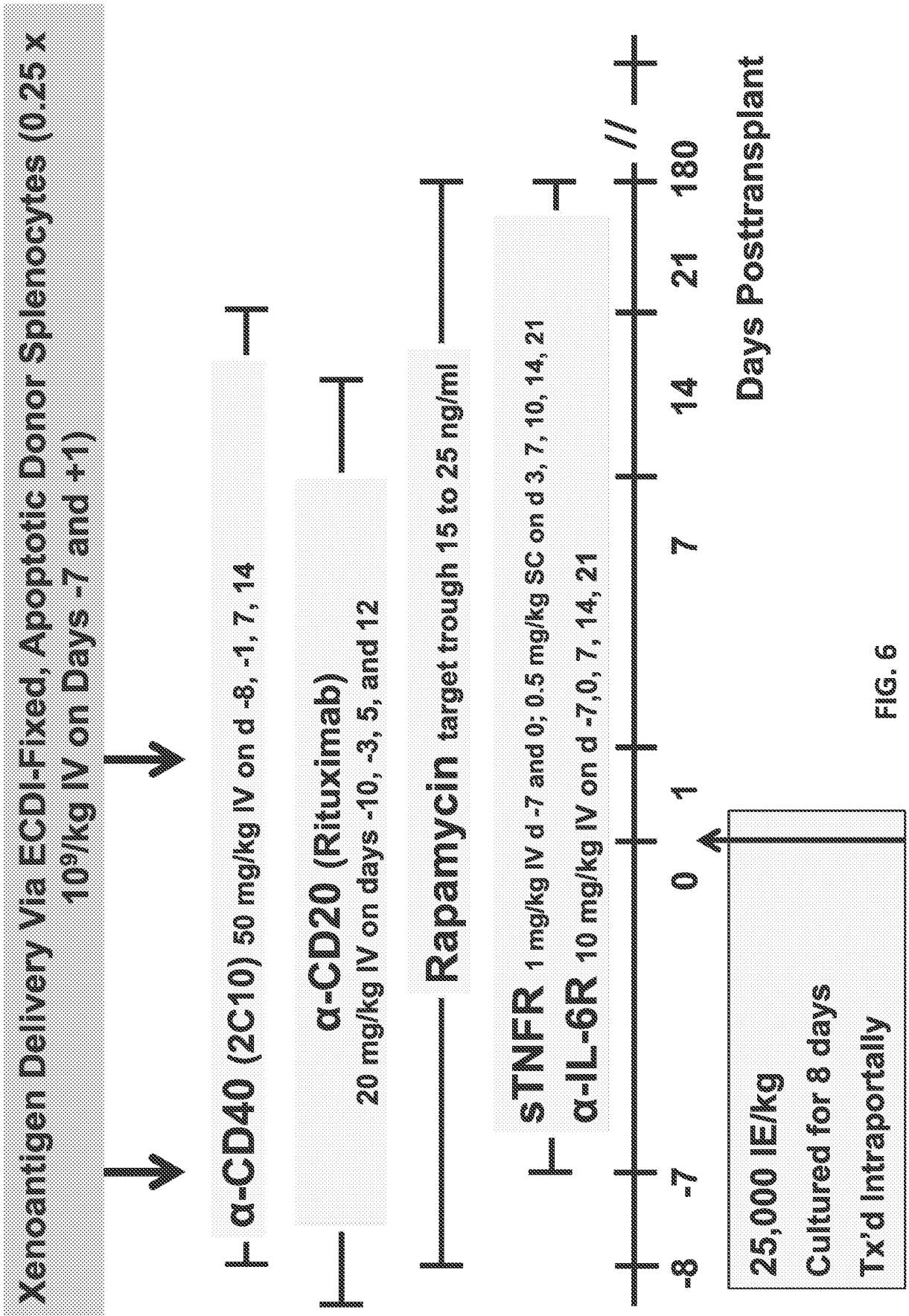

Xenoantigen Delivery Via ECDI-Fixed, Apoptotic Donor Splenocytes (0.25 x 10^9/kg IV on Days -7 and +1)
α-CD40 (2C10) 50 mg/kg IV on d -8, -1, 7, 14
α-CD20 (Rituximab) 20 mg/kg IV on days -10, -3, 5, and 12
Rapamycin target trough 15 to 25 ng/ml
sTNFR 1 mg/kg IV d -7 and 0; 0.5 mg/kg SC on d 3, 7, 10, 14, 21
α-IL-6R 10 mg/kg IV on d -7,0, 7, 14, 21
-8
-7
0
1
7
14
21
180
//
Days Posttransplant
25,000 IE/kg
Cultured for 8 days
Tx'd Intraportally

FIG. 6

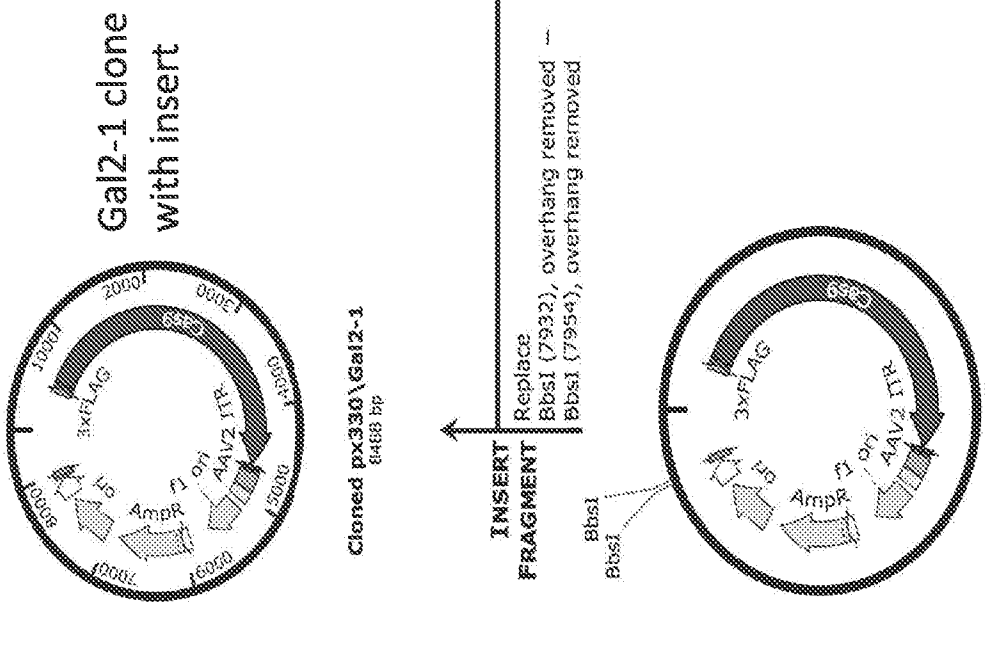

Gal2-1 clone
with insert
Cloned px330\Gal2-1
8468 bp
INSERT FRAGMENT
Replace
BbsI (7932), overhang removed
BbsI (7954), overhang removed
Insert
Start (0), filled-in
End (26), filled-in
SEQ ID NO: 266
Construct: Gal2-1_annealed.dna
Operation: Anneal Oligos
Gal2-1_Forward (26-mer):
ACACCGGCAGAAGCAGAGATGG
Gal2-1_Reverse (26-mer):
AAAACCATCCTCTGCTTCTCTCCCCG
SEQ ID NO: 267
<Start>
<End>
Gal2-1_annealed
26 bp
BbsI
BbsI
px330-U6-Chimeric_BB-CBh-hSpCas9
8484 bp
3xFLAG
SV40
U6
Ampr
f1 ori
AAV2 ITR

FIG. 7A

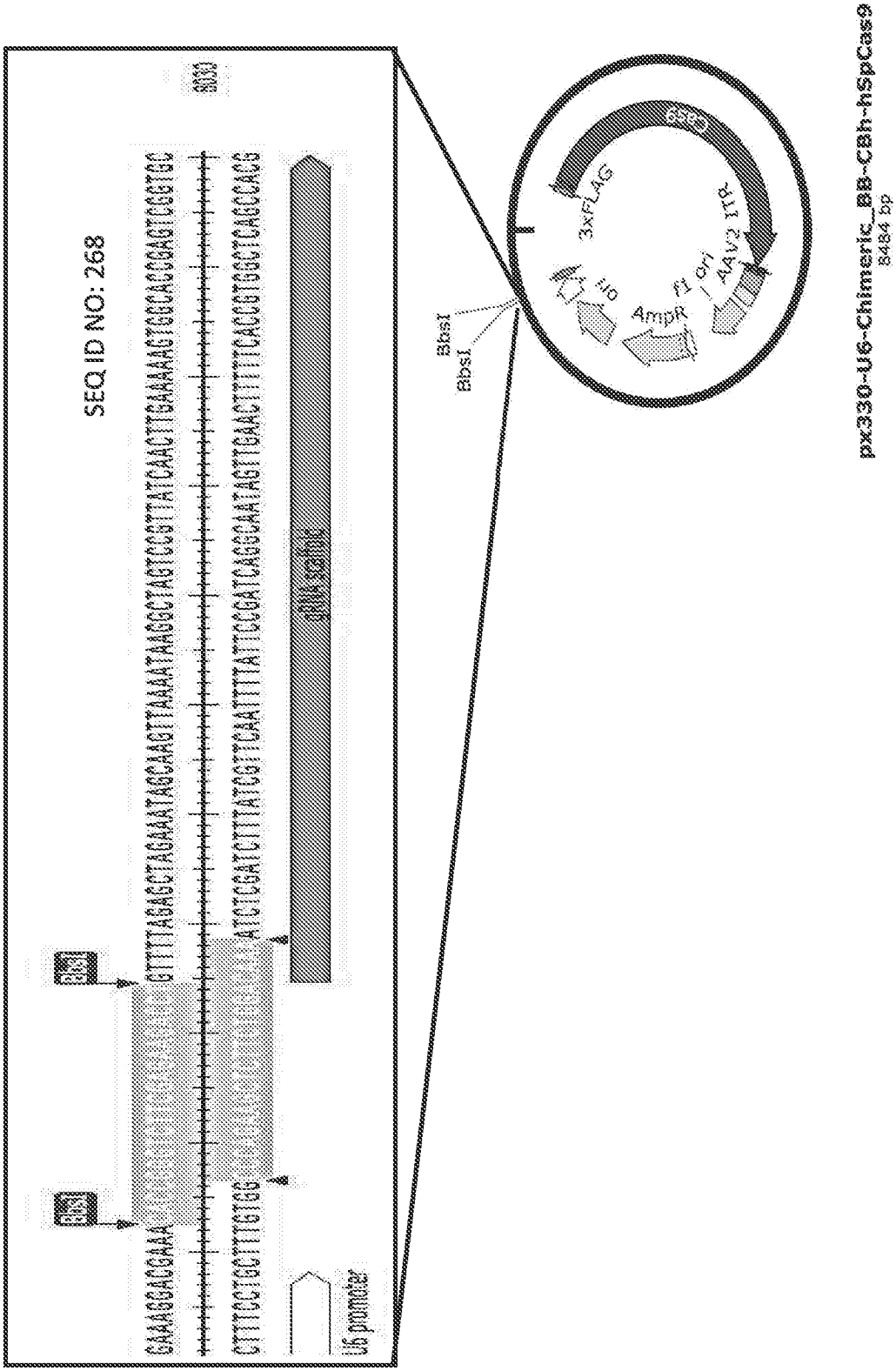

SEQ ID NO: 268
BbsI
BbsI
U6 promoter
sgRNA (N20)
GAAAGGACGAAA
GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGC
CTTTCCTGCTTTGTGG
ATCTCGATCTTTATCGTTCAATTTTATTCGGATCAGGCAATAGTTGAACTTTTTCACCGTGGCTCAGGCACG
BbsI
BbsI
3xFLAG
Cas9
U6
AmpR
f1 ori
AAV2 ITR
px330-U6-Chimeric_BB-CBh-hSpCas9
8484 bp

FIG. 7B

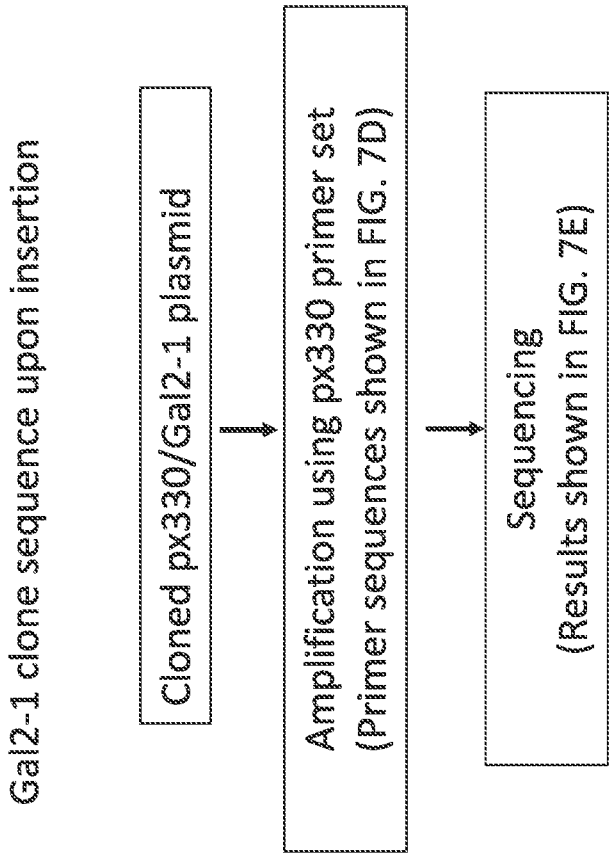

Gal2-1 clone sequence upon insertion
Cloned px330/Gal2-1 plasmid
Amplification using px330 primer set
(Primer sequences shown in FIG. 7D)
Sequencing
(Results shown in FIG. 7E)

FIG. 7C

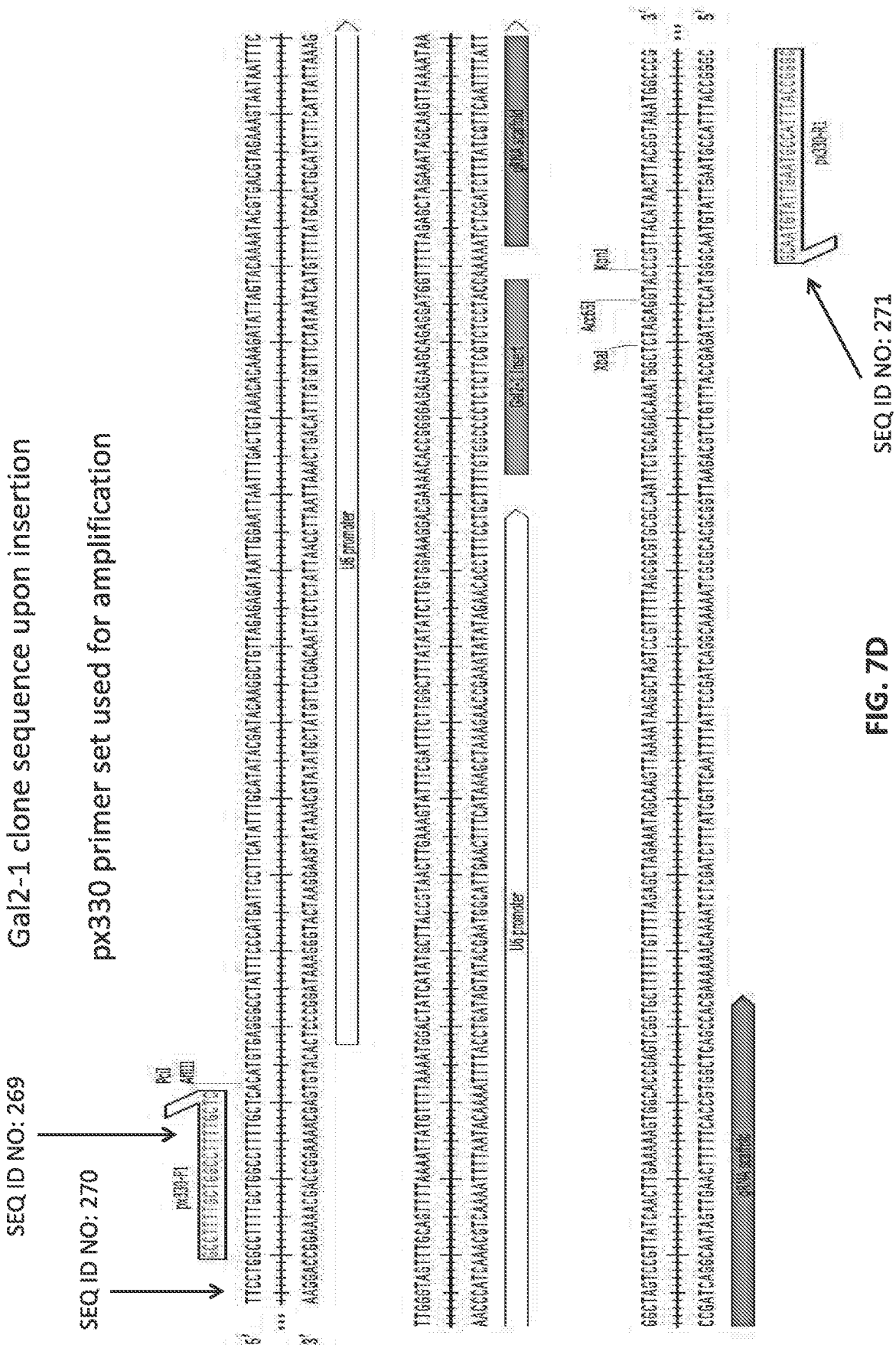

SEQ ID NO: 269
Gal2-1 clone sequence upon insertion
SEQ ID NO: 270
px330 primer set used for amplification
px330-F1
PstI
AflIII
U6 promoter
Gal2-1 insert
XbaI
Acc65I
KpnI
px330-R1
SEQ ID NO: 271

FIG. 7D

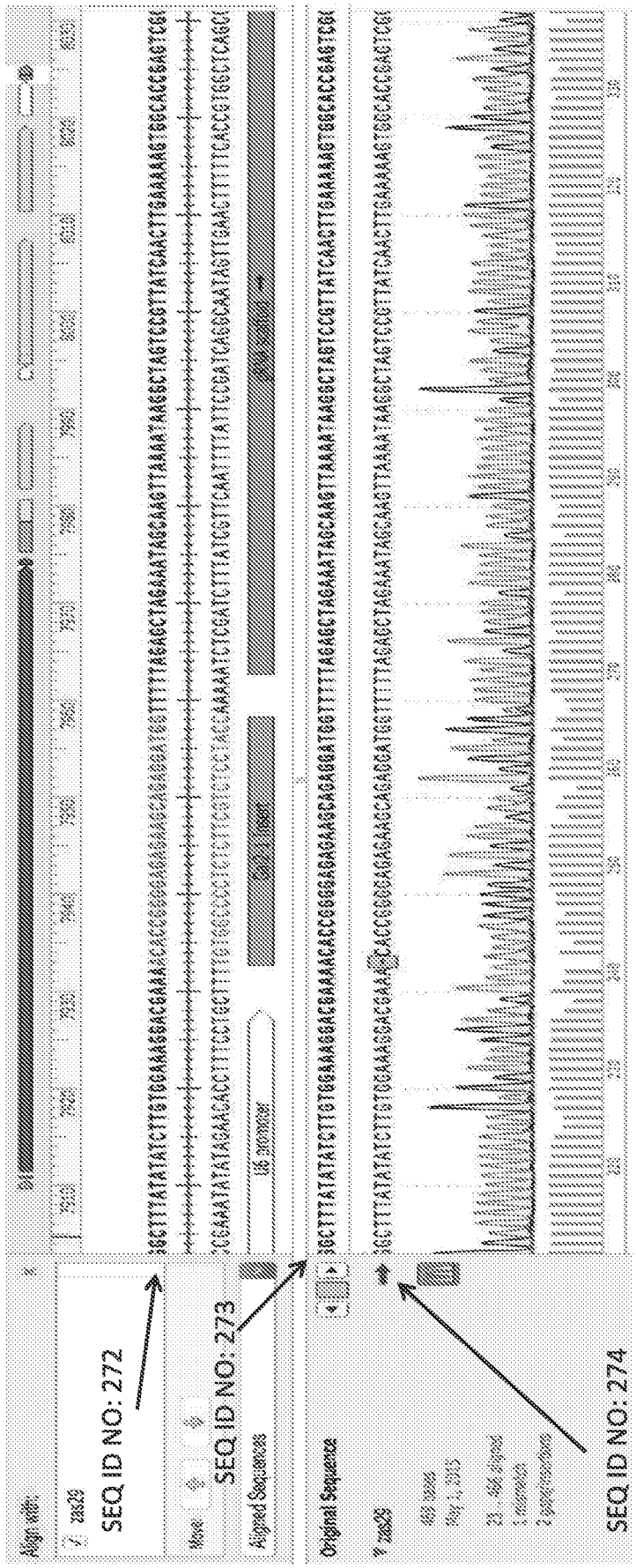

Zas29 sequencing result of constructed plasmid (bottom)
shown against the expected clone (top)
SEQ ID NO: 272
SEQ ID NO: 273
SEQ ID NO: 274

FIG. 7E

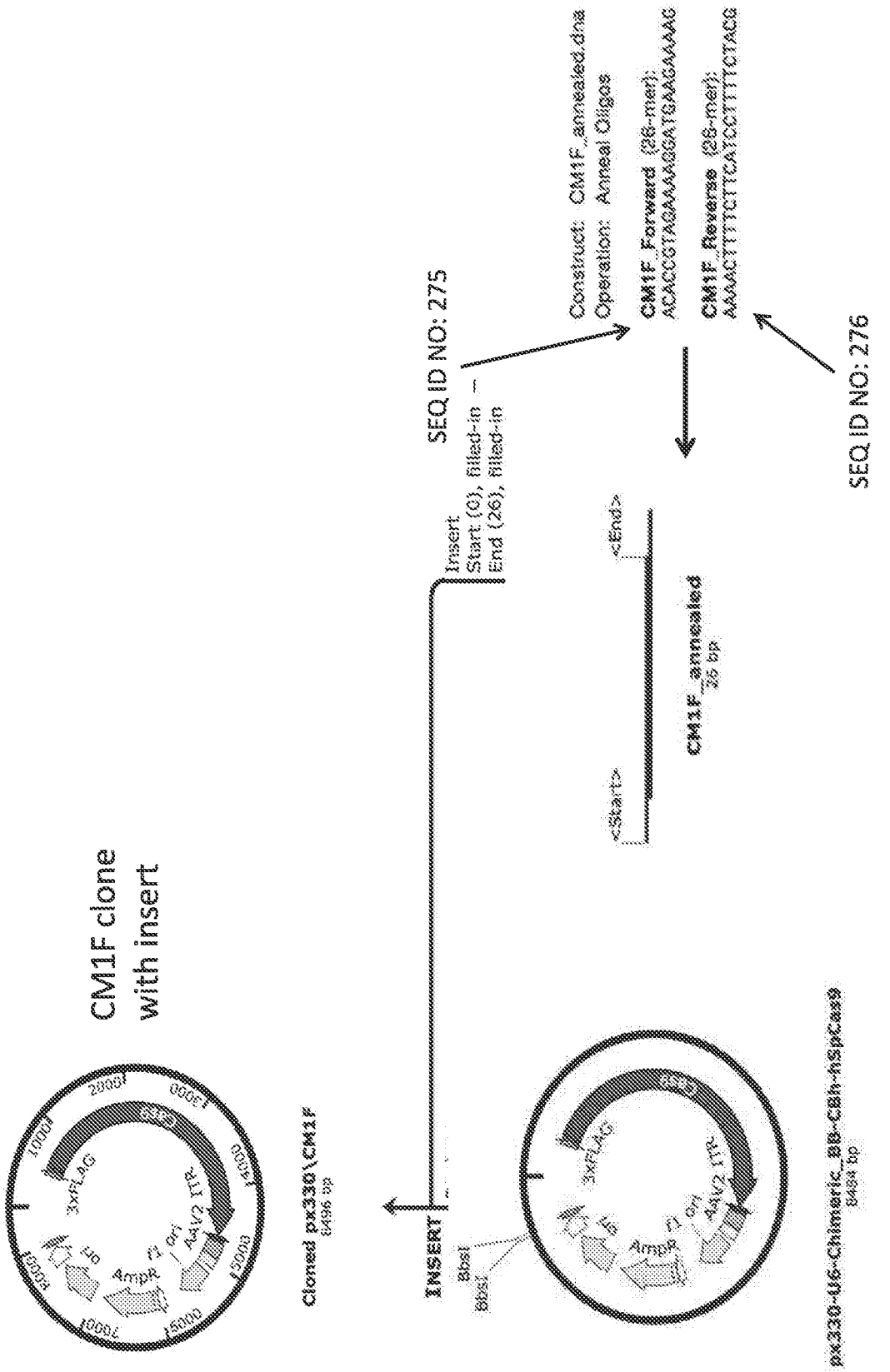

CM1F clone with insert
Cloned px330\CM1F
8496 bp
INSERT
BbsI
BbsI
px330-U6-Chimeric_BB-CBh-hSpCas9
8484 bp
SEQ ID NO: 275
Insert
Start (0), filled-in
End (26), filled-in
Construct: CM1F_annealed.dna
Operation: Anneal Oligos
CM1F_Forward (26-mer):
ACACCGTAGAAAAGGATGAAGAAAAG
CM1F_Reverse (26-mer):
AAAACTTTTCTTCATCCTTTTCTACG
SEQ ID NO: 276
<End>
<Start>
CM1F_annealed
26 bp

FIG. 8A

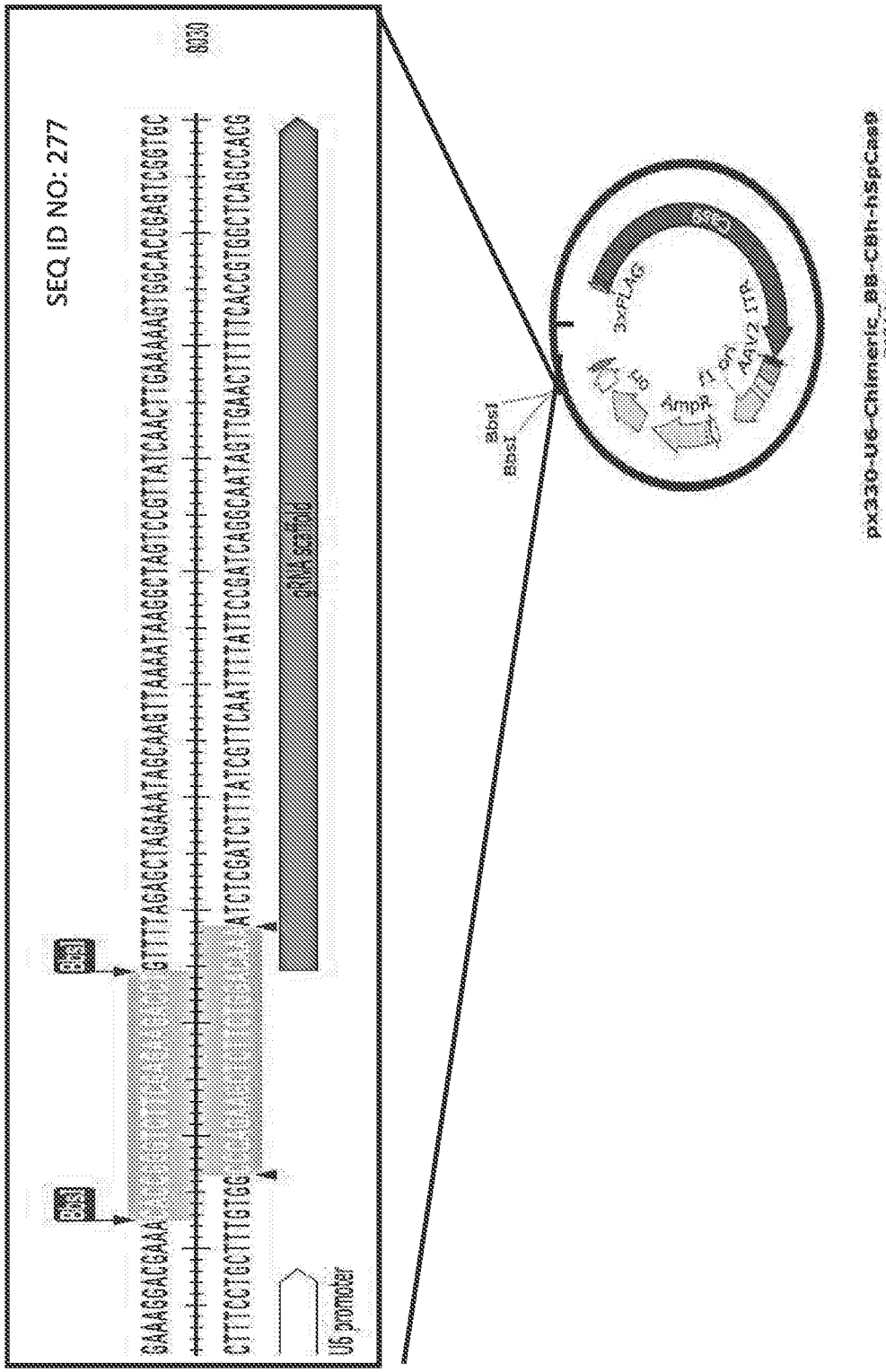

SEQ ID NO: 277
8030
GAAAGGACGAAA
GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGC
ATCTCGATCTTTATCGTTCAATTTTATTCCGATCAGGCAATAGTTGAACTTTTTCACCGTGGCTCAGCCACG
U6 promoter
Bbsl
Bbsl
3xFLAG
SV40
AAV2 ITR
AmpR
px330-U6-Chimeric_BB-CBh-hSpCas9
8484 bp

FIG. 8B

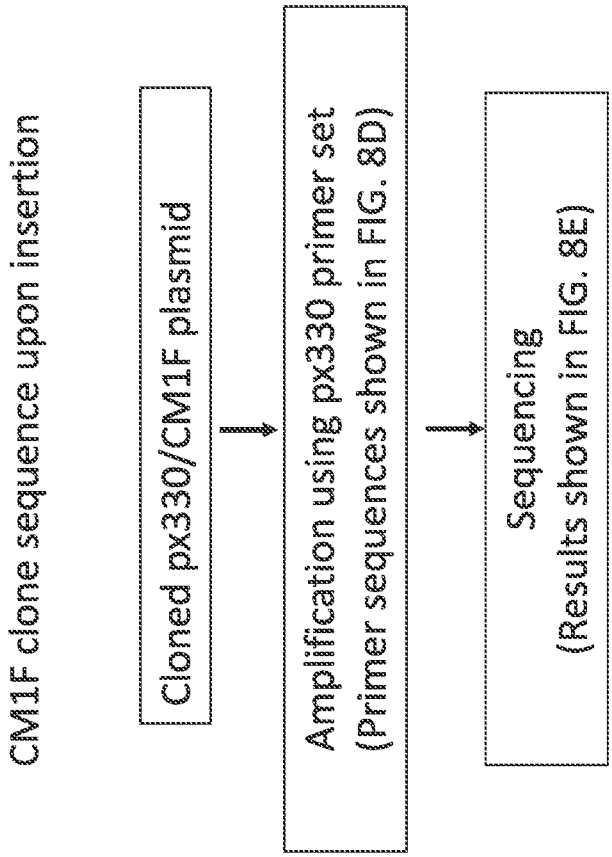

CM1F clone sequence upon insertion
Cloned px330/CM1F plasmid
Amplification using px330 primer set
(Primer sequences shown in FIG. 8D)
Sequencing
(Results shown in FIG. 8E)

FIG. 8C

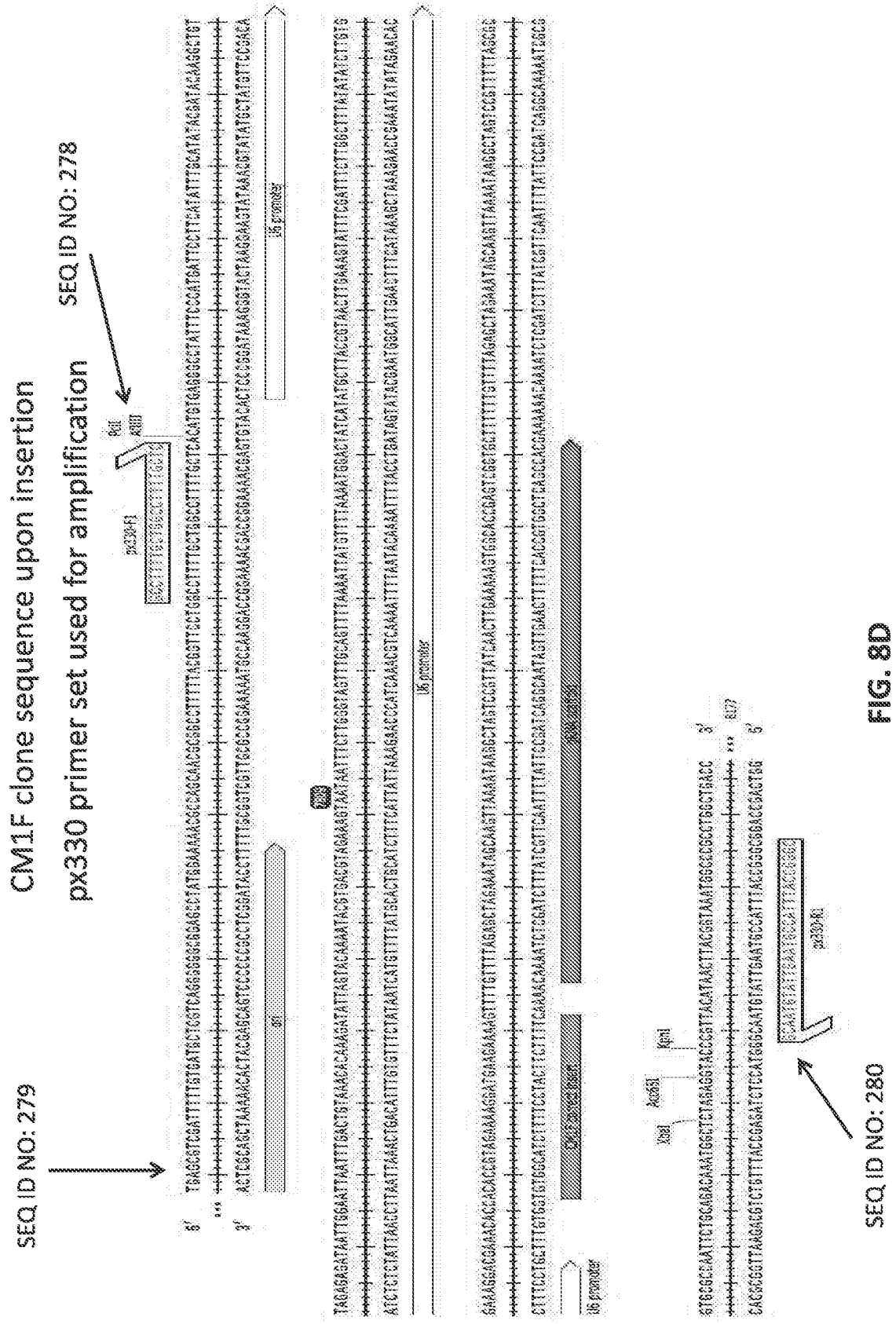

CM1F clone sequence upon insertion
SEQ ID NO: 279
px330 primer set used for amplification
SEQ ID NO: 278
SEQ ID NO: 280
px330-F3
PciI
AflIII
U6 promoter
gRNA
sgRNA scaffold
XbaI
AccIII
KpnI
px330-R3

FIG. 8D

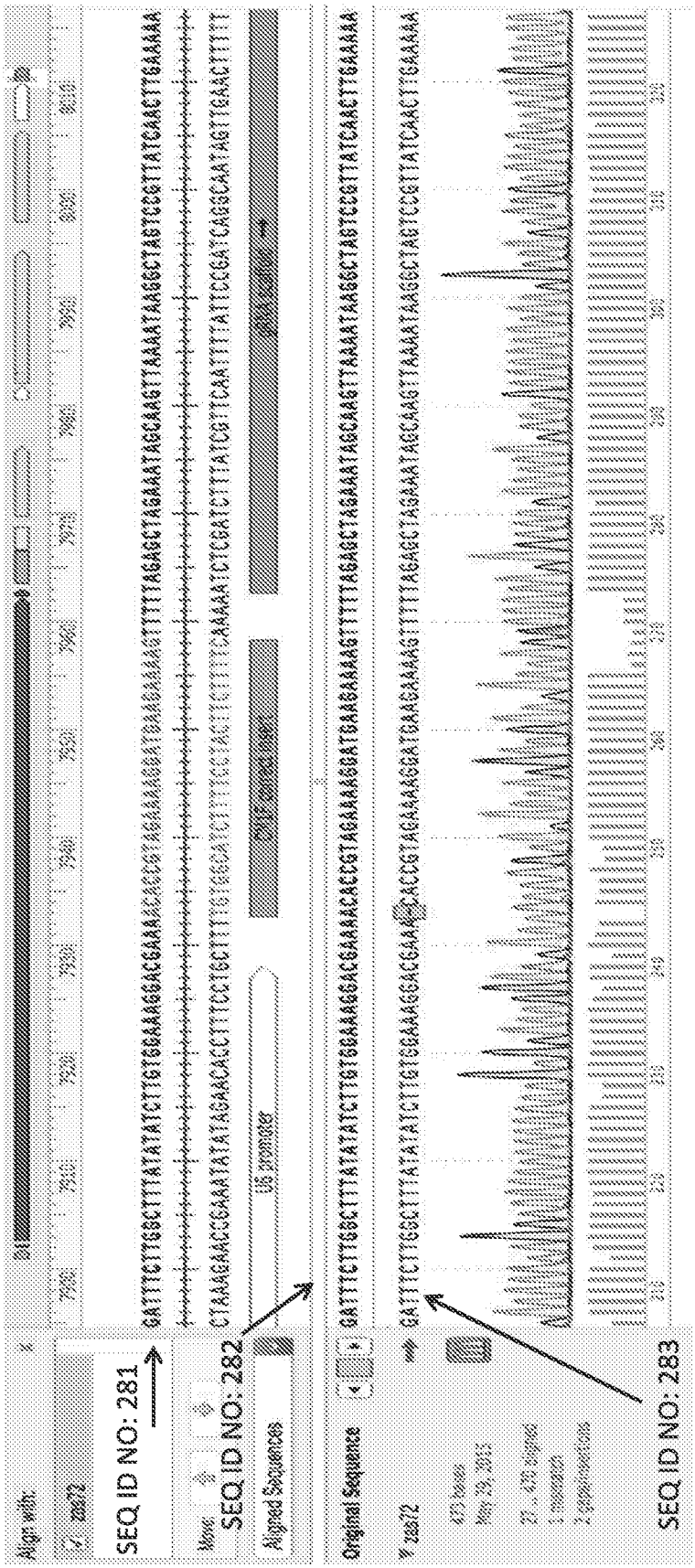

zas72 sequencing result of constructed plasmid (bottom)
shown against the expected clone (top)
SEQ ID NO: 281
SEQ ID NO: 282
SEQ ID NO: 283
Align with:
Aligned Sequences
Original Sequence
zas72
US promoter

FIG. 8E

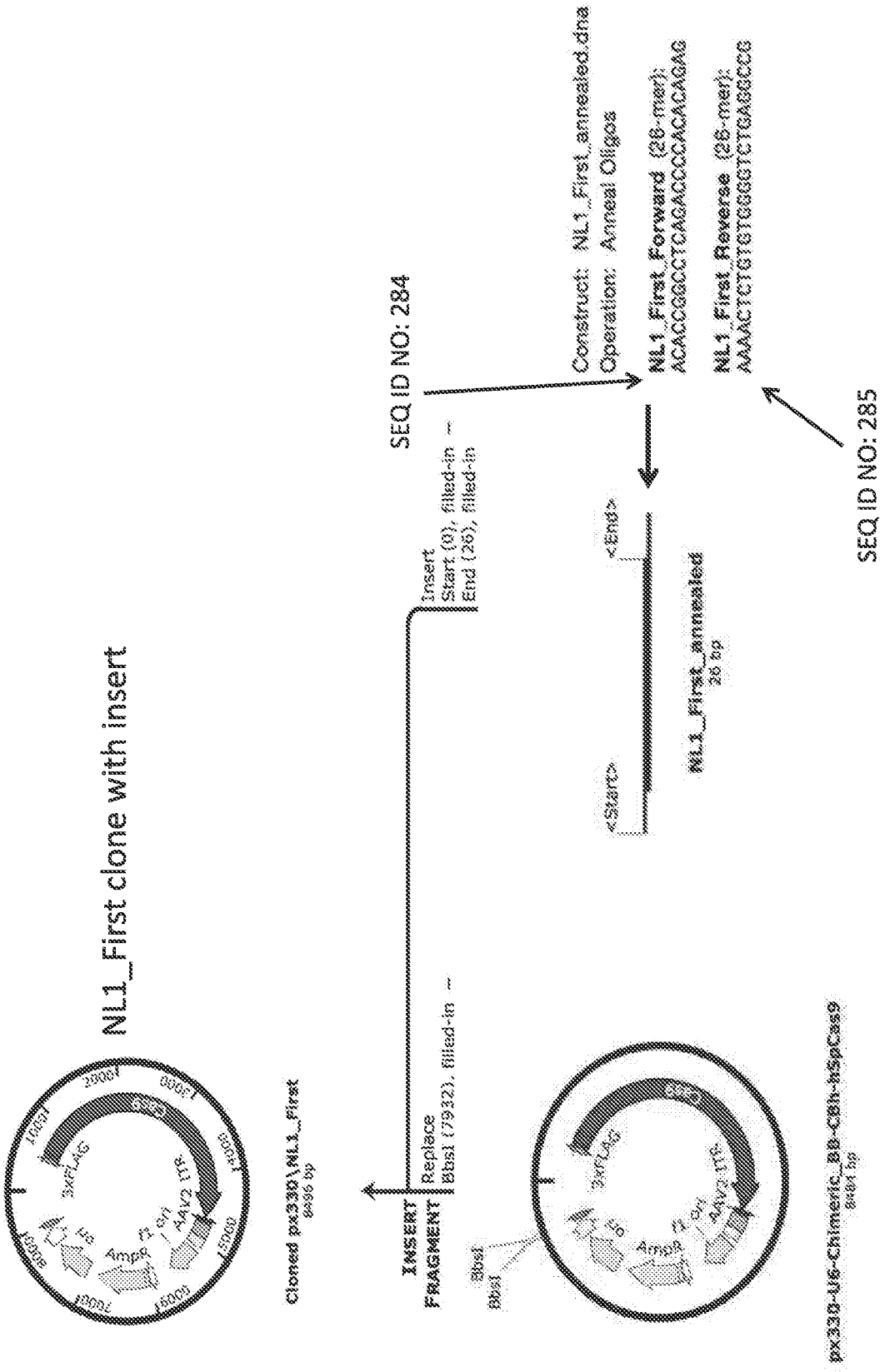

NL1_First clone with insert
Cloned px330\NL1_First
8496 bp
INSERT FRAGMENT
Replace
BbsI (7932), filled-in
BbsI
BbsI
px330-U6-Chimeric_BB-CBh-hSpCas9
8484 bp
Insert
Start (0), filled-in
End (26), filled-in
SEQ ID NO: 284
Construct: NL1_First_annealed.dna
Operation: Anneal Oligos
NL1_First_Forward (26-mer):
ACACCGGCCTCAGACCCCACACAGAG
NL1_First_Reverse (26-mer):
AAACCTCTGTGTGGGGTCTGAGGCCG
SEQ ID NO: 285
<Start>
<End>
NL1_First_annealed
26 bp

FIG. 9A

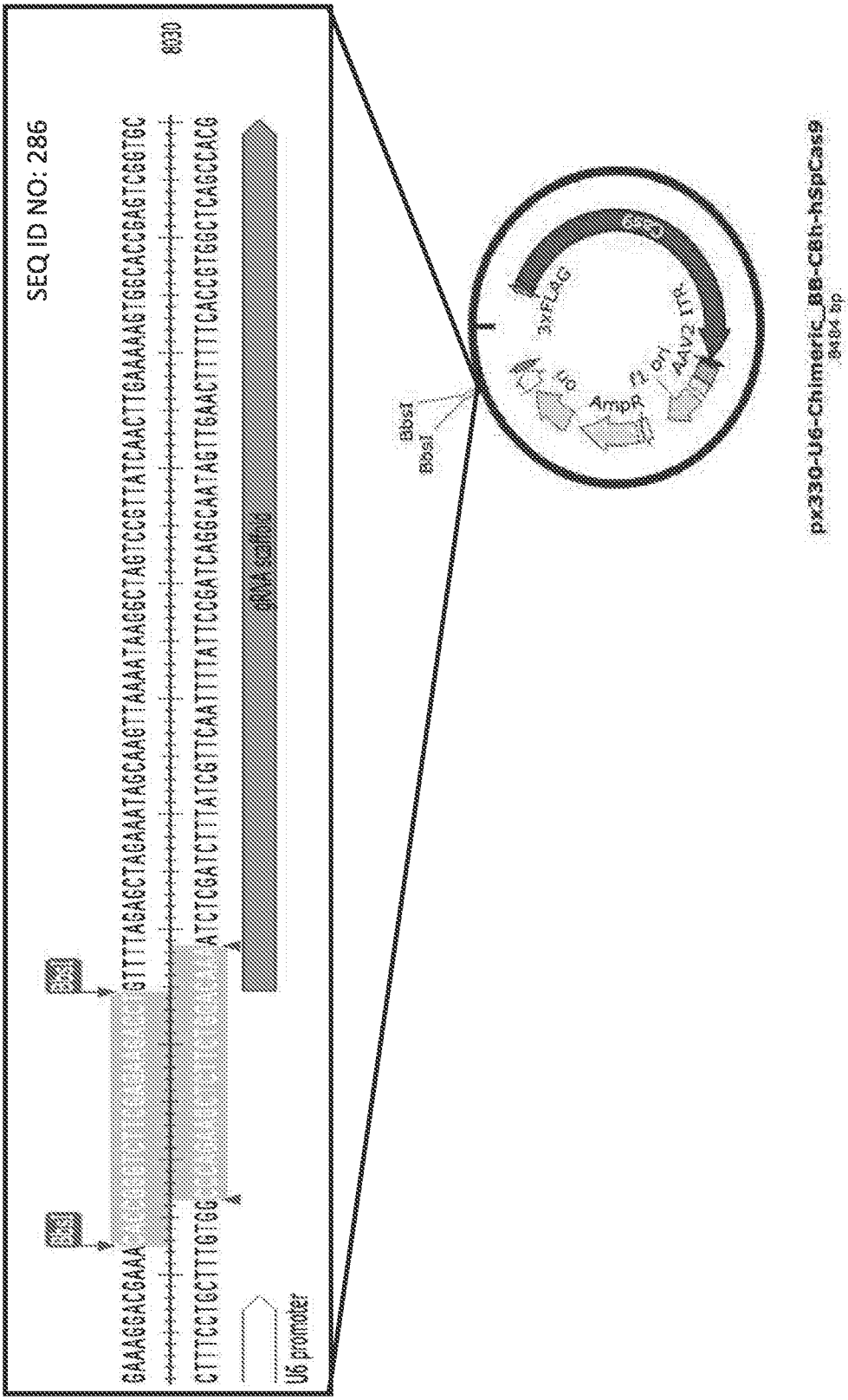

SEQ ID NO: 286
BbsI
BbsI
GAAAGGACGAAA
GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGC
8630
CTTTCCTGCTTTGTGC
ATCTCGATCTTTATCGTTCAATTTTATTCGATCAGGCAATAGTTGAACTTTTTCACCGTGGCTCAGCCACG
gRNA scaffold
U6 promoter
BbsI
BbsI
3xFLAG
CBh
ori
AmpR
f1 ori
AAV2 ITR
px330-U6-Chimeric_BB-CBh-hSpCas9
8484 bp

FIG. 9B

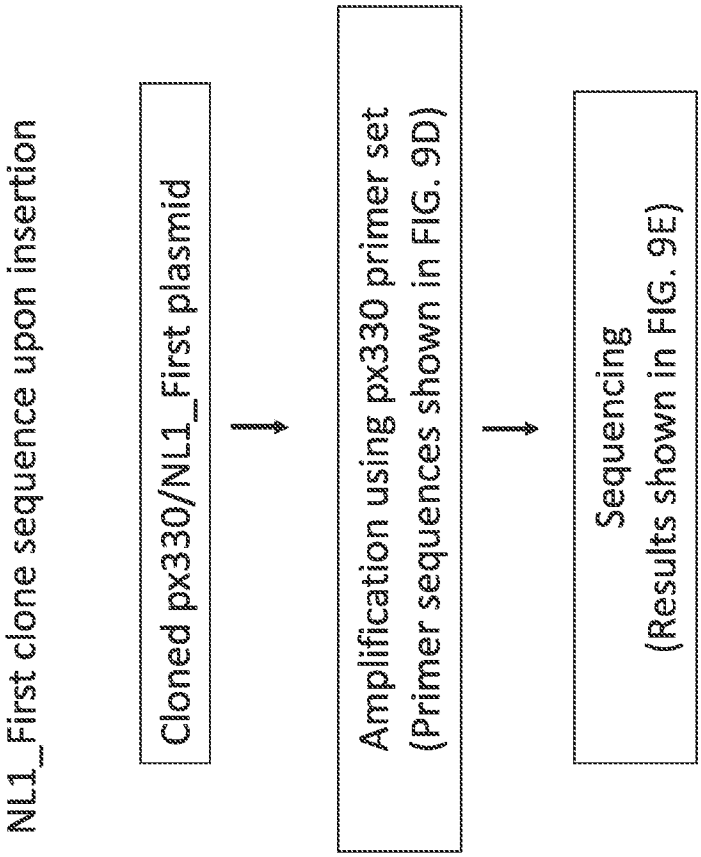

NL1_First clone sequence upon insertion
Cloned px330/NL1_First plasmid
Amplification using px330 primer set
(Primer sequences shown in FIG. 9D)
Sequencing
(Results shown in FIG. 9E)

FIG. 9C

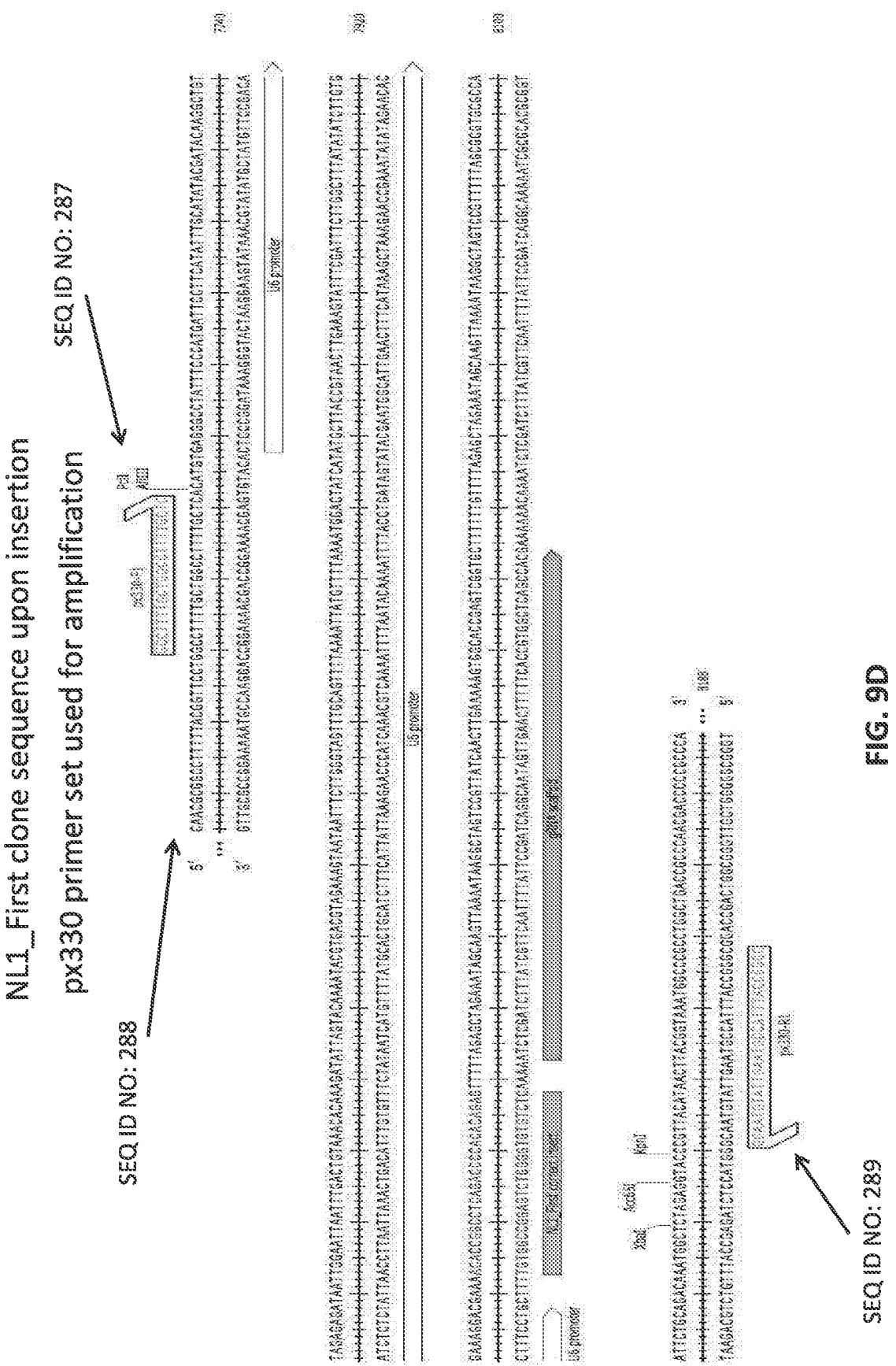

NL1_First clone sequence upon insertion
px330 primer set used for amplification
SEQ ID NO: 287
SEQ ID NO: 288
SEQ ID NO: 289
U6 promoter
XbaI
AccIII
KpnI

FIG. 9D

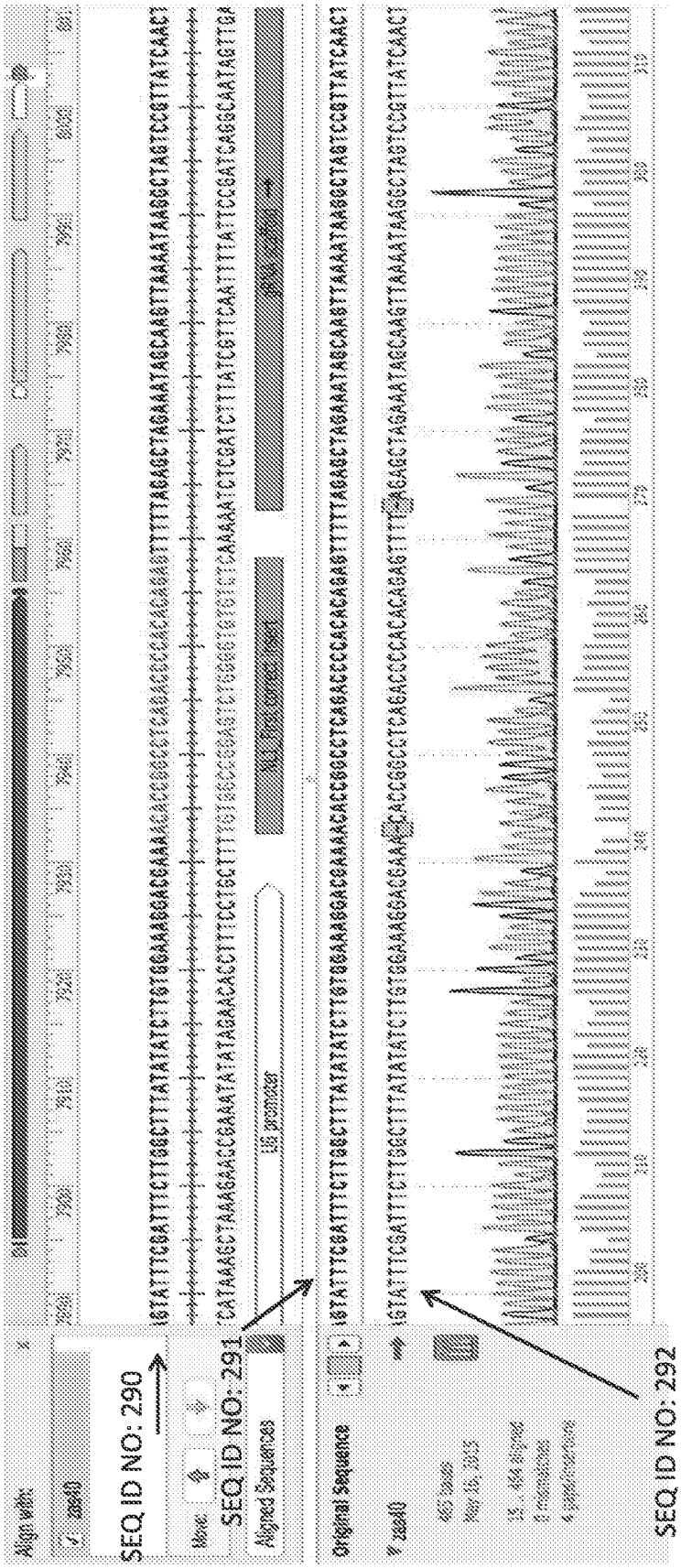

zas40 sequencing result of constructed plasmid (bottom)
shown against the expected clone (top)
SEQ ID NO: 290
SEQ ID NO: 291
SEQ ID NO: 292
Align with:
zas40
Move:
Aligned Sequences
Original Sequence
zas40
U6 promoter
sgRNA scaffold

FIG. 9E

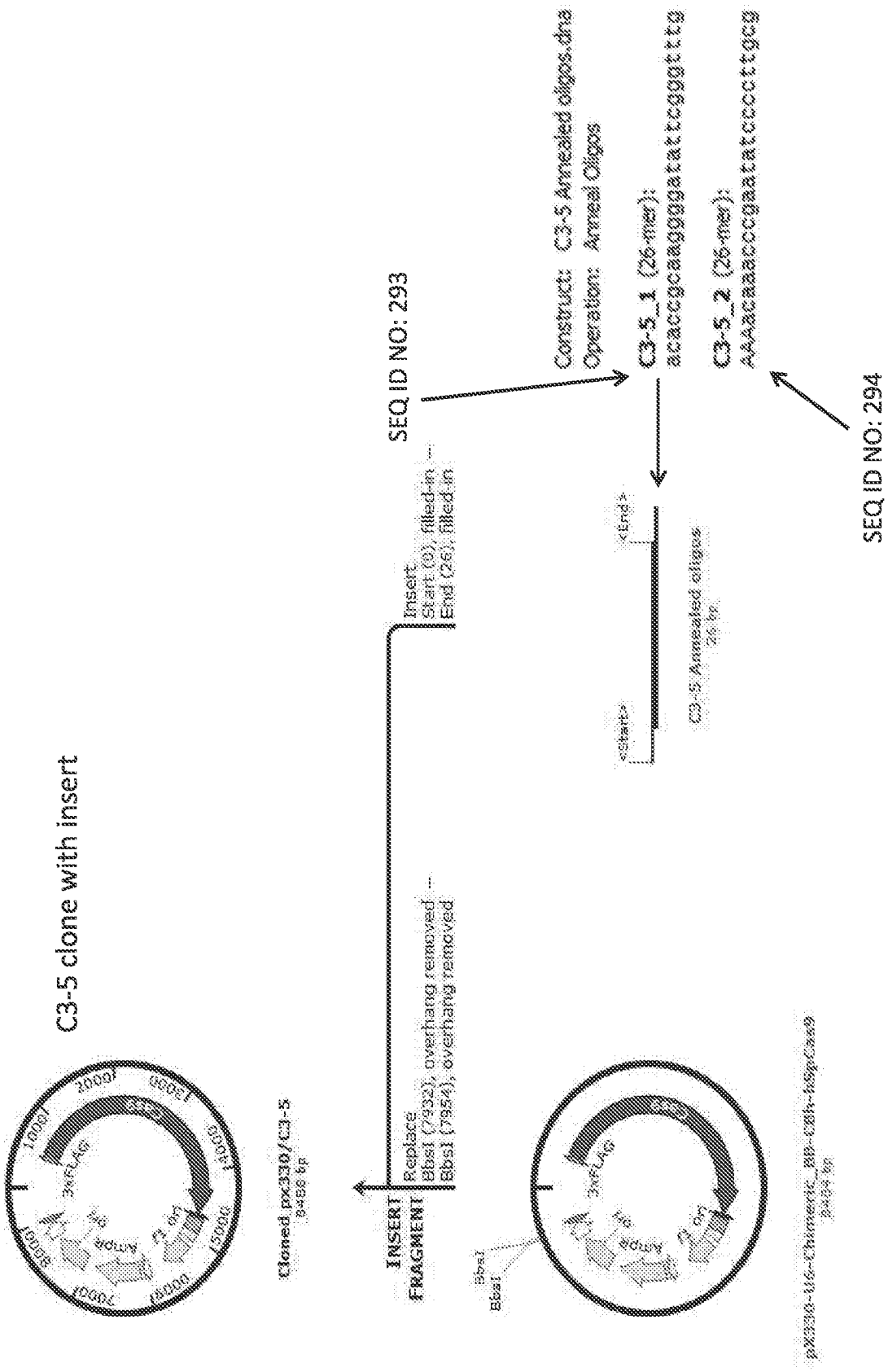

C3-5 clone with insert
Cloned px330/C3-5
INSERT FRAGMENT
Replace
BbsI (7932), overhang removed
BbsI (7954), overhang removed
Insert
Start (0), filled-in
End (26), filled-in
SEQ ID NO: 293
Construct: C3-5 Annealed oligos.dna
Operation: Anneal Oligos
C3-5_1 (26-mer):
acaccgcaaggggatattcgggtttg
C3-5_2 (26-mer):
AAAacaaaacccgaatatcccccttgcg
SEQ ID NO: 294
<start>
<end>
C3-5 Annealed oligos
BbsI
BbsI

FIG. 10A

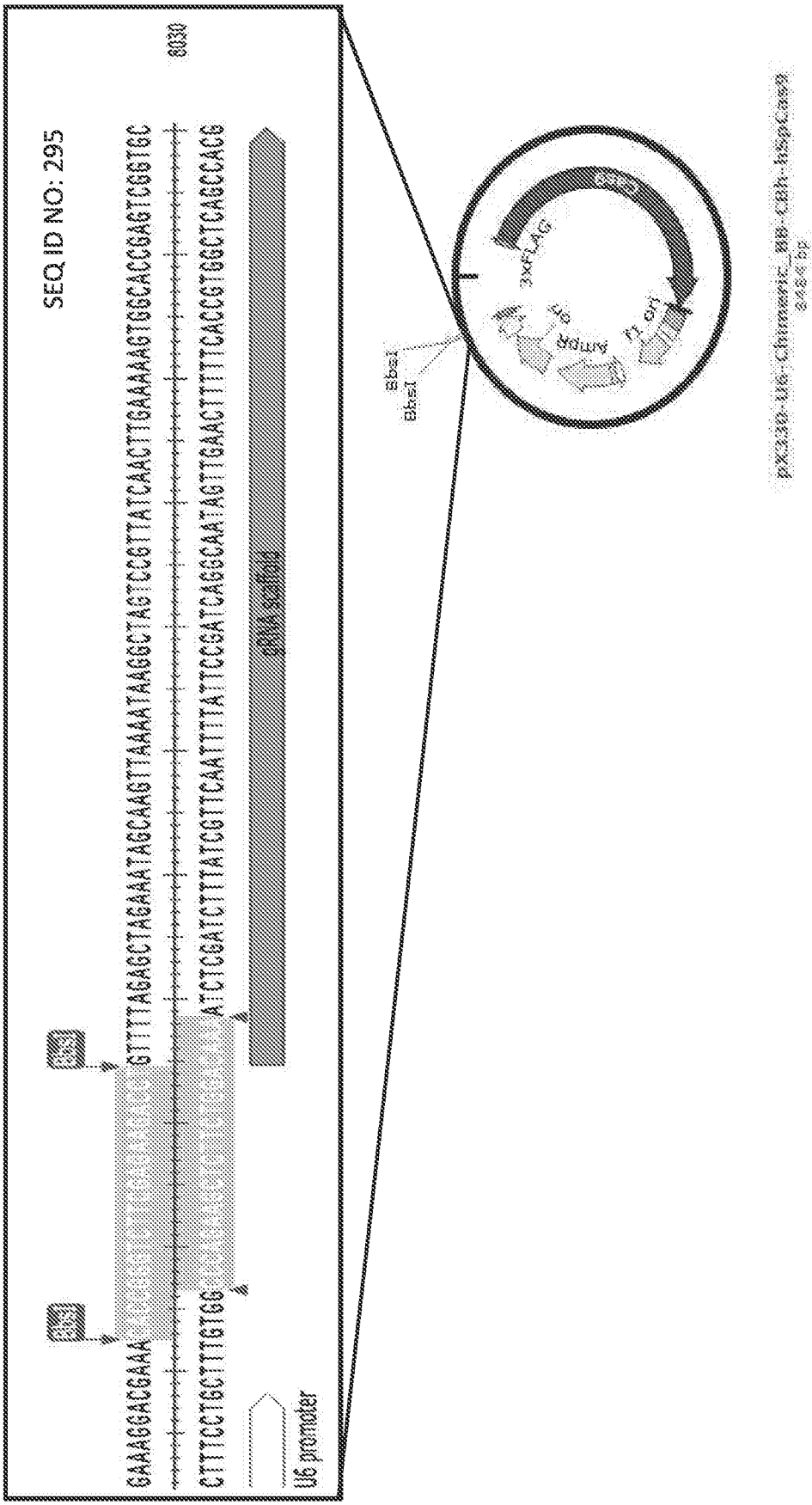

SEQ ID NO: 295
BbsI
BbsI
GAAAGGACGAAA
CTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGC
ATCTCGATCTTTATCGTTCAATTTTATTCCGATCAGGCAATAGTTGAACTTTTTCACCGTGGCTCAGCCAAGG
CTTTCCTGCTTTGTGG
sgRNA scaffold
U6 promoter
pX330-U6-Chimeric_BB-CBh-hSpCas9
8484 bp
3xFLAG
NLS
hSpCas9
NLS
CBh
AmpR
f1 ori
U6

FIG. 10B

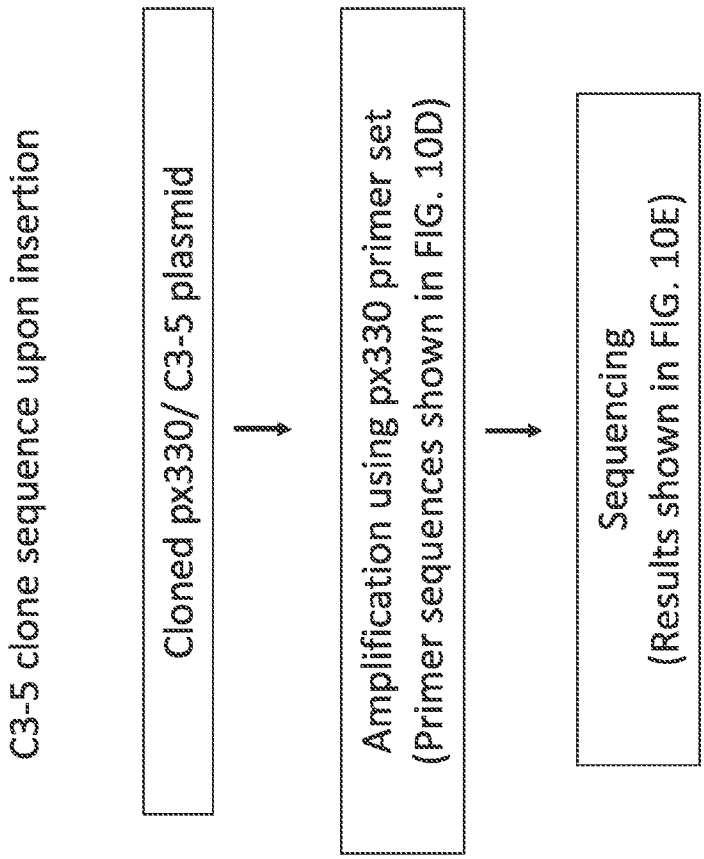

C3-5 clone sequence upon insertion
Cloned px330/ C3-5 plasmid
Amplification using px330 primer set
(Primer sequences shown in FIG. 10D)
Sequencing
(Results shown in FIG. 10E)

FIG. 10C

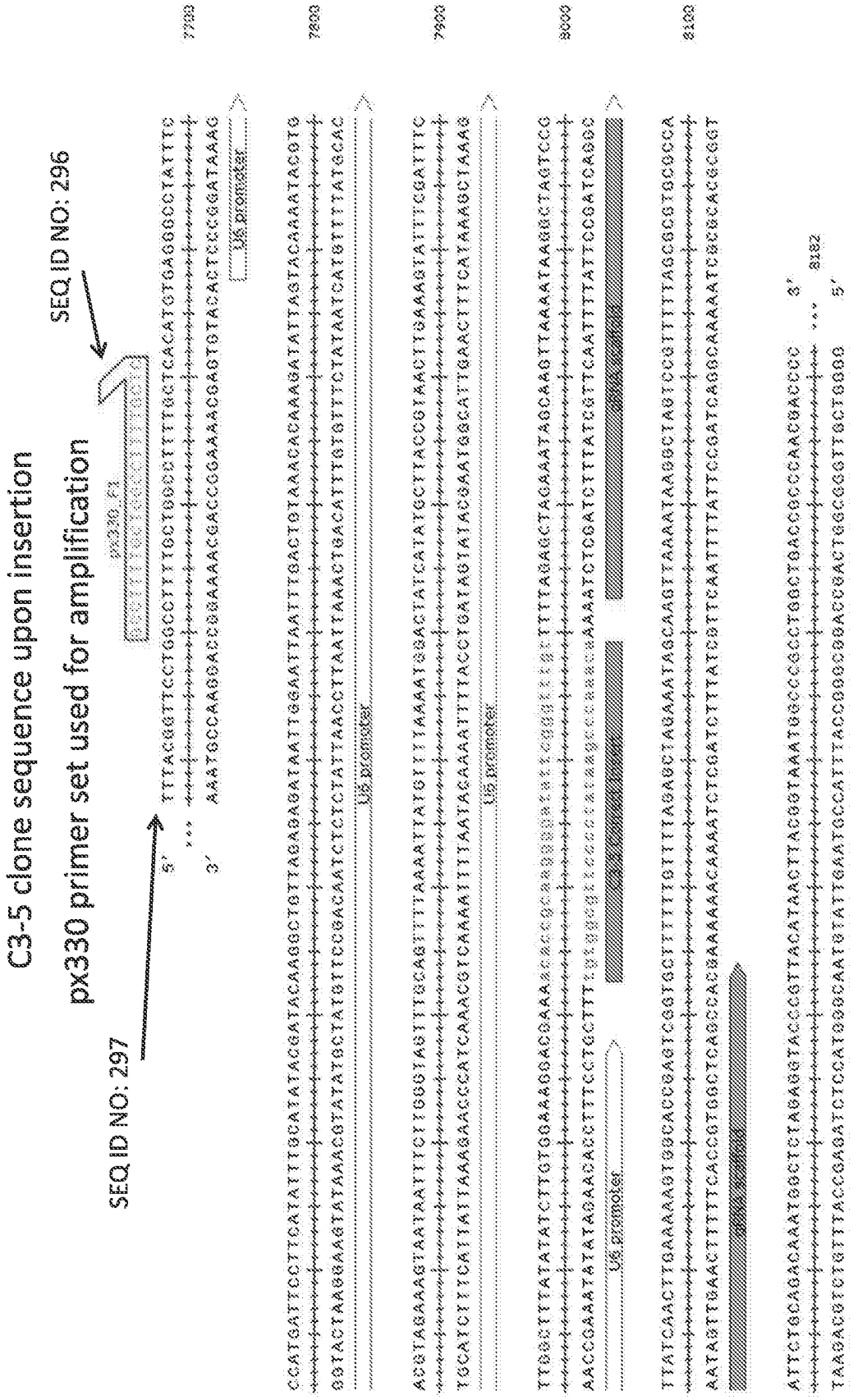

C3-5 clone sequence upon insertion
px330 primer set used for amplification
SEQ ID NO: 296
SEQ ID NO: 297
SEQ ID NO: 298
px330_F1
px330_R1
U6 promoter
U6 promoter
U6 promoter
U6 promoter
5'
3'
7200
7800
7900
8000
8100
8182

FIG. 10D

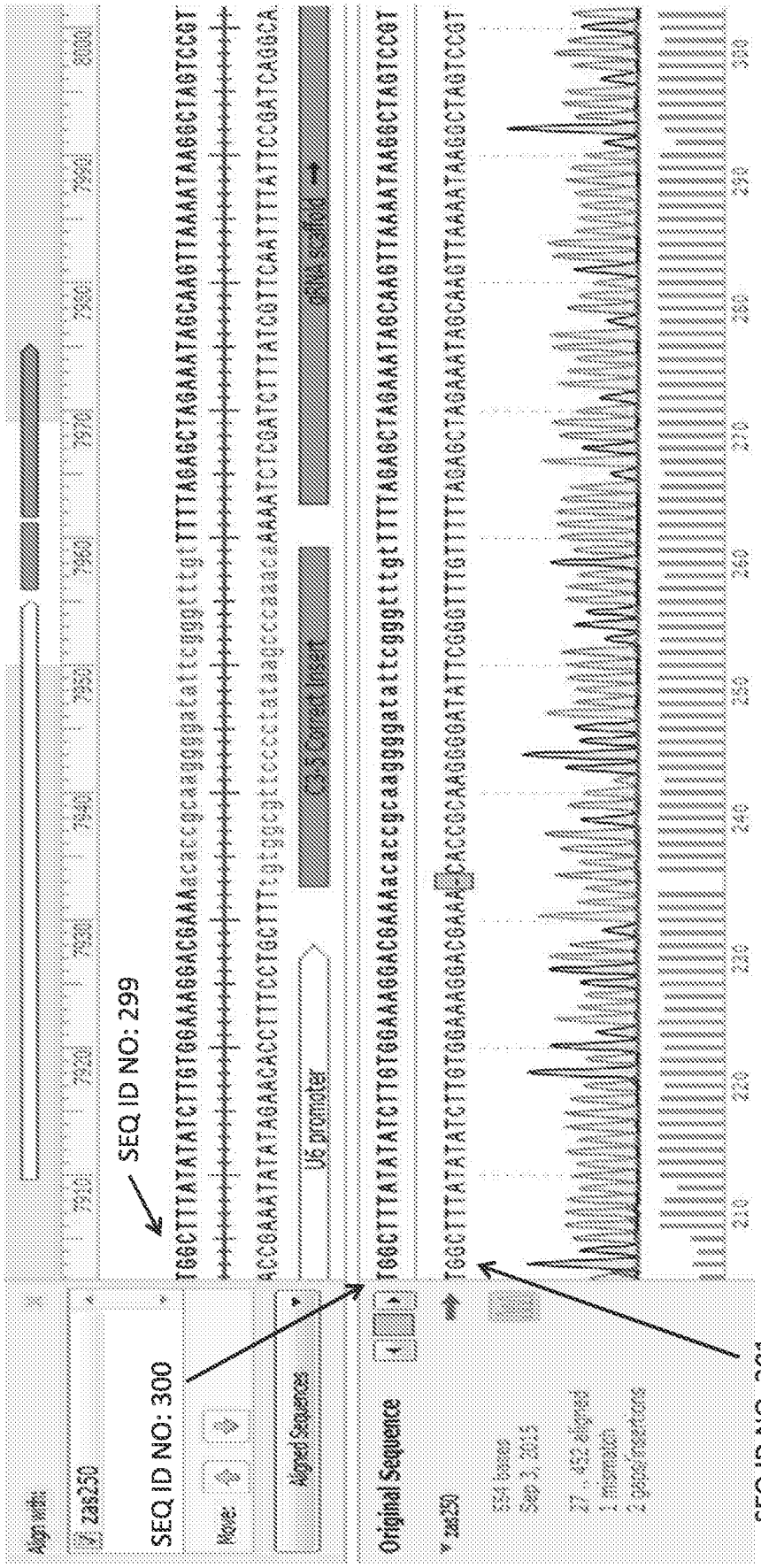

zas250 sequencing result of constructed plasmid (bottom)
shown against the expected clone (top)
SEQ ID NO: 299
SEQ ID NO: 300
SEQ ID NO: 301
U6 promoter
Original Sequence
zas250

FIG. 10E

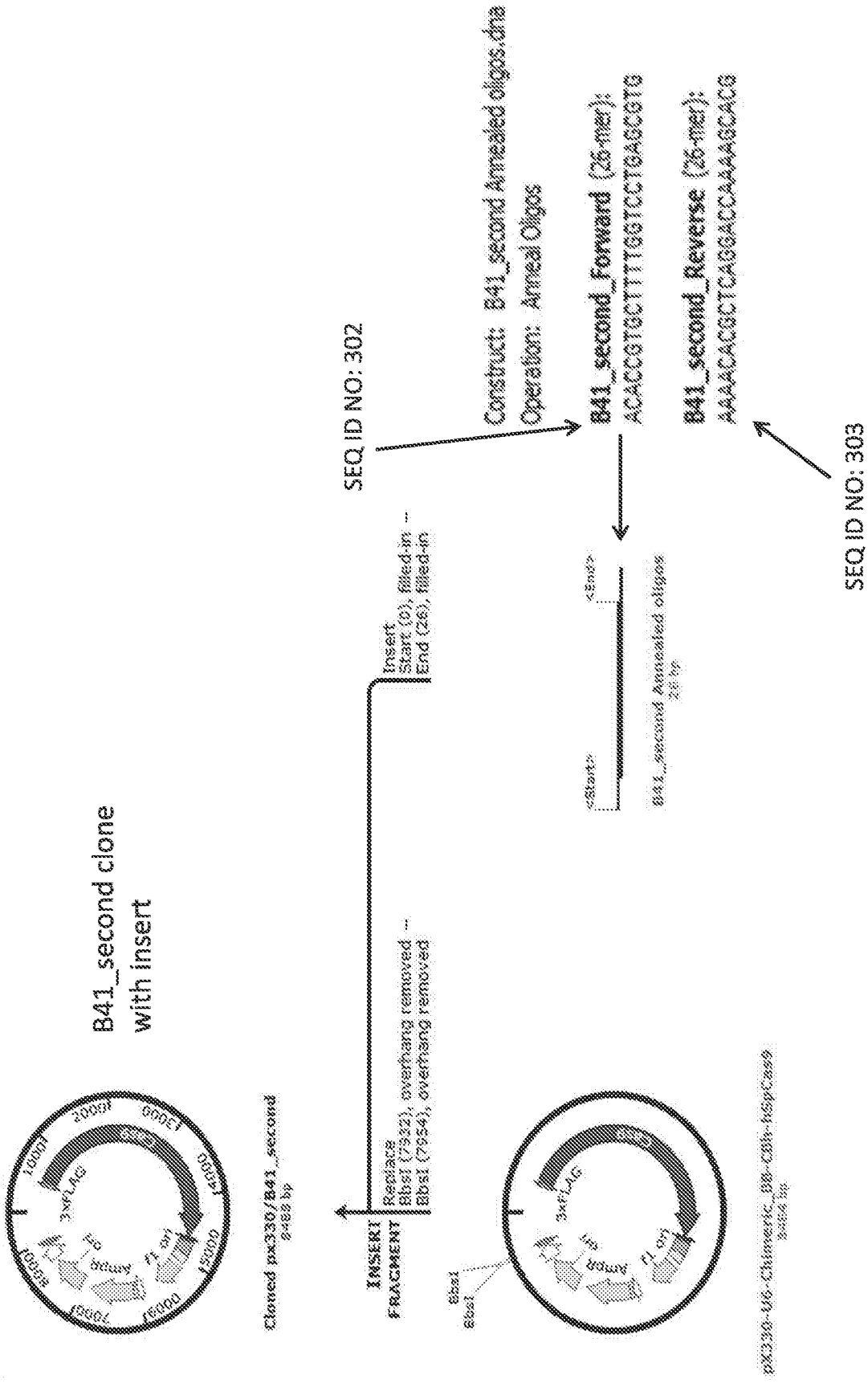

B41_second clone
with insert
SEQ ID NO: 302
Construct: B41_second Annealed oligos.dna
Operation: Anneal Oligos
B41_second_Forward (26-mer):
ACACCGTGCTTTTGGTCCTGAGCGTG
B41_second_Reverse (26-mer):
AAAACACGCTCAGGACCAAAAGCACG
SEQ ID NO: 303
INSERT FRAGMENT
Replace
BbsI (7332), overhang removed
BbsI (7654), overhang removed
Insert
Start (0), filled-in
End (26), filled-in
<Start>
<End>
B41_second Annealed oligos
2.6 kb
BbsI
BbsI
pX330-U6-Chimeric_BB-CBh-hSpCas9

FIG. 11A

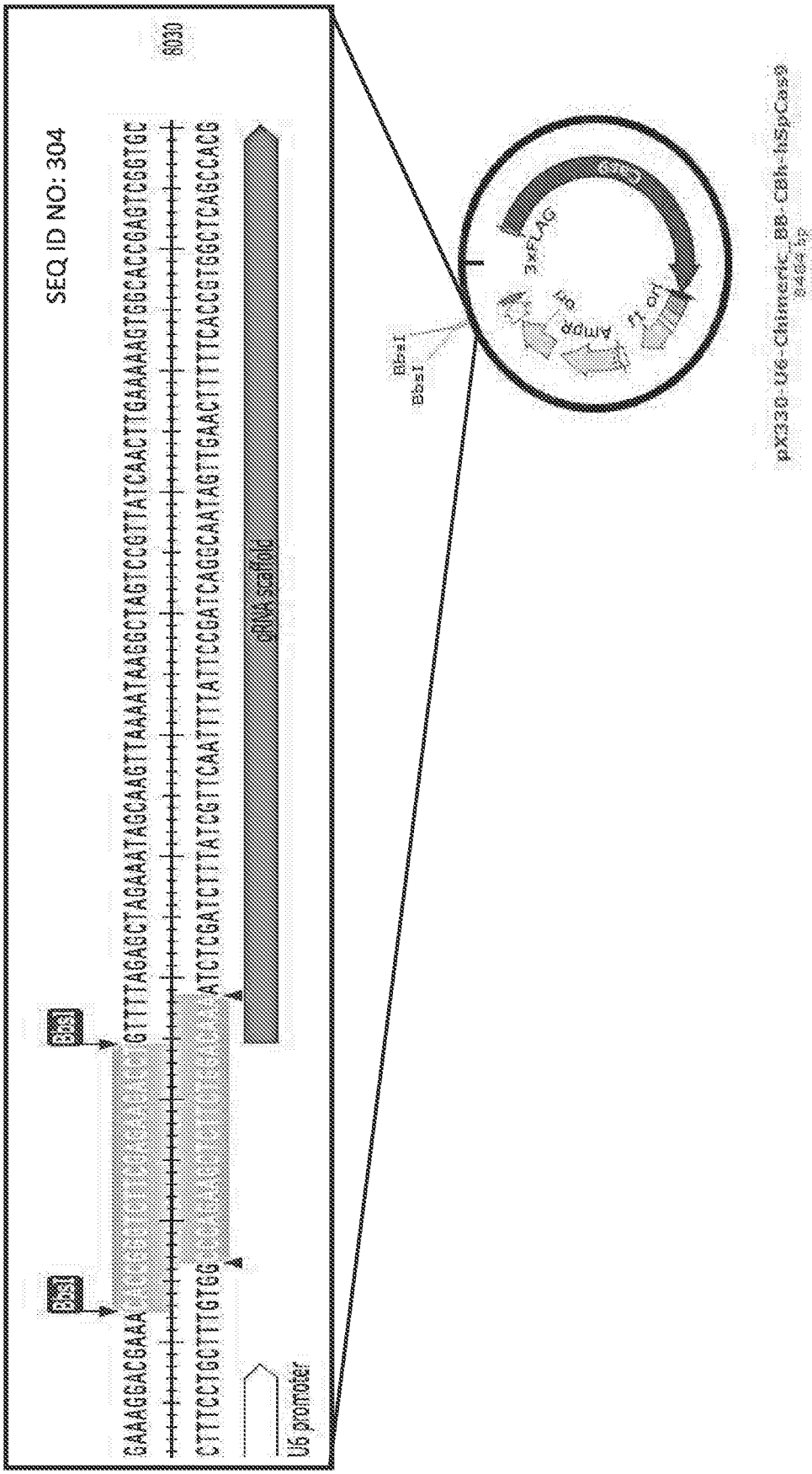

SEQ ID NO: 304
BbsI
BbsI
GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGC
ATCTCGATCTTTATCGTTCAATTTTATTCGATCAGGCAATAGTTGAACTTTTTCACCGTGGGTCAGGCACG
CTTTCCTGCTTTGTGG
gRNA scaffold
U6 promoter
8030
BbsI
BbsI
3xFLAG
AmpR
f1 ori
pX330-U6-Chimeric_BB-CBh-hSpCas9
8464 bp

FIG. 11B

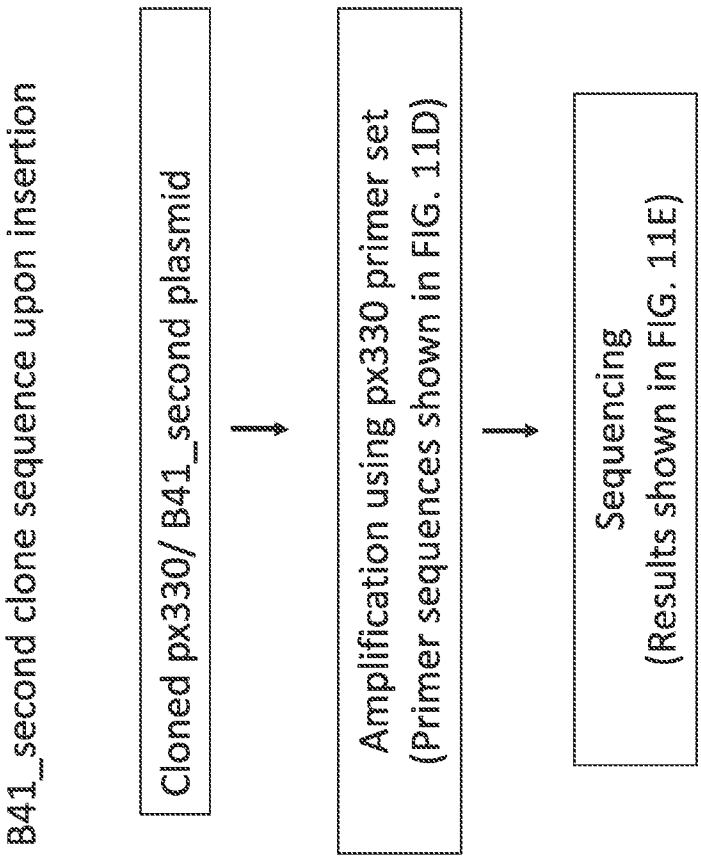

B41_second clone sequence upon insertion
Cloned px330/ B41_second plasmid
Amplification using px330 primer set
(Primer sequences shown in FIG. 11D)
Sequencing
(Results shown in FIG. 11E)

FIG. 11C

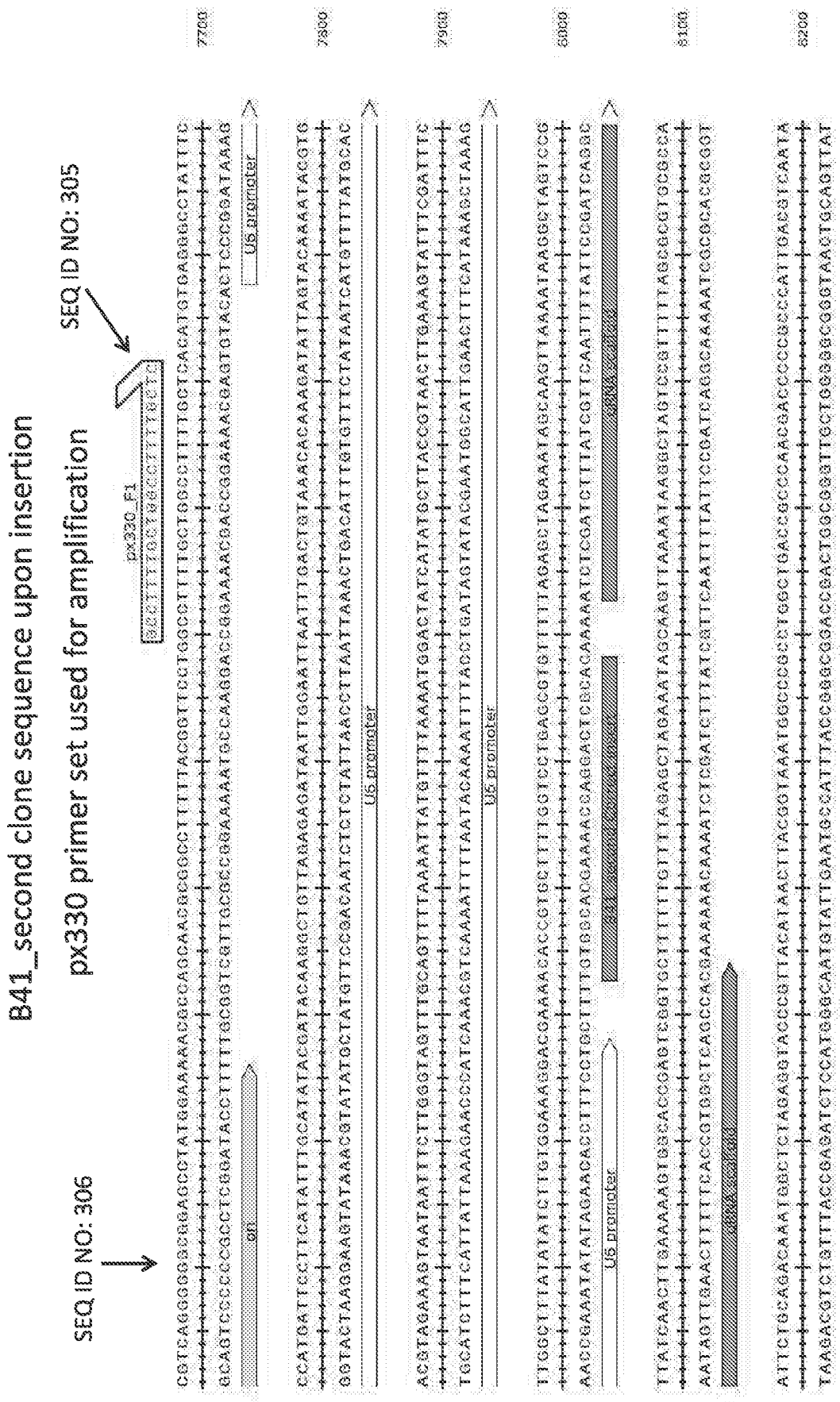

B41_second clone sequence upon insertion
px330 primer set used for amplification
SEQ ID NO: 305
SEQ ID NO: 306
SEQ ID NO: 307
px330_F1
px330-R1
U6 promoter
gRNA scaffold
7700
7800
7900
8000
8100
8200

FIG. 11D

KVM1_F01_005 sequencing result of constructed plasmid (bottom)
shown against the expected clone (top)

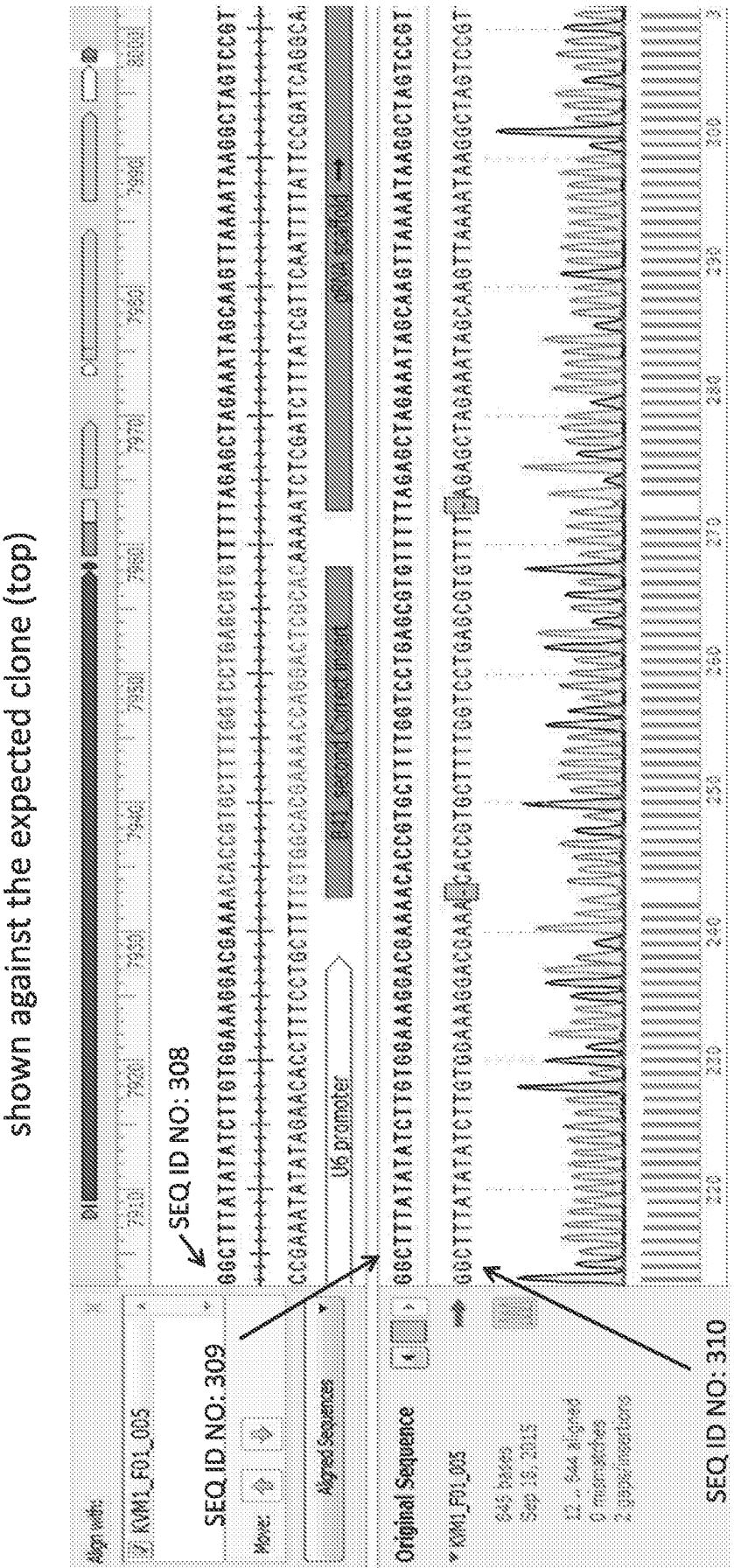


FIG. 11E

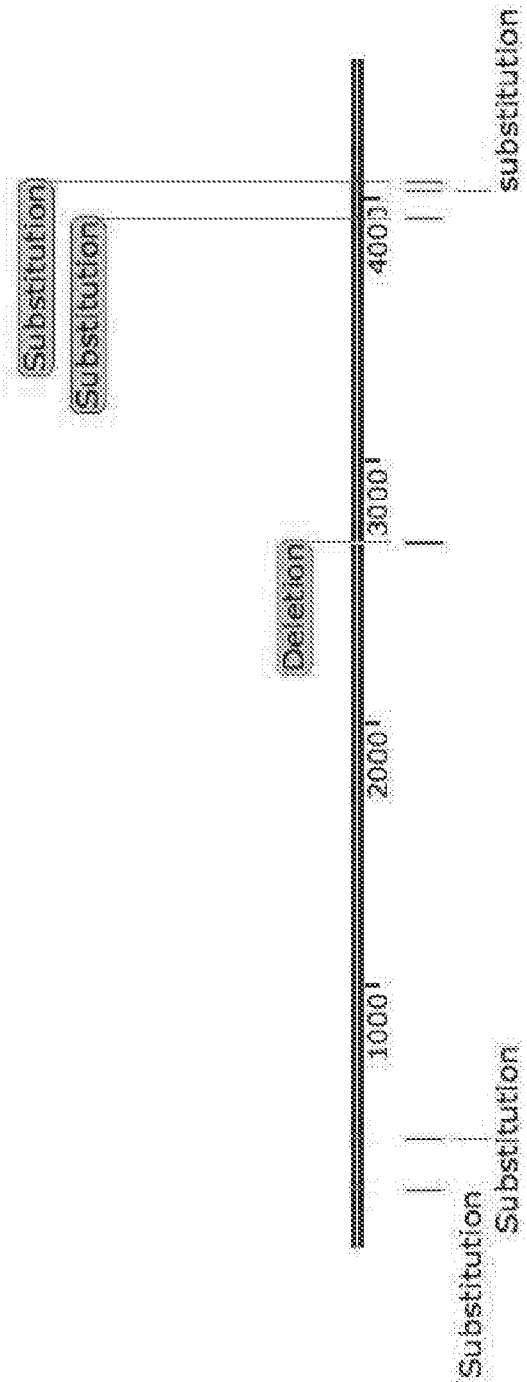

Substitution
Substitution
Deletion
Substitution
Substitution
1000
2000
3000
4000
4524 bp

FIG. 12

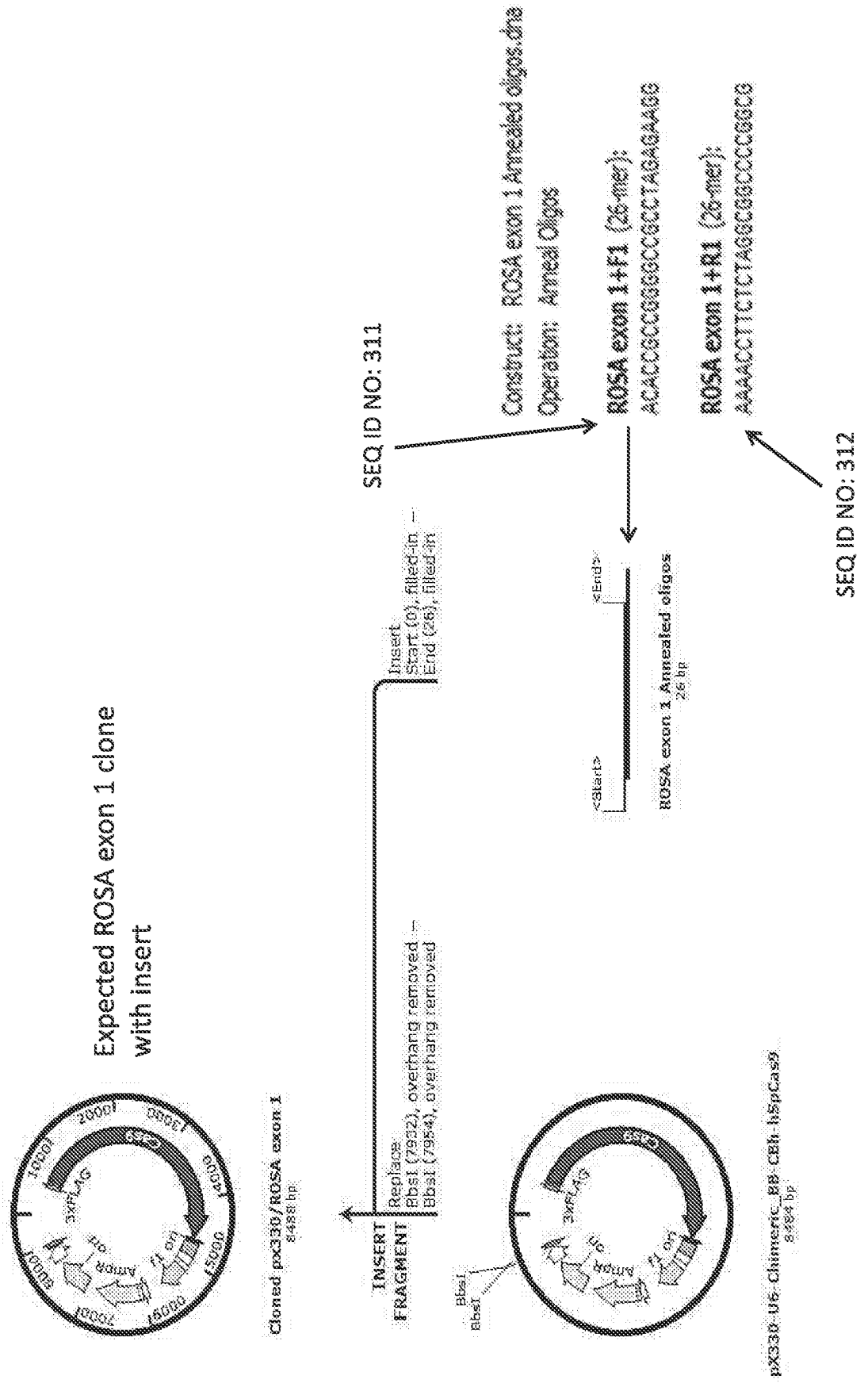

Expected ROSA exon 1 clone with insert
Cloned px330/ROSA exon 1
8488 bp
INSERT FRAGMENT
Replace
BbsI (7932), overhang removed
BbsI (7954), overhang removed
Insert
Start (0), filled-in
End (26), filled-in
pX330-U6-Chimeric_BB-CBh-hSpCas9
8464 bp
BbsI
BbsI
SEQ ID NO: 311
Construct: ROSA exon 1 Annealed oligos.dna
Operation: Anneal Oligos
ROSA exon 1+F1 (26-mer):
ACACCGCCCGGGGCCGCCTAGAGAAGG
ROSA exon 1+R1 (26-mer):
AAAACCTTCTCTAGGCGGCCCCGGGCG
<Start>
<End>
ROSA exon 1 Annealed oligos
26 bp
SEQ ID NO: 312

FIG. 13A

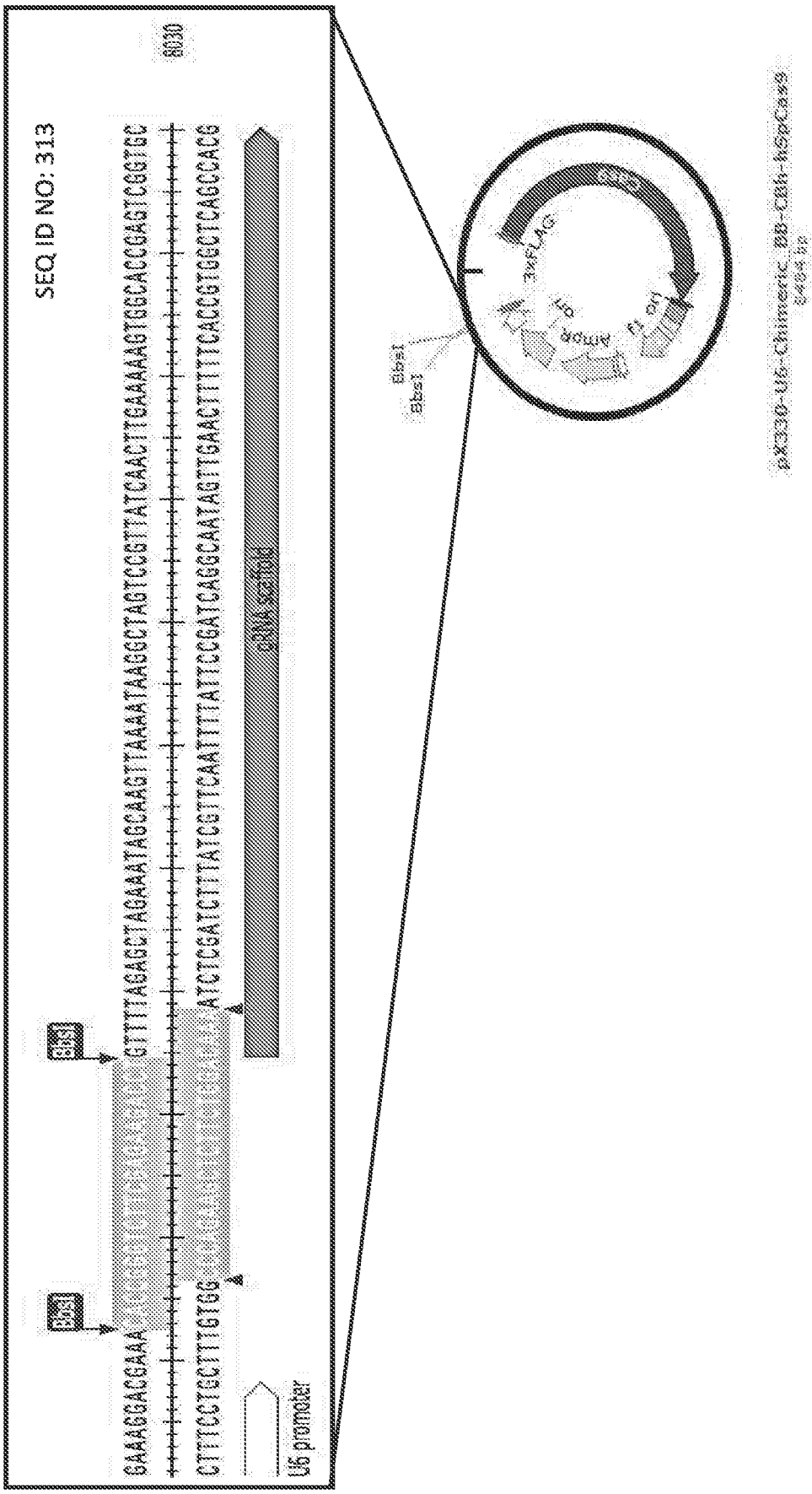

SEQ ID NO: 313
8030
BbsI
BbsI
GAAAGGACGAAA
GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGC
CTTTCCTGCTTTGTGG
ATCTCGATCTTTATCGTTCAATTTTATTCCGATCAGGCAATAGTTGAACTTTTTCACCGTGGCTCAGGCACG
gRNA scaffold
U6 promoter
BbsI
BbsI
CBh
3xFLAG
NLS
SpCas9
f1 ori
pX330-U6-Chimeric_BB-CBh-hSpCas9
8486 bp

FIG. 13B

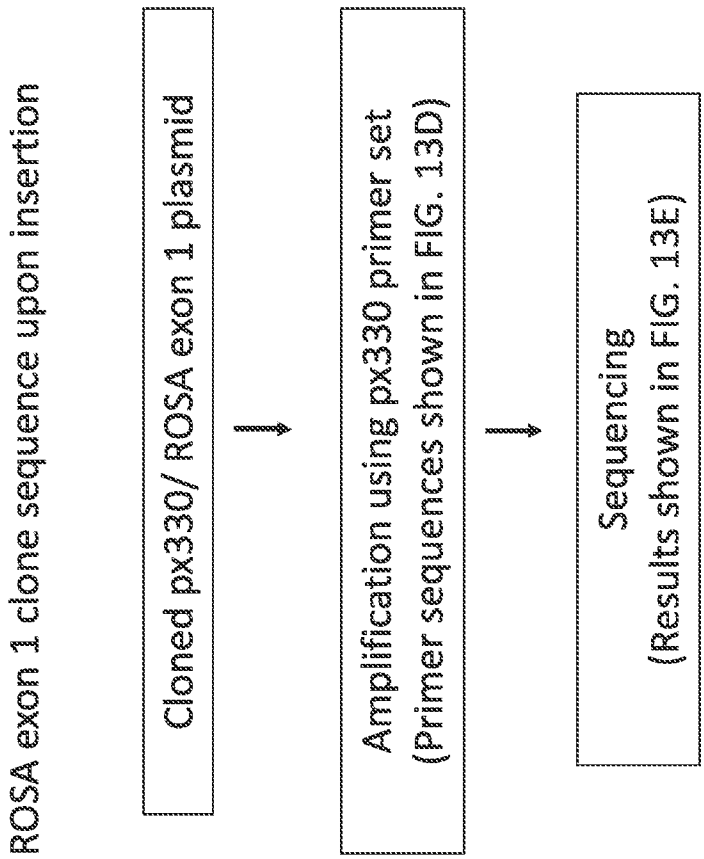

ROSA exon 1 clone sequence upon insertion
Cloned px330/ ROSA exon 1 plasmid
Amplification using px330 primer set
(Primer sequences shown in FIG. 13D)
Sequencing
(Results shown in FIG. 13E)

FIG. 13C

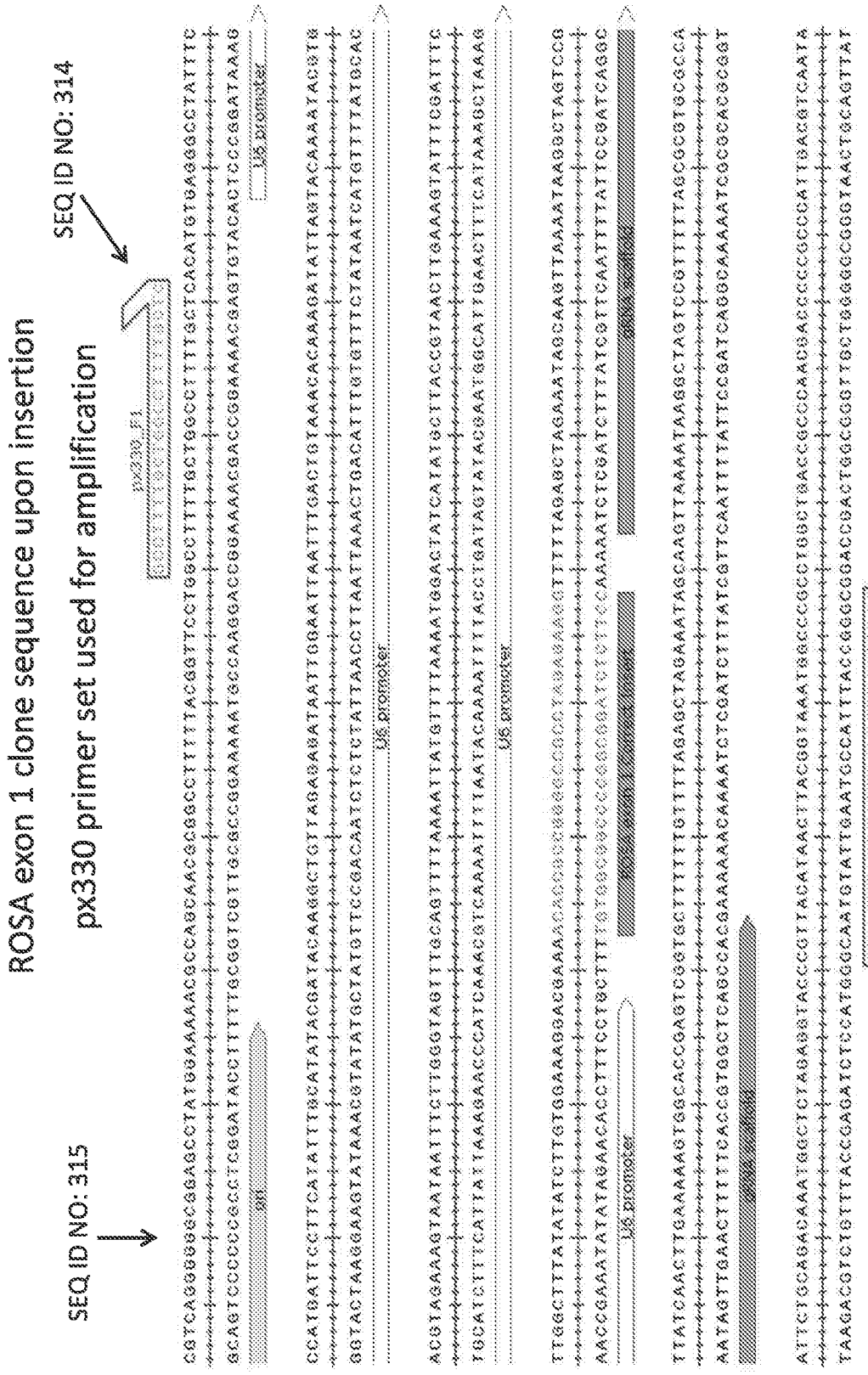

ROSA exon 1 clone sequence upon insertion
SEQ ID NO: 315
px330 primer set used for amplification
SEQ ID NO: 314
px330_F1
U6 promoter
SEQ ID NO: 316
px330-R1

FIG. 13D

RNC1_E02_008 sequencing result of constructed plasmid (bottom)
shown against the expected clone (top)

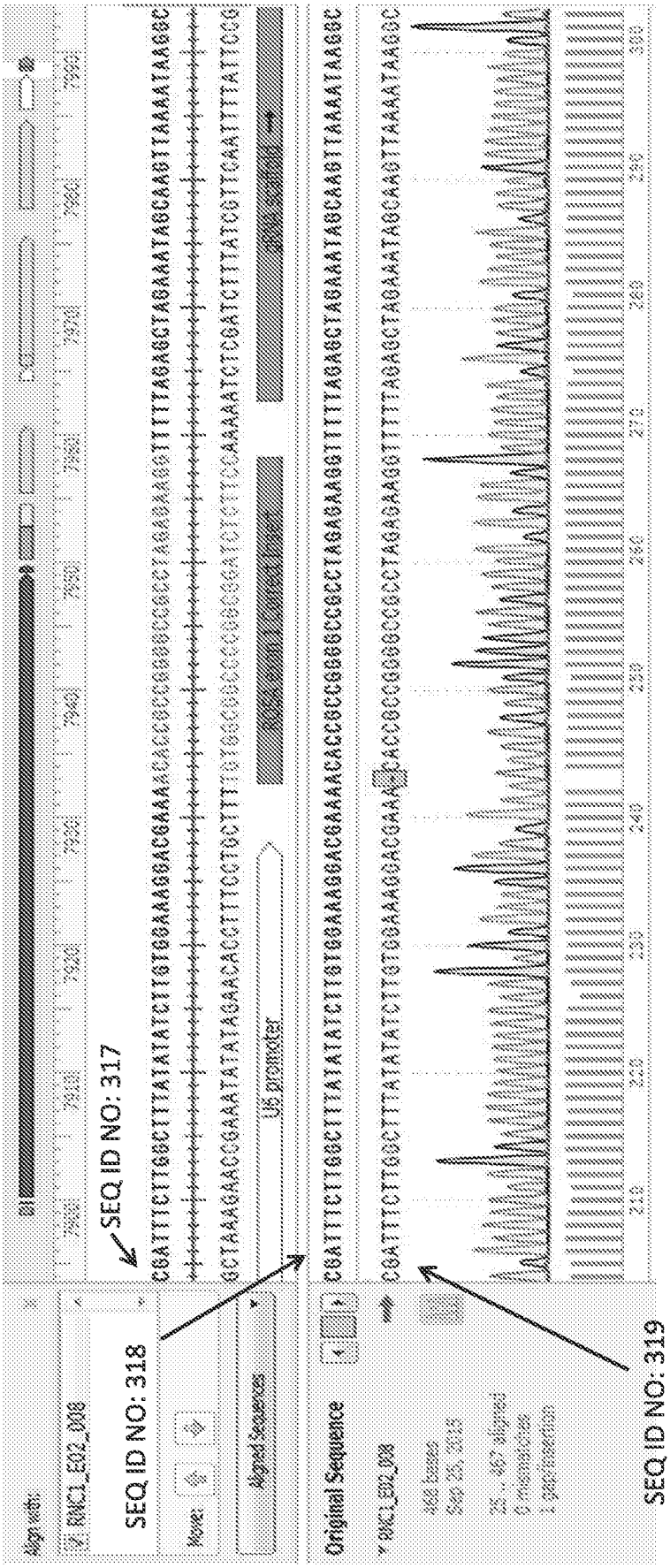


FIG. 13E

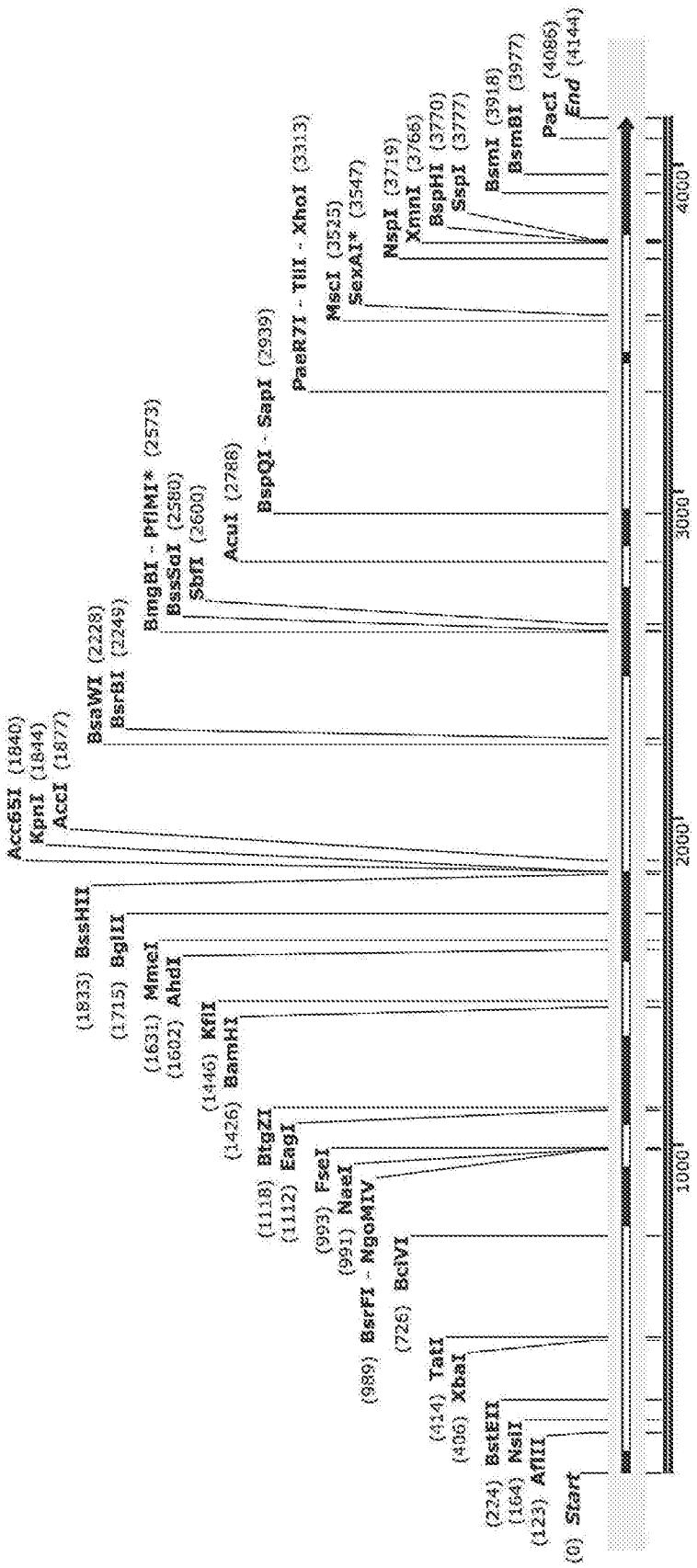

(0) Start
(123) AflII
(164) NsiI
(224) BstEII
(406) XbaI
(414) TatI
(726) BclVI
(989) BsrFI - NgoMIV
(991) NaeI
(993) FseI
(1112) EagI
(1118) BtgZI
(1426) BamHI
(1446) KflI
(1602) AhdI
(1631) MmeI
(1715) BglII
(1833) BssHII
Acc65I (1840)
KpnI (1844)
AccI (1877)
BsaWI (2229)
BsrBI (2249)
BmgBI - PflMI* (2573)
BssSaI (2580)
SbfI (2600)
AcuI (2786)
BspQI - SapI (2939)
PaeR7I - XhoI (3313)
MscI (3535)
SexAI* (3547)
NspI (3719)
XmnI (3766)
BspHI (3770)
SspI (3777)
BsmI (3918)
BsmBI (3977)
PacI (4086)
End (4144)
1000
2000
3000
4000

FIG. 14A

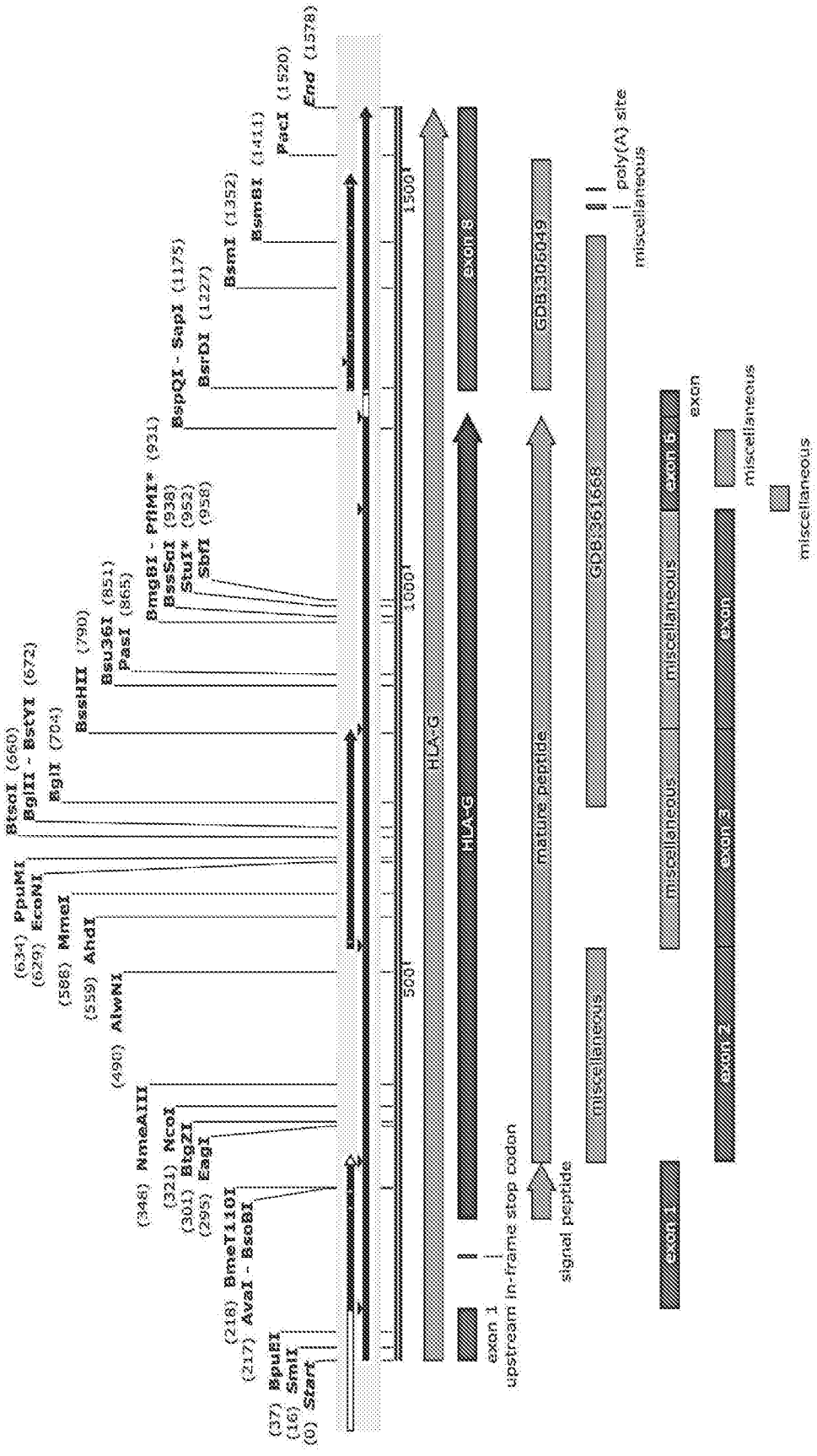

BtsaI (660)
BglII - BstYI (672)
BglI (704)
BssHII (790)
Bsu36I (851)
PasI (865)
BmgBI - PflMI* (931)
BssSaI (938)
StuI* (952)
SbfI (958)
BspQI - SapI (1175)
BsrDI (1227)
BsmI (1352)
BsmBI (1411)
PacI (1520)
End (1578)
(634) PpuMI
(629) EcoNI
(586) MmeI
(559) AhdI
(496) AlwNI
(348) NmeAIII
(321) NcoI
(301) BtgZI
(299) EagI
(218) BmeT110I
(217) AvaI - BsoBI
(37) BpuEI
(16) SmlI
(0) Start
500
1000
1500
HLA-G
exon 8
exon 1
upstream in-frame stop codon
signal peptide
mature peptide
miscellaneous
GDB:361668
GDB:306049
poly(A) site
miscellaneous
exon 7
miscellaneous
exon 6
exon 5
exon 4
exon 3
exon 2
exon
miscellaneous
miscellaneous

FIG. 14B

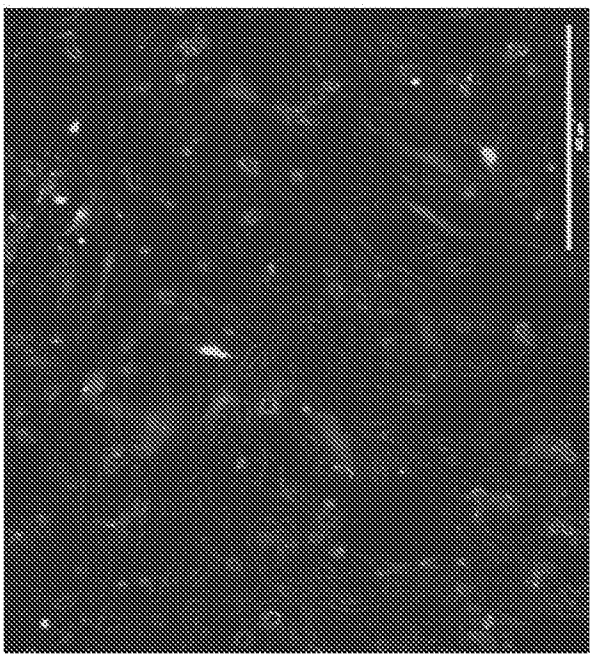


FIG. 15

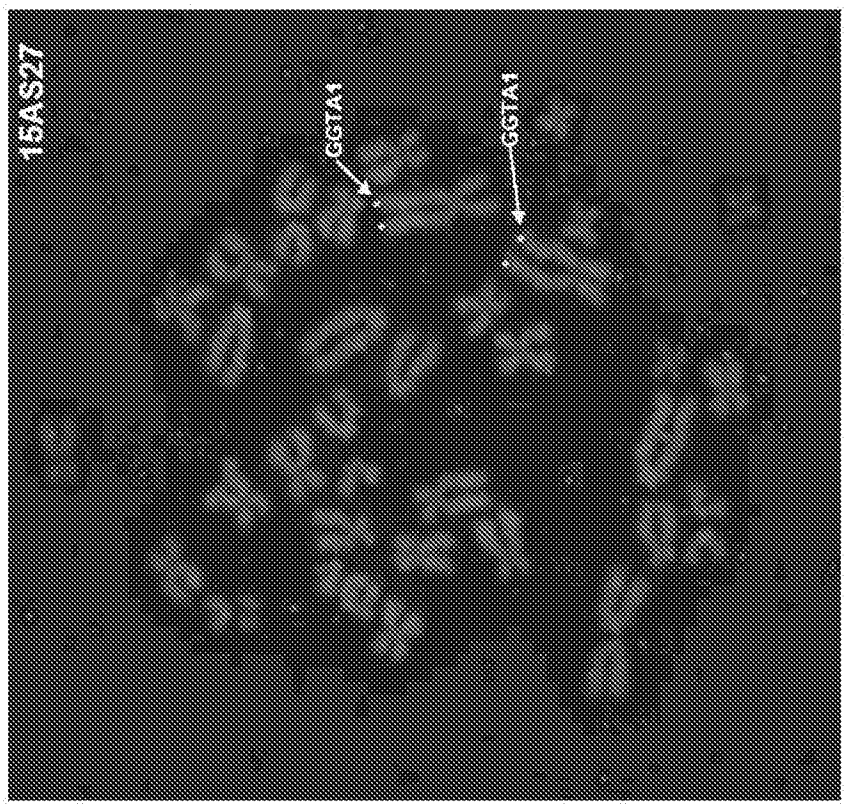
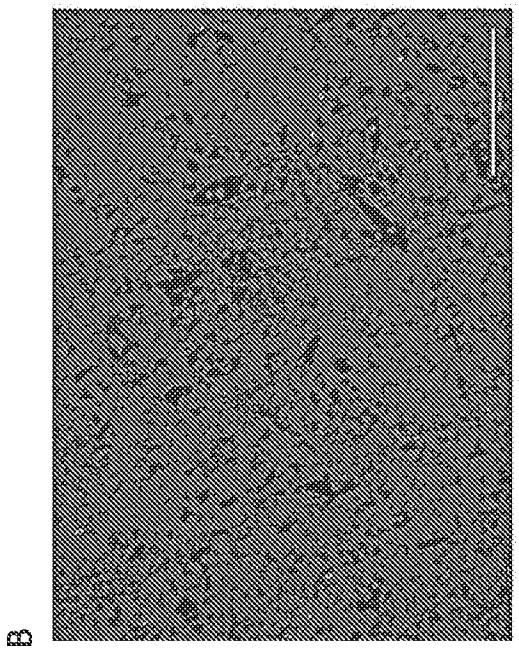


FIG. 16



B

FIG. 17B

A

FIG. 17A

Pregnancy 1 Fetuses:
Sequencing for GGTA1 gene
SEQ ID NO: 320
CRISPR target site
Reference +
Reference -
Target gene
SEQ ID NO: 321
Met Asn Val Lys Gly Arg Val Val Leu Ser Met
Fetus 1
Fetus 2
Fetus 3
Fetus 4
Fetus 5
Fetus 6
Fetus 7
SEQ ID NO: 322
SEQ ID NO: 323
SEQ ID NO: 324
SEQ ID NO: 325
SEQ ID NO: 326
SEQ ID NO: 327
SEQ ID NO: 328

FIG. 18A

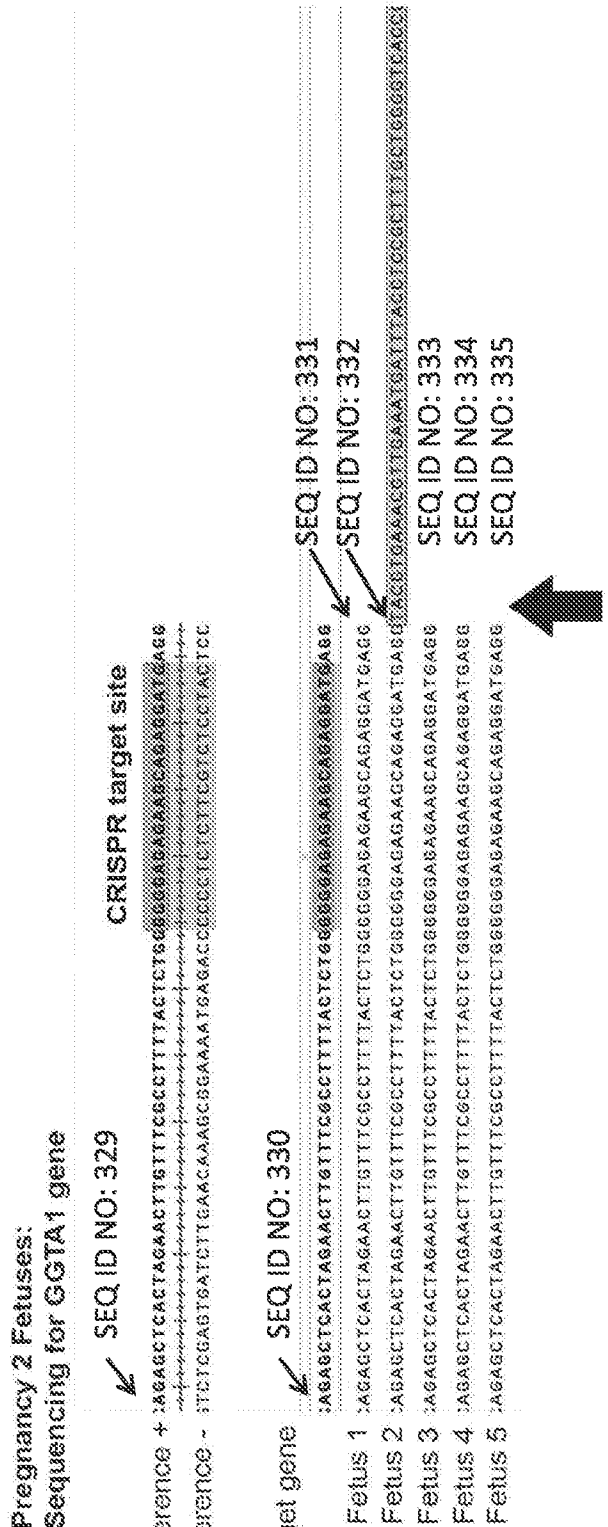

Pregnancy 2 Fetuses:
Sequencing for GGTA1 gene
SEQ ID NO: 329
CRISPR target site
Reference +
Reference -
SEQ ID NO: 330
Target gene
Fetus 1
Fetus 2
Fetus 3
Fetus 4
Fetus 5
SEQ ID NO: 331
SEQ ID NO: 332
SEQ ID NO: 333
SEQ ID NO: 334
SEQ ID NO: 335

FIG. 18B

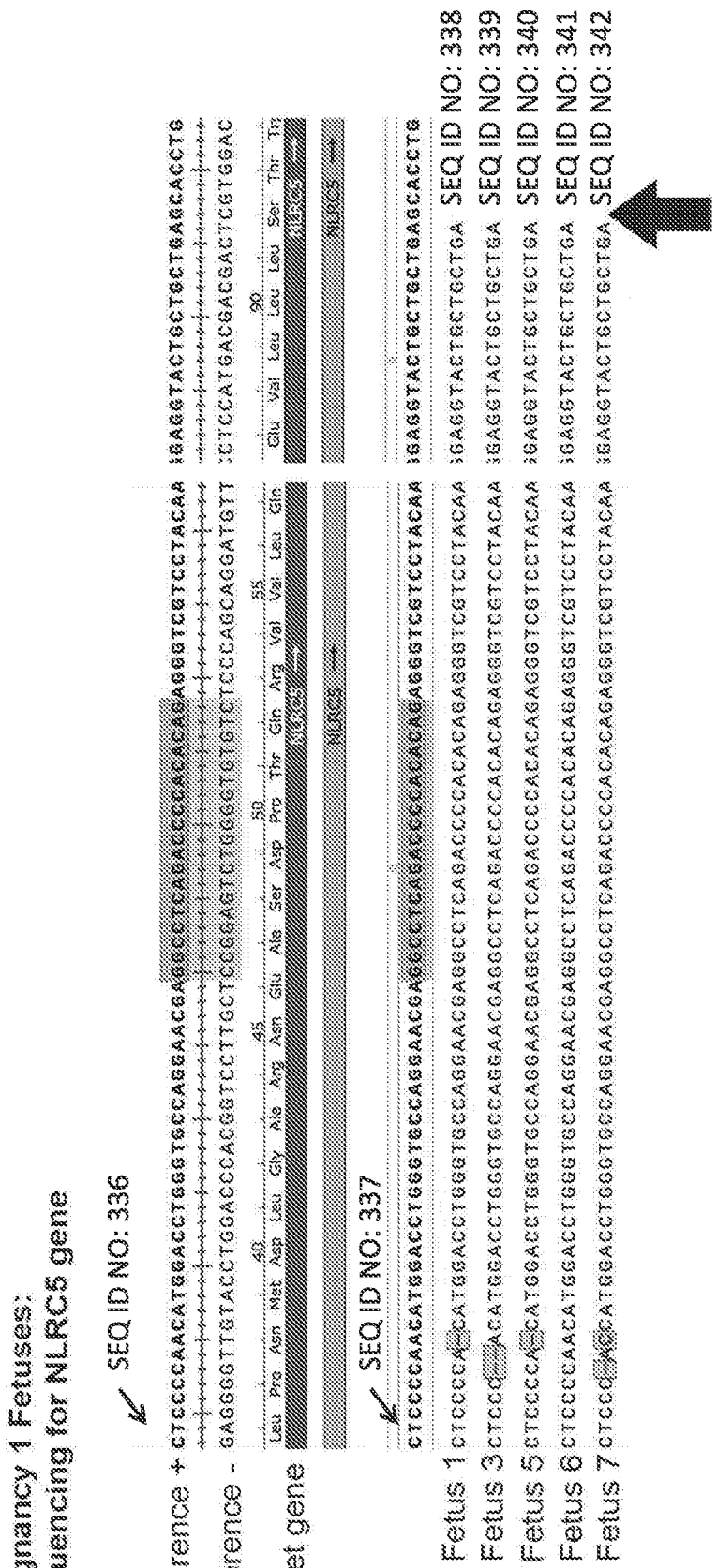

Pregnancy 1 Fetuses:
Sequencing for NLRC5 gene
SEQ ID NO: 336
Reference +
Reference -
Target gene
SEQ ID NO: 337
Fetus 1
Fetus 3
Fetus 5
Fetus 6
Fetus 7
SEQ ID NO: 338
SEQ ID NO: 339
SEQ ID NO: 340
SEQ ID NO: 341
SEQ ID NO: 342

FIG. 19A

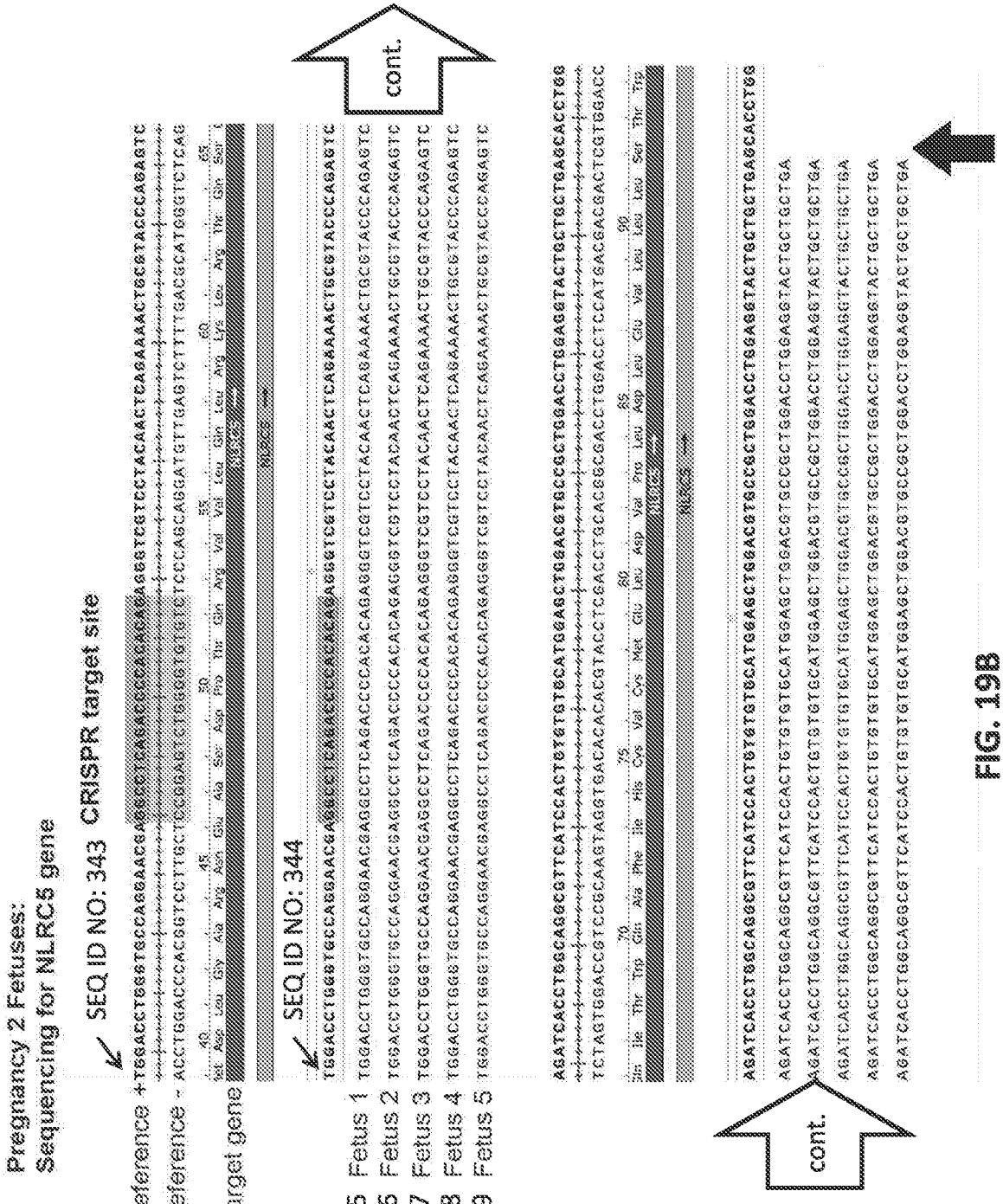

Pregnancy 2 Fetuses:
Sequencing for NLRC5 gene
SEQ ID NO: 343 CRISPR target site
Reference +
Reference -
Target gene
SEQ ID NO: 344
cont.
SEQ ID NO: 345 Fetus 1
SEQ ID NO: 346 Fetus 2
SEQ ID NO: 347 Fetus 3
SEQ ID NO: 348 Fetus 4
SEQ ID NO: 349 Fetus 5
cont.

FIG. 19B

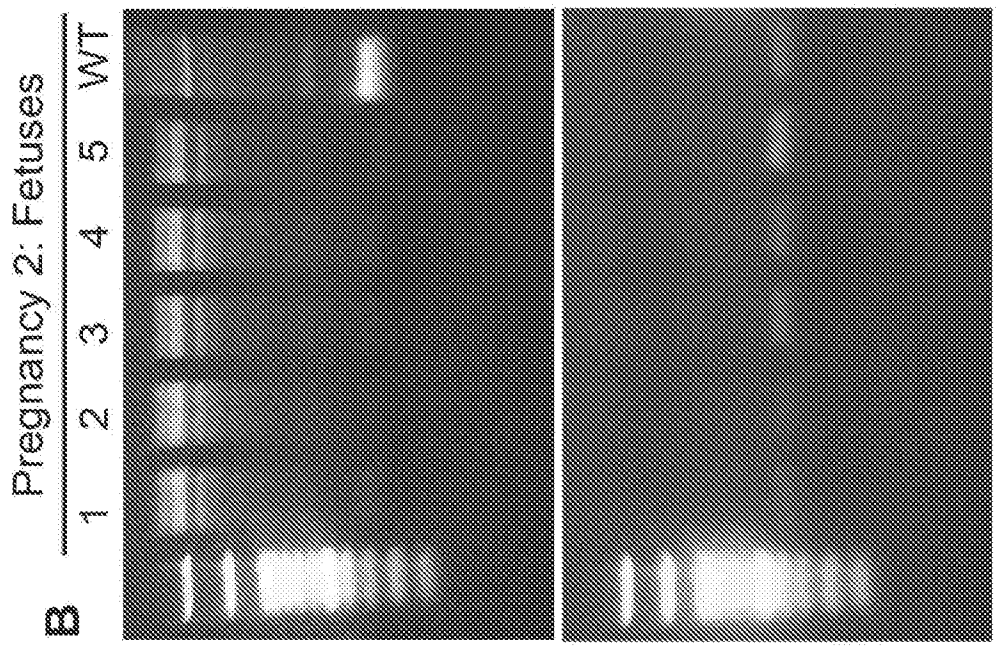


FIG. 20B

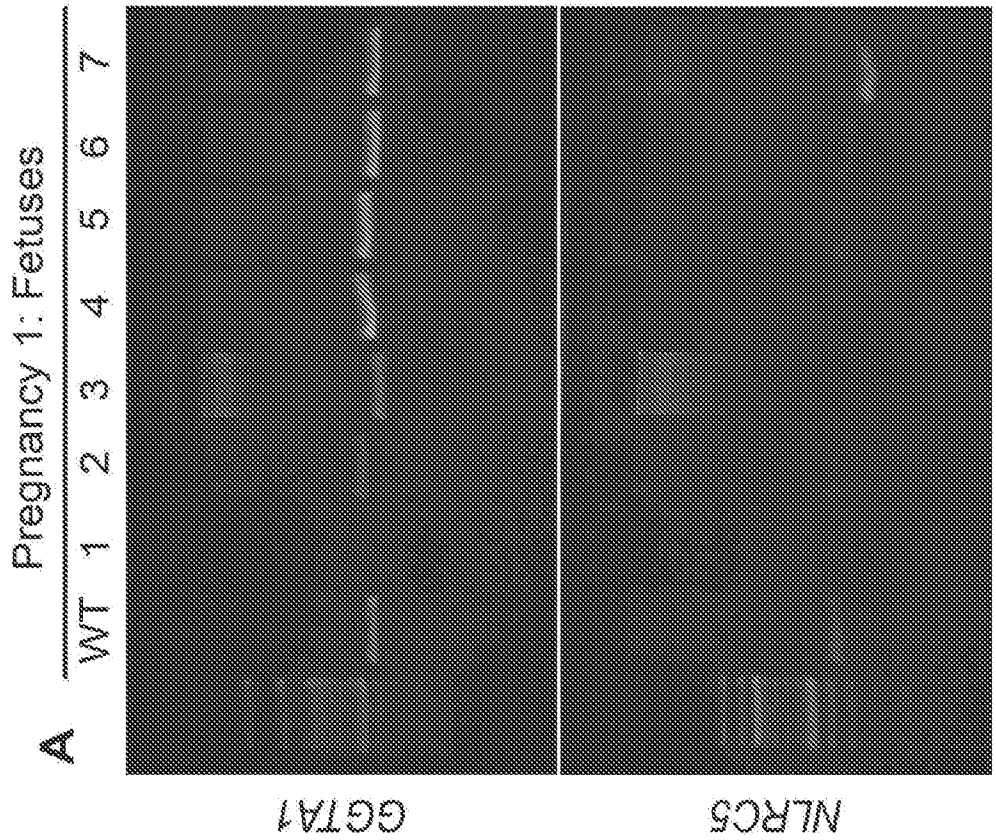


FIG. 20A

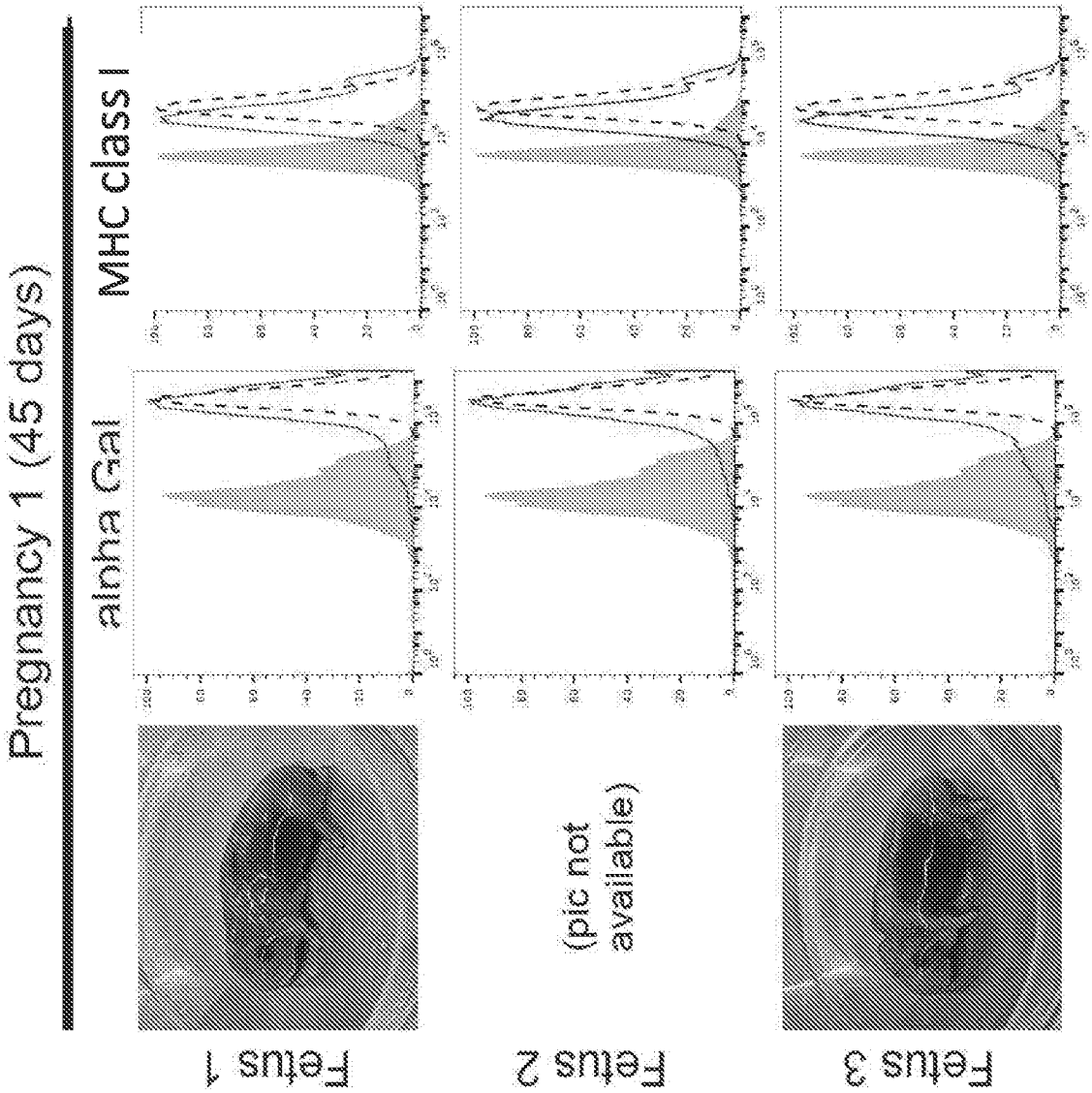

Pregnancy 1 (45 days)
alpha Gal
MHC class I
Fetus 1
Fetus 2
(pic not available)
Fetus 3
Wild-type fetal cells (positive control)
Fetal cells(alpha Gal or MHC class I)
Fetal cells (Unlabeled or isotype control)

FIG. 21A

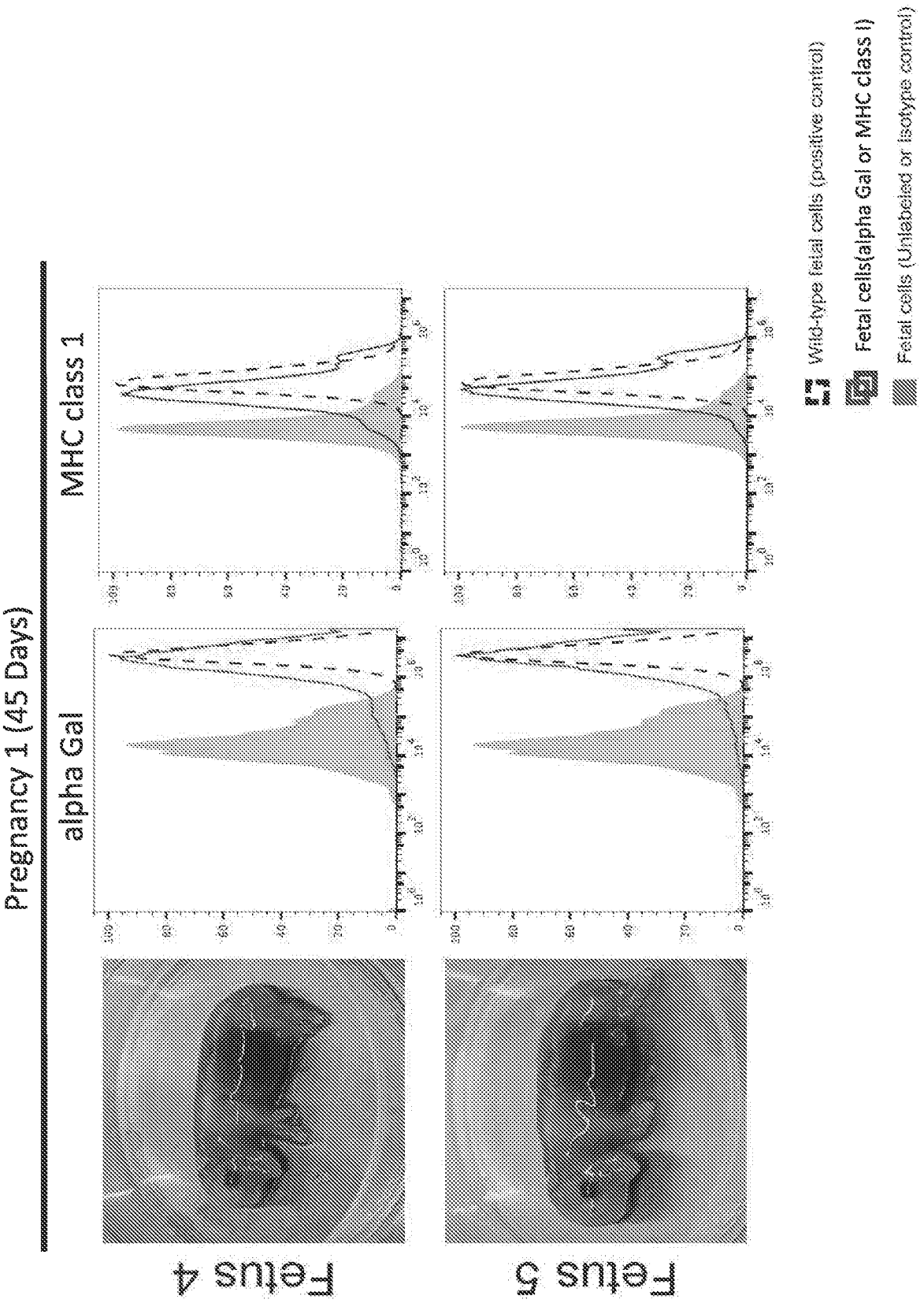

Pregnancy 1 (45 Days)
alpha Gal
MHC class 1
Fetus 4
Fetus 5
Wild-type fetal cells (positive control)
Fetal cells(alpha Gal or MHC class I)
Fetal cells (Unlabeled or isotype control)

FIG. 21B

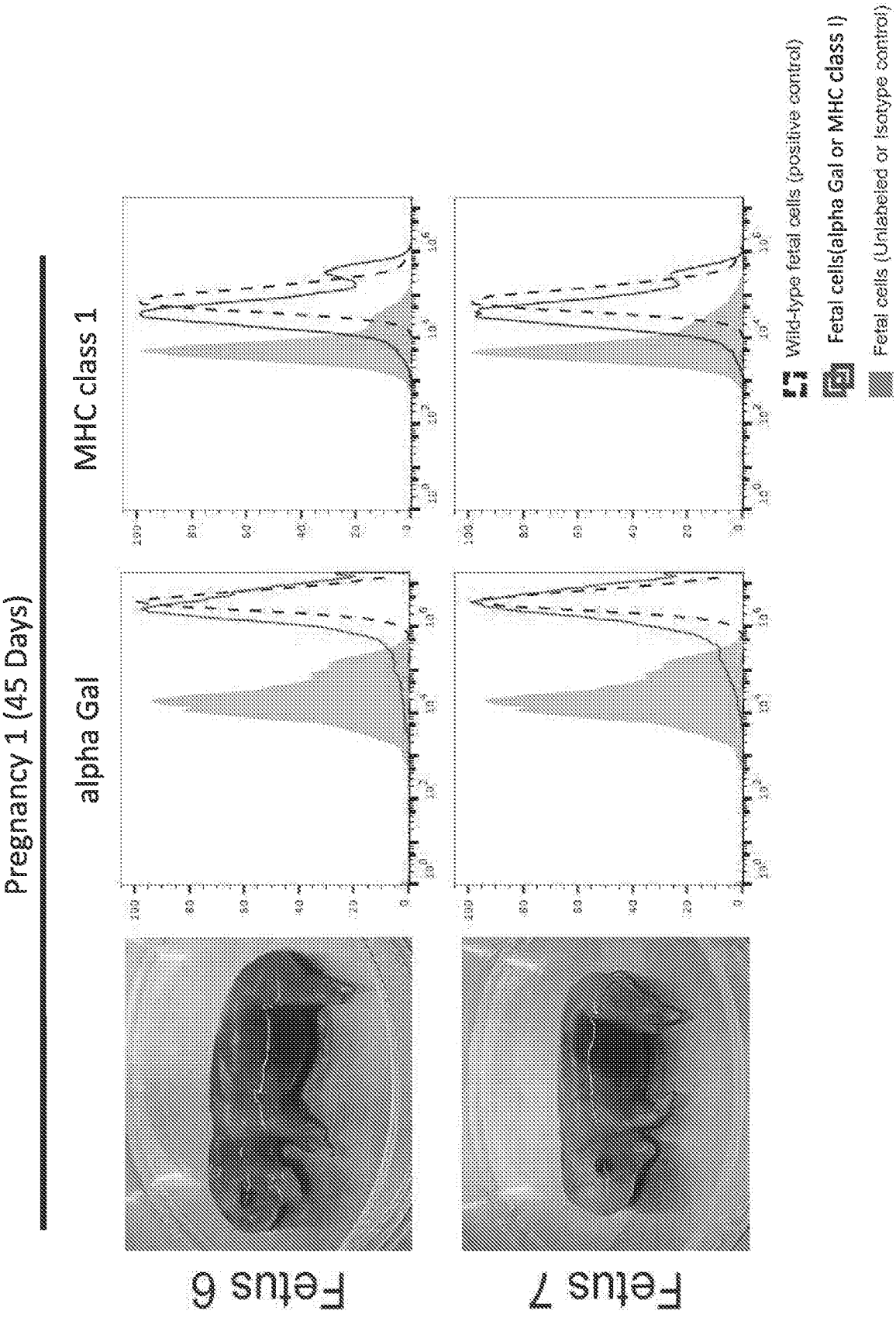

Pregnancy 1 (45 Days)
alpha Gal
MHC class 1
Fetus 6
Fetus 7
Wild-type fetal cells (positive control)
Fetal cells(alpha Gal or MHC class I)
Fetal cells (Unlabeled or isotype control)

FIG. 21C

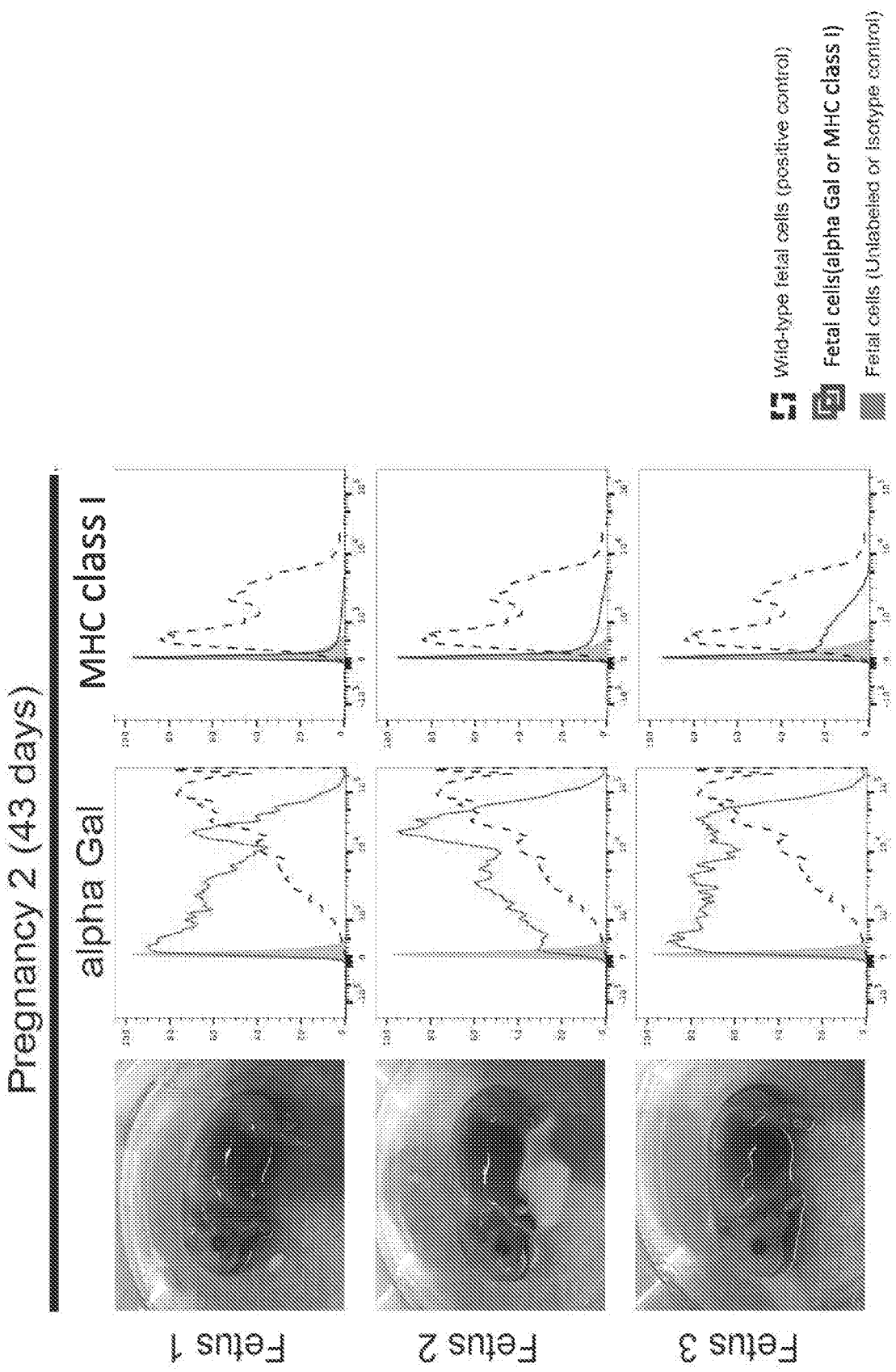

Pregnancy 2 (43 days)
alpha Gal
MHC class I
Fetus 1
Fetus 2
Fetus 3
Wild-type fetal cells (positive control)
Fetal cells(alpha Gal or MHC class I)
Fetal cells (Unlabeled or isotype control)

FIG. 21D

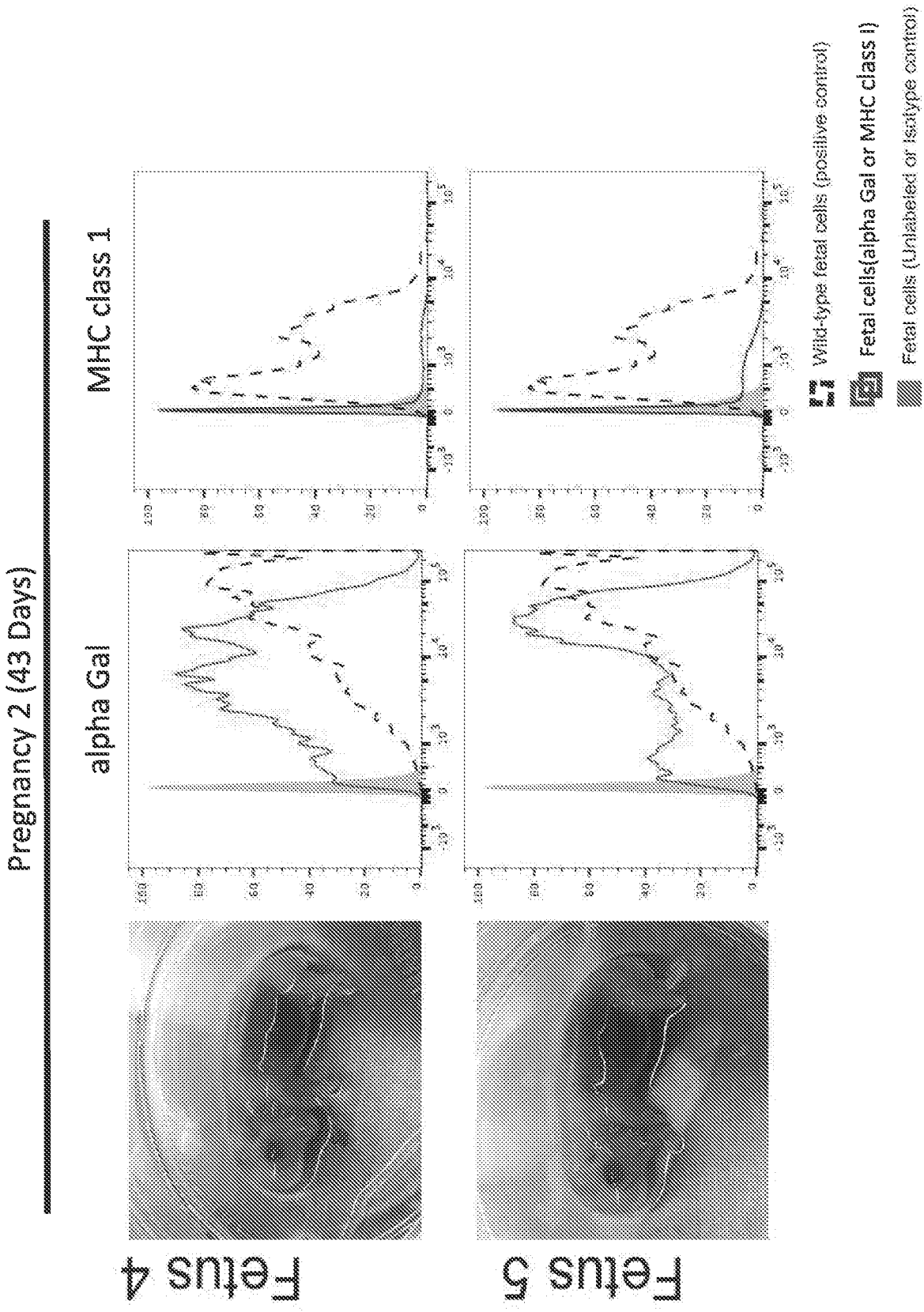

Pregnancy 2 (43 Days)
alpha Gal
MHC class 1
Fetus 4
Fetus 5
Wild-type fetal cells (positive control)
Fetal cells(alpha Gal or MHC class I)
Fetal cells (Unlabeled or isotype control)

FIG. 21E

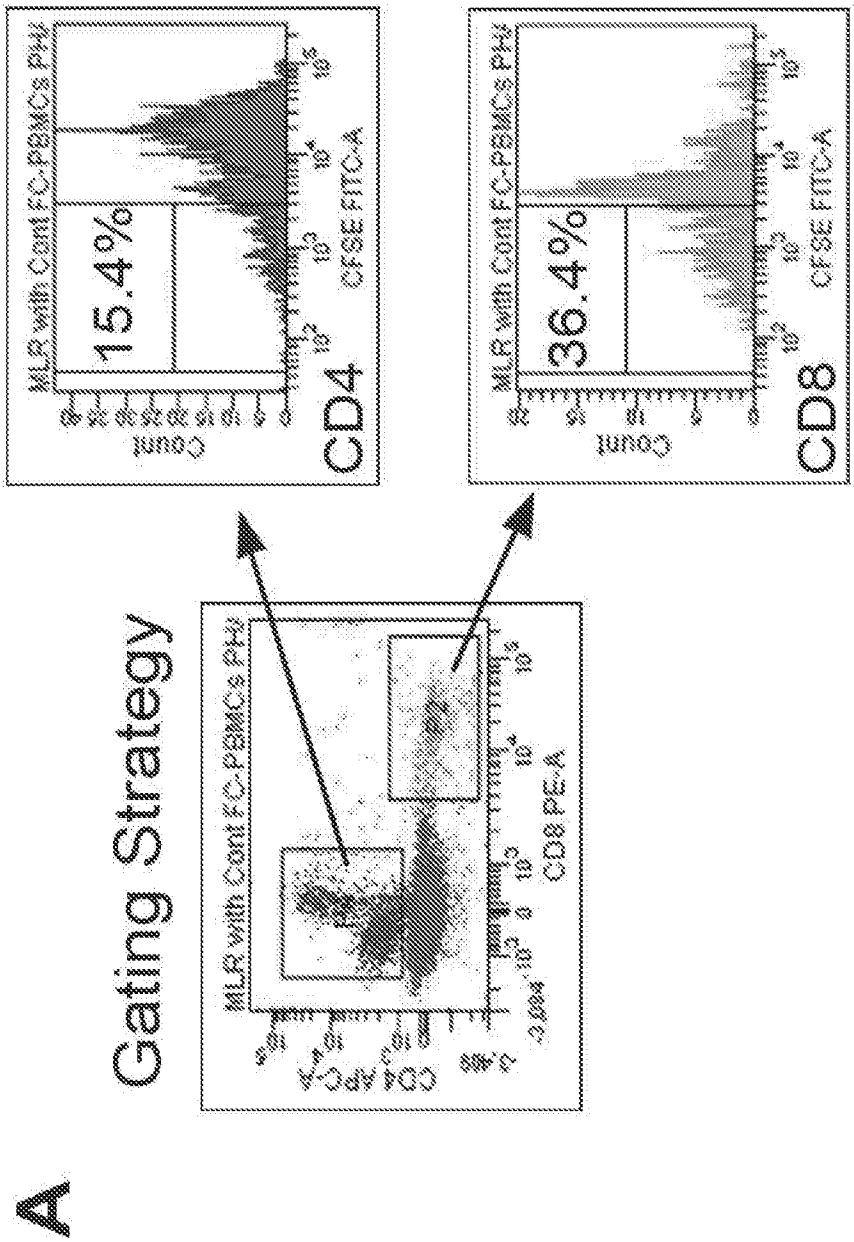

A
Gating Strategy
MLR with Cont FC-PBMCs PHA
CD4 APC-A
CD8 PE-A
MLR with Cont FC-PBMCs PHA
15.4%
CD4
CFSE FITC-A
Count
MLR with Cont FC-PBMCs PHA
36.4%
CD8
CFSE FITC-A
Count

FIG. 22A

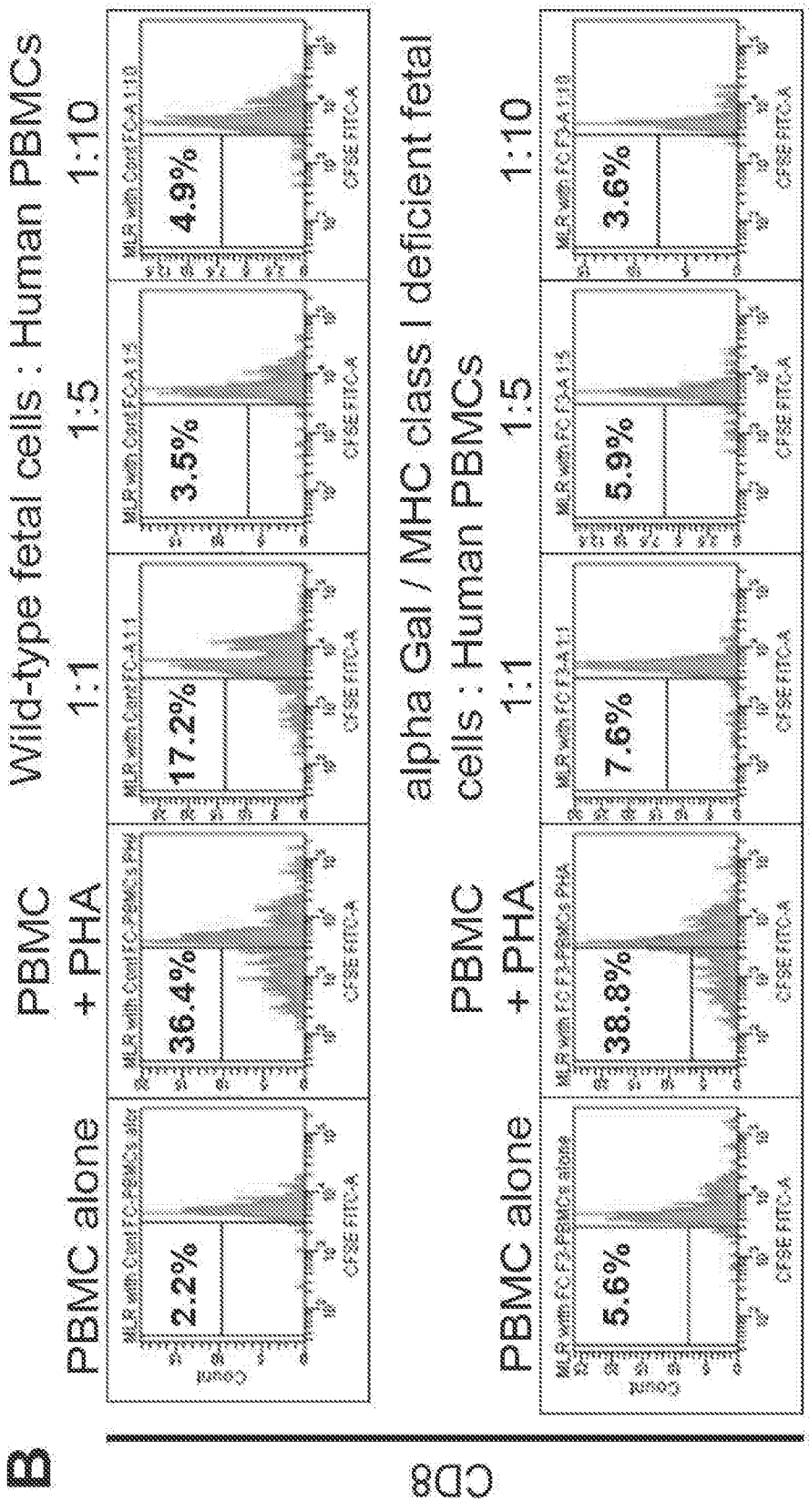

B
CD8
PBMC alone
PBMC + PHA
Wild-type fetal cells : Human PBMCs
alpha Gal / MHC class I deficient fetal cells : Human PBMCs
1:1
1:5
1:10
2.2%
36.4%
17.2%
3.5%
4.9%
5.6%
38.8%
7.6%
5.9%
3.6%
Count
CFSE FITC-A

FIG. 22B

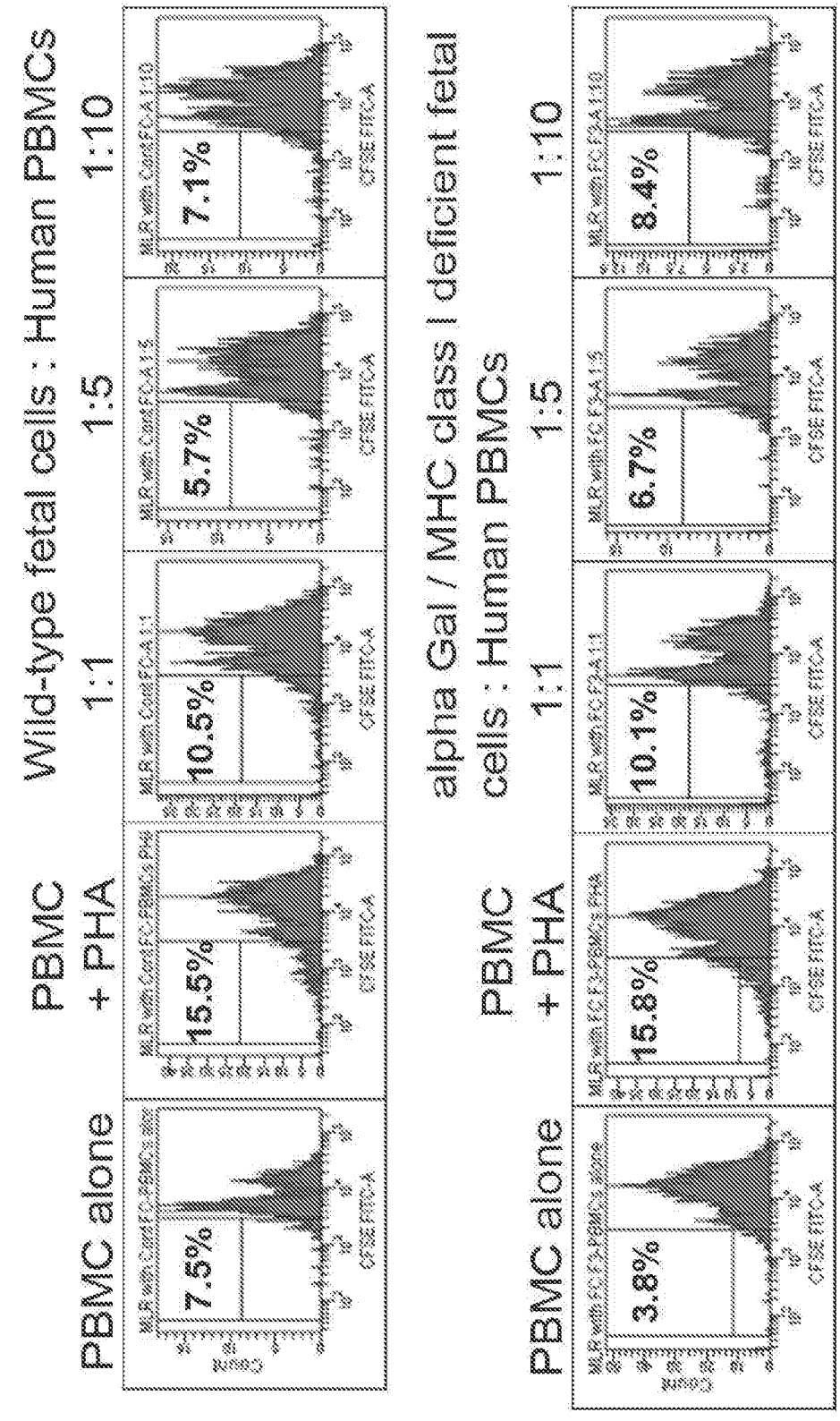

Wild-type fetal cells : Human PBMCs
alpha Gal / MHC class I deficient fetal cells : Human PBMCs
PBMC alone
PBMC + PHA
1:1
1:5
1:10
7.5%
15.5%
10.5%
5.7%
7.1%
3.8%
15.8%
10.1%
6.7%
8.4%
CD4
CFSE FITC-A
Count

FIG. 22C

FIG. 23

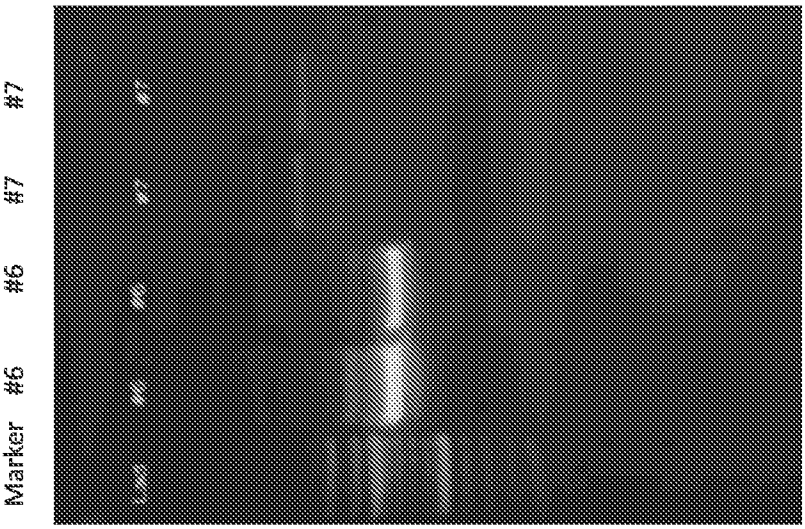


FIG. 24A

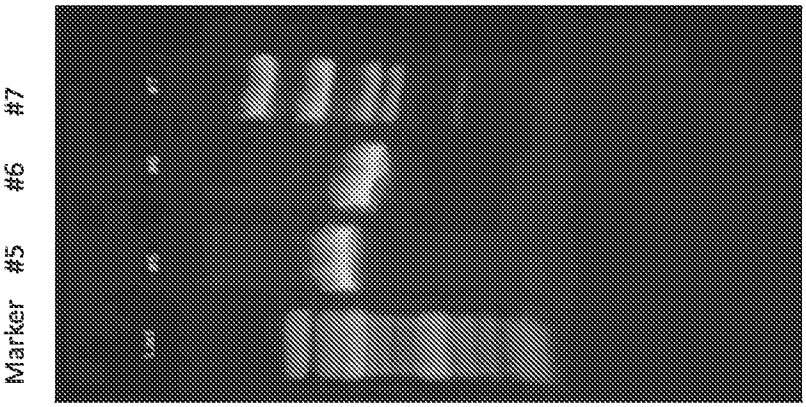


FIG. 24B

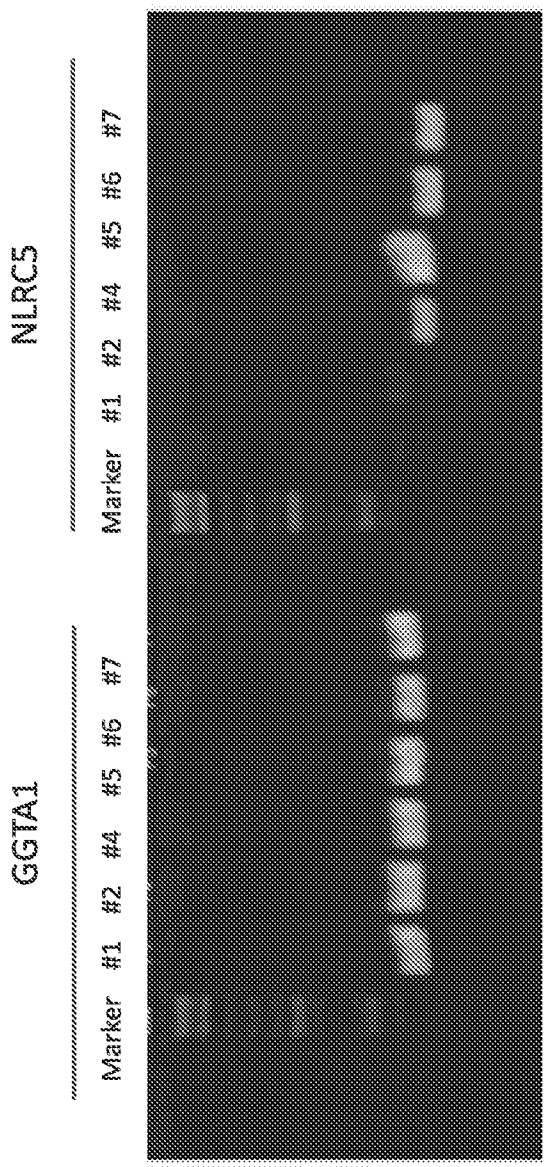
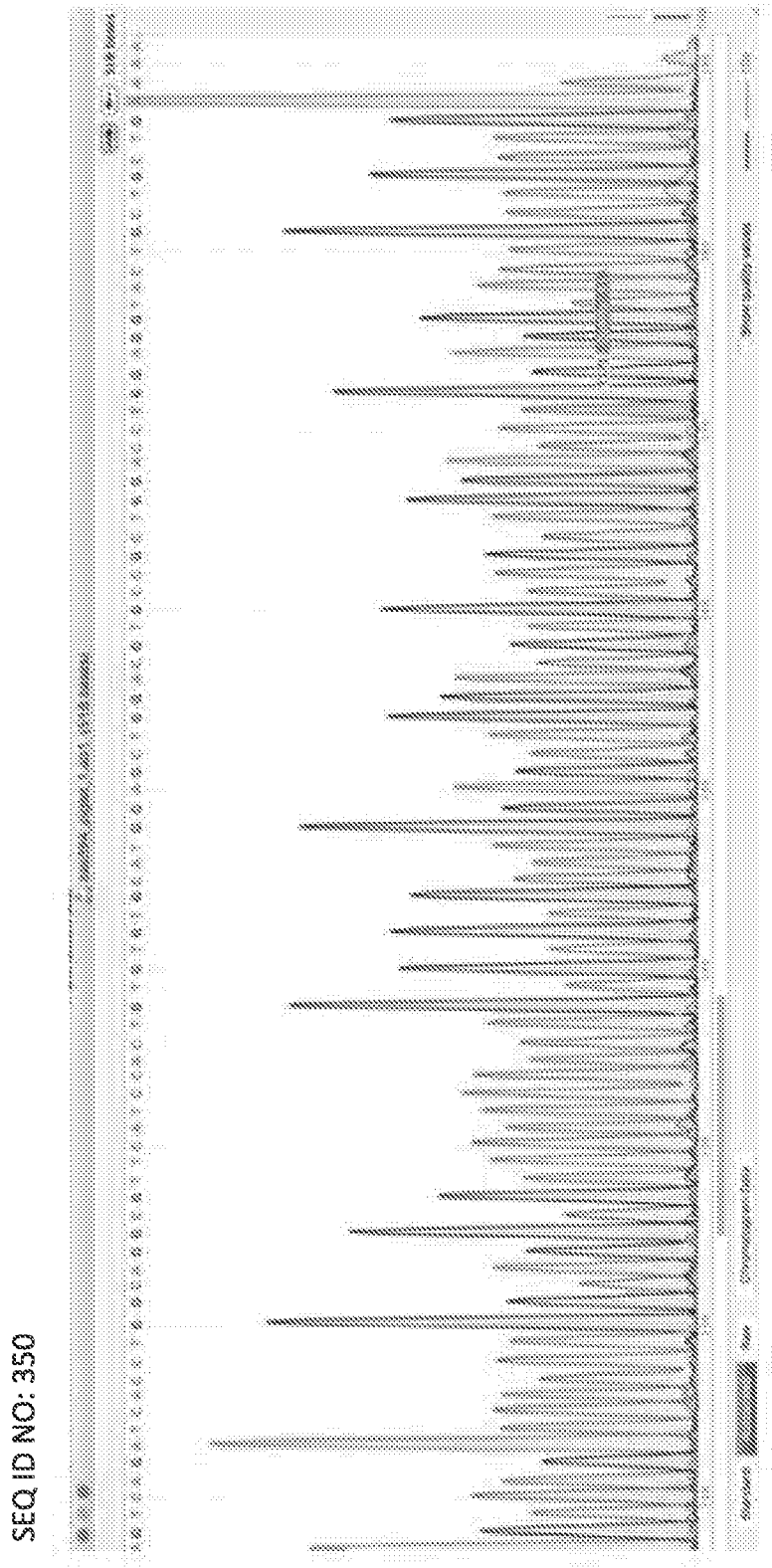
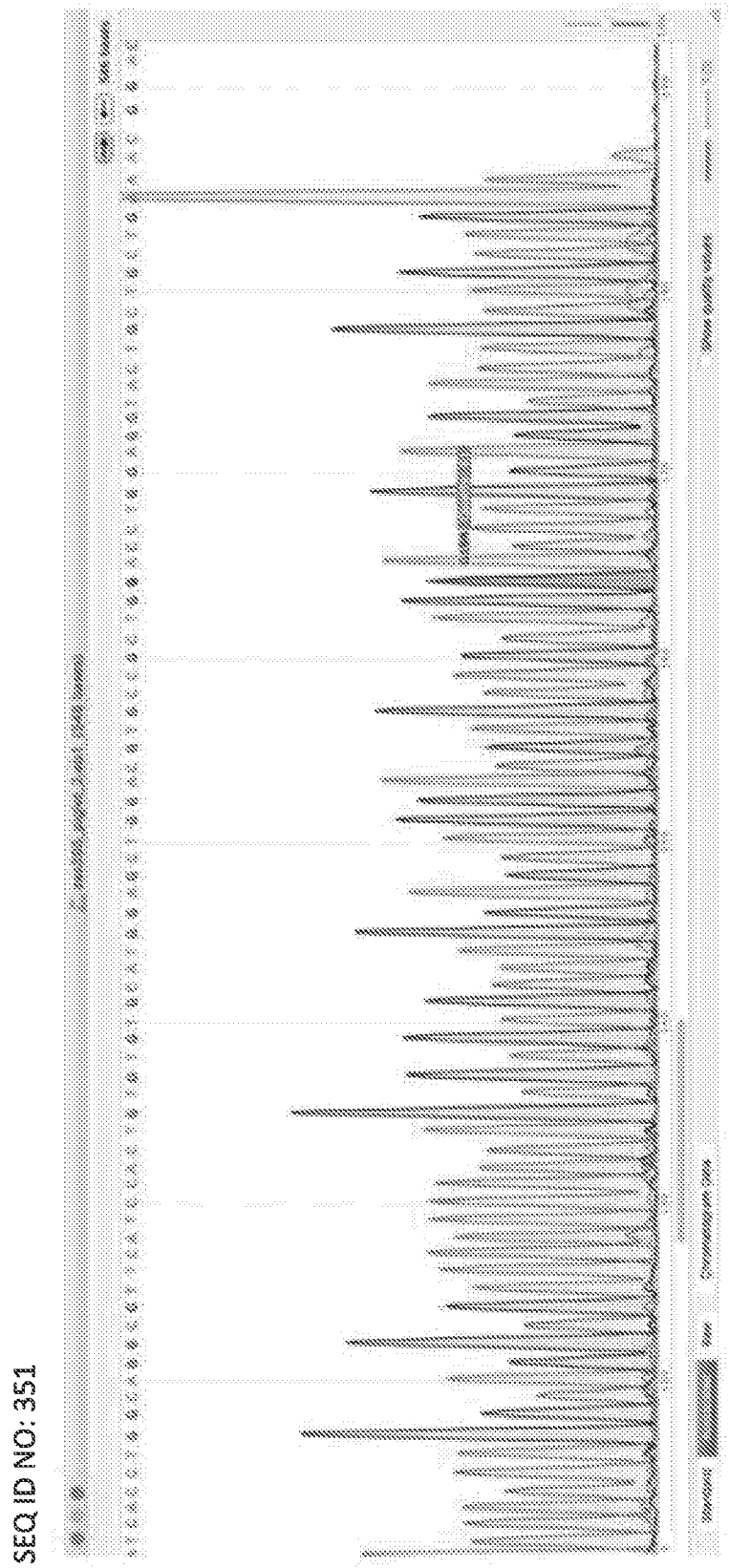


FIG. 24C



Piglet #1: Sequence substitution at 183 and 186, T for A

FIG. 25A



Piglet #2: Sequence variation beginning near 179/180 with GC to AA substitution at 186

FIG. 25B

SEQ ID NO: 352

Piglet #4:
118 T to G; 135 C to G, deletion; 179 CT to G with deletion,
181 C to G, 182 T to A, 185/186 TG deletion to A, 188/189 GC
substitution to AA

FIG. 25C

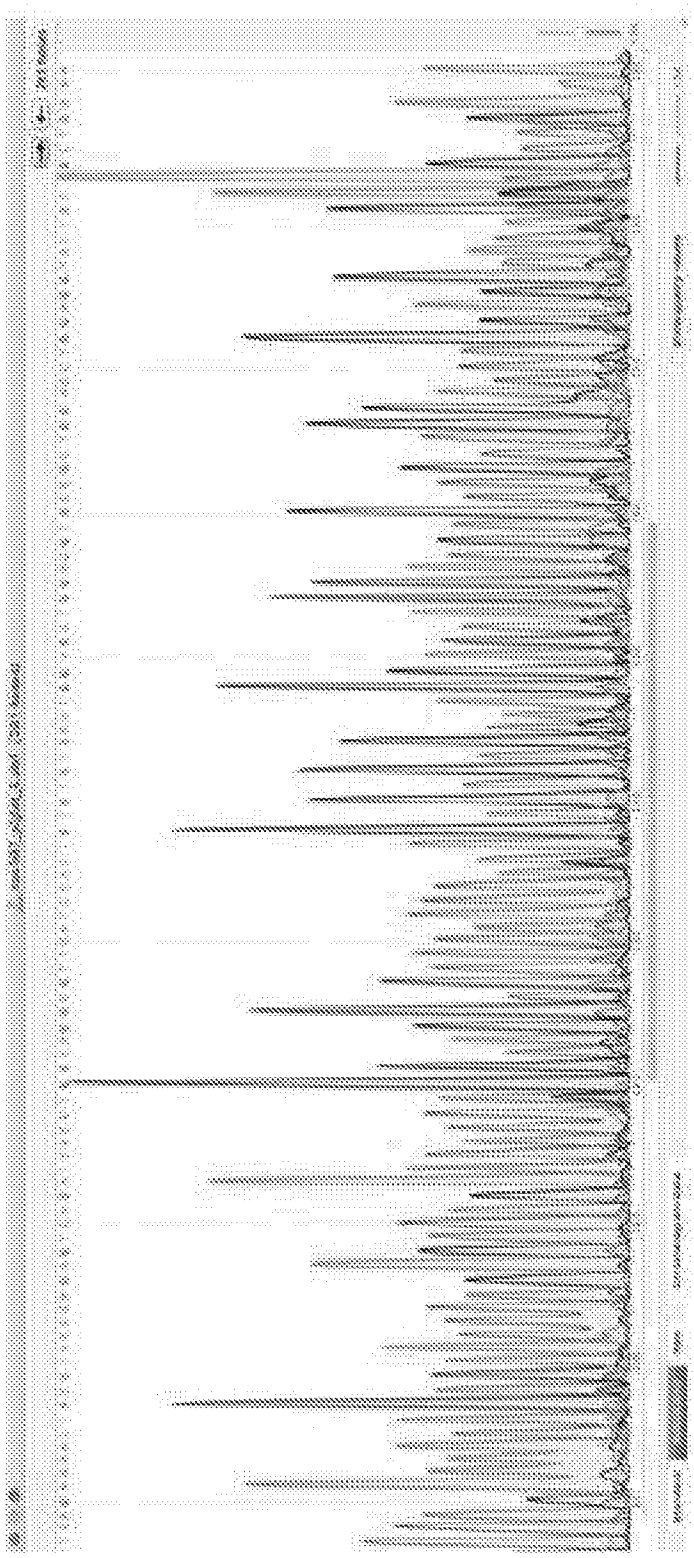
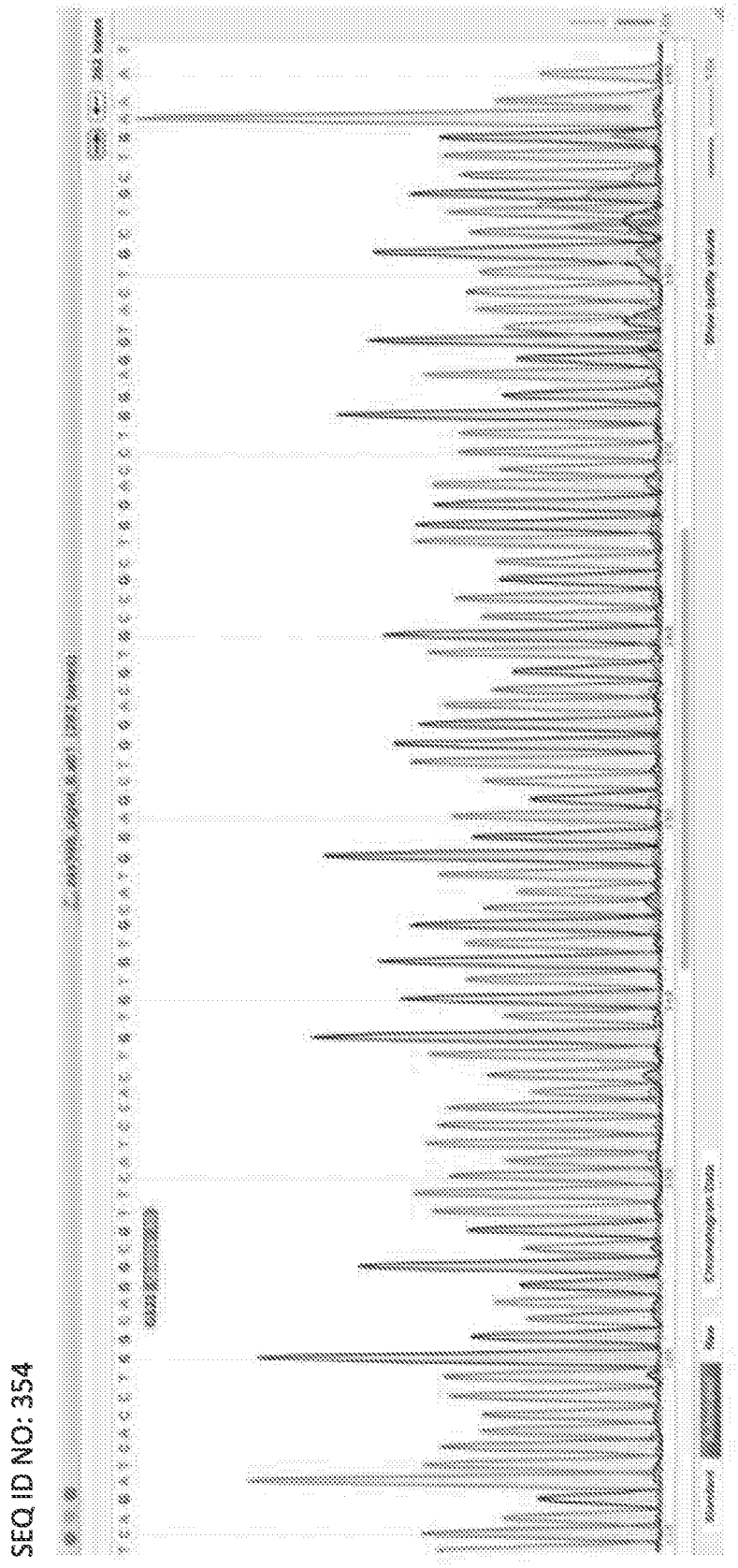
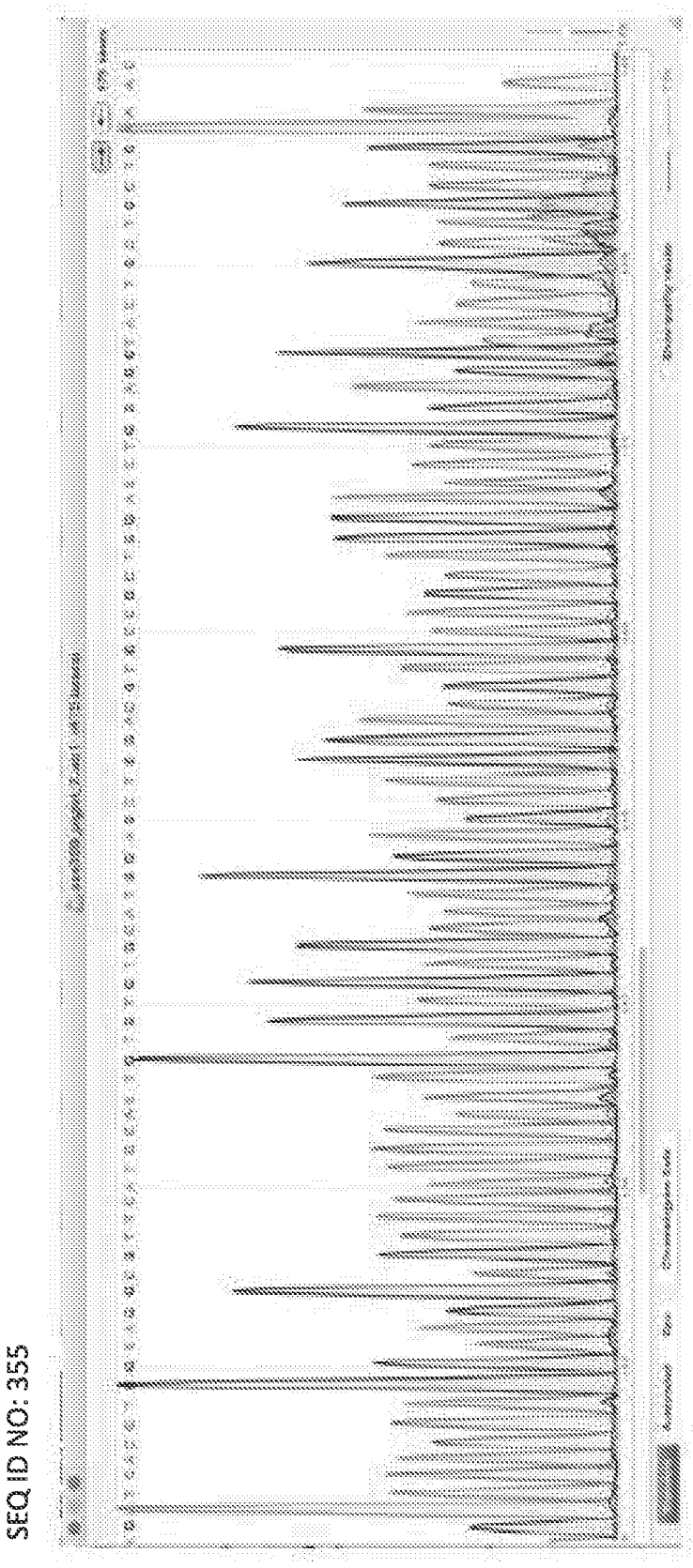

SEQ ID NO: 353
Piglet #5:
119 T to G; 136 C to G; 181 to 183 GCT to TGA; 186/187 deletion substitution TG to A

FIG. 25D



Piglet #6: Substitution or deletion at 177/178 with substitutions at 182 to 184, 187, 188, and 189

FIG. 25E



Piglet #7: Significant mutation 181, 182, 183 CTG to TAA, 188, 189 GC to AA

FIG. 25F

SEQ ID NO: 356

```
GGTGAACACATTGCACAAGTAACATGAGAAAGCAGAAATGCAGGTCATACACGCACCCCT      60
GACCCAGACCAGCAGAGCTGGCTGCAGCATCAATATCCAAGAGAAAGACCACTTATTCCC     120
AAGAAGTGAGACAAGCAAAGACGCTCTATAGAATAAATTAGCATAGAAGGGGCTTTCCCA     180
ACAGTTAAACTTTCCCTBTCAHGCGATTYACCTACTTAAAAACCAGGGCTTTTTCYCACT     240
ACCATTCACTTCGCATYCCTGGCTTVCACGCAGAGGGAAAGGCAATTCATARAGGSWATA     300
TTTTTCTGCCTTTAAAGATATTCTCAAAAGATCGCTCTCCACGCCCAAGGCAGGGAAAAC     360
GACACAATCTGGCTCAACTCCAGGCTAGAACCCTACAAATTCAACGGGGCTATCTCAGAG     420
ATACTGGGGCATACGCCCACDGGGAGCCCAAGAATGTGAGGTGGGGGTGGCGAAGGTCAAT     480
GTCTTTGGTGTGGGAARGAAGCAGCCATCTGAGATAGGAASCCDGAAAACGAGAGGAAAG     540
GCGTCCAGGAAGATTCTTABGGAGGGGAGATCGVGGCCCCCACGAGCGACCAGATTGTCT     600
GTCACAAGGCCGCGAGAACGGGGGTGGGGGGHTCGGGGAGAGAAAAAAAWGTGT 660
GCTGTGTATTTTGAGMGGAGGGCRGCGAGAGGCCTVTCCTCAADKAAAAGGYAAACGTGG     720
AGTAGGCAGTTCCCAGGAAAAGGGGTGAAGAGGCGTDGGGGGAGGGGAAGCGTCCCTGAC     780
CCAGGAAAGACATGAAAAAGGGTAGTGGGGTCGACTAGATTAAGAGGGGGGCCTCTCTCCC     840
TGGGAAAGAGGGGGTGTTGCAATGGTGTGTRCAAGGBGGCGAGGGGGGATGAGAAGGGGCA     900
GCATCCTCCTGCTAAGAGCCTGGGGAGGGCCAGGCCCCACGACCCMGAGGAGAGCGAGCGV     960
GGGAGACGGAGGAGGTGACCCTTCCCTCCCCCGGGGCCGGTCGTGAGGTTCGGTCTCTCT    1020
TTTCTGTCGGGACCCCTTACCTTGTCCCAGGCGCTGCCGGGCCCTGGGCCCGGGCTGCGGCGC    1080
ACGGCACTCCCGGGAGGCAGCAGGACTCGACTTAGGCCCAACGCGGCGCCACGGCGTTTTC    1140
CTGGCCGGAATGGCCCGTACCCGTGAGGTGGGGGGTGGGGGGCAGAAAAAGGCGGAGCGAGC    1200
AAAGGCGGGGAGAGGGGGGGCAGGGCCAGGGAAGGAGGGGGGGGCCGGCACTACTGTGTTG    1260
GCGGACTGGCGGGACTGGGGCTGCGTGAGTCTCTGAGCGCAGGCGGGCGGCGCCGCCCC    1320
TCCCCCGCAGCGGCGGCCAGCGCCGGCCACCCGGGACACGCCCCCTCCC    1380
GCCGCGCCATTGGCCTCTCCGCCCACCGCCCCGCACCCATTGGCCVGCTCGCCGCCAATC    1440
AGC GGAAGCCGCCGGGGCCGCCTAGAGAAGAGGCTGTGCTTTGGGGCTCCGGCTCCTCAG    1500
AGAGCCTCGGCTAGGTAGGGGAGCGGGGACTCTGGTGGGAGGGVGGGTGCGGTGCDTTGGC    1560
GGGGGATGGGTGG CTGVGGBGGCCGTCTGDCCGVTHGCGGGGGGTYGCCTTTCCYAGTGGG    1620
ACAGTCGGGAACATAWYGTTTGTTACGCTGGAAGGGGAAGRGGRGCGGGAGGCAGGCGG    1680
GAGTGCGGCCCCGCCCTGCGGCAACCGGAGAGGGGGAGAAGGGAGCGGAAACBCTCGAA    1740
WCCGGACGGAGCCATTGCTCBCGCAGAGGGGGGCAGCGGAGGAGCGCTTCCGGCTVDCCT    1800
CTCTTGTCGCTGATTGGCCGCTTCTCCTCCCGCCGTCCCGCCGTGTGTGAAAACAC    1850
```

FIG. 26A

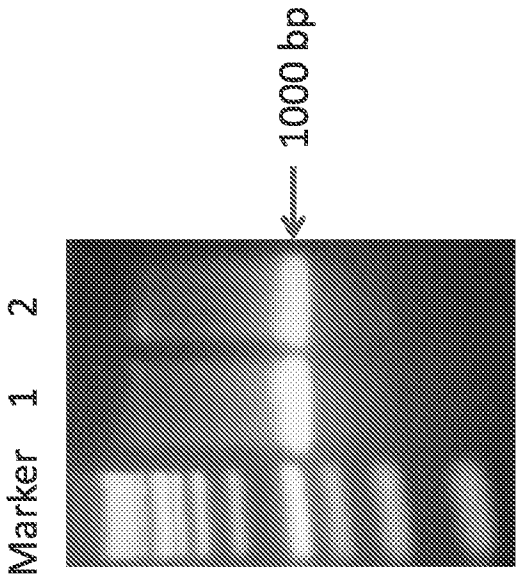


FIG. 26B

SEQ ID NO: 357

GCTCTGGGGCTCCGGCTCCTCAGAGAG
CCTCGGCTAGGTAGGGGAGCGGGACTCTGGTTTGGGGGAGGGCCGGCGGTTTGGCGGGGG
ATGGGTGCTTGAGGTGGTCTGACCGGTAGCGGGGGTCGCCTTCCCTAGCGGGAAGTCGGG
AGCATATCGTTTTGTTACGCTGGAAGGGGAAGAGGTGGTGAGAGGCAGGCGGGAGTGCGGC
CCGCCCTGCGGCAACCGGAGGGGGAGGGAAGGGAGCGGAAAAGCCTGGAATACGGACG
GAGCCATTGCTCCCGCAGAGGGAGGAGCGCTTCCTGCTCTTCTCTTGTCACTGATTGGCC
GCTTCTCCTCCCGCCGTGTGTGAAAACACAAATGGCGTGTTTTTGGTTGGAGTAAAGCTCC
TGTCAGTTACAGCCTCGGGAGTGCGCAGCCTCCCAGGAACTCTCGCATTGCCCCCCTGGGT
GGGTAGGTAGGTGGGGTGGAGAGAGCTGCACAGGCGGGCGCTGTCGGCCTCCTGCGGGGGG
GAGGGGAGGGTCAGTGAAAGTGGCTCCCGCGCGGGCGTCCTGCCACCCTCCCCTCCGGGG
GAGTCGGTTTACCCGCCGCCTGCTCGGCTTTGGTATCTGATTGGCTGCTGAAGTCCTGGG
AACGGCCCCCTTGTTATTGGCTTGGGTCCCAAATGAGCGAAACCACTACGCGAGTCGGCAG
GGAGGCGGTCTTTGGTACGGCCCTCCCCGAGGCCAGCGCCGCAGTGTCTGGCCCCCTCGCC
CCTGCGCAACGTGGCAGGAAGCGCGCGCAGGAGGCGGGGGCGGGCTGCCGGGCCGAGGCT
TCTGGGTGGTGGTGACTGCGGCTCCGCCCCTGGGCGTCCGCCGCCTGAAGGACGAGACTAG
CTCTCTACCTGCTCTCGGACCCGTGGGGGGTGGGGGTGGAGGAAGGAGTGGGGGGGTCGGT
CCTGCTGGCTTGTGGGTGGGAGGCGCATGTTCTCCAAAAACCCGCGCGAGCTGCAATCCT
GAGGGAGCTGCAGTGGAGGAGGCGGAGAGAAGGCCGCACCCCTTCTCCGCAGGGGGGAGGGGG
AGTGCCGCAATACCTTTAT

FIG. 26C

SEQ ID NO: 358

Left Arm Rosa26:

AATGTCTTTGGTGTGGGAAAGGAAGCAGCCATCTGAGATAGGAACCCTGAAAACGAGAGGAAAGGCGTCCAGGAAG
ATTCTTGGGGAGGGGGAGATCGAGGCCCCCACGAGCGACCAGATTGTCTGTCACAAGGCCGCGAGAACGGGGGTGGG
GGGTGGGGGTTCGGGGAGAGAAAAAAAAGTGTGCTGTGTATTTGAGGGGAGGGCGGCGAGAGGCCTATCCTCAA
GTAAAAGGTAAACGTGGAGTAGGCAGTTCCCAGGAAAAAGGGGTGAAGAGGCGTGGGGGGGAGGGGAAAGCGTCCCT
GACCCAGGAAAGACATGAAAAAGGGTAGTGGGGTCGACTAGATTAAGAGGGGGGGCCTCTCTCCCTGGGAAAGAGGG
GTGTTGCAATGGTGTGTCAAGGGGGCGAGGGGGGATGAGAAGGGGGCAGCATCCTCCTGCTAAGAGCCTGGGGAGG
GCCAGGCCCACGACCCCGAGGAGAGCGAGCGGCGGGAGACGGAGGTGACCCTTCCCTCCCCGGGGCCGGTCG
TGAGGTTCGGTCTCTCTTTTCTGTCGGACCCTTACCTTGTCCCAGGCGCTGCCGGGCCCGGGCTGCGGCGCA
CGGCACTCCCGGGAGGCAGGACTCGACTTAGGCCCAACGCGGCGCCACGGCGTTTCCTGGCCGGAATGGCCCG
TACCCGTGAGGTGGGGGTGGGGGCAGAAAAGGCGAGCAAAGGCGGGGAGGGGGGCAGGGGCCAGGG
AAGGAGGGGGGGGGGCCGGCACTACTGTGTTGGCGGACTGGGGGCTGCGTGAGTCTCTGAGCGCAGGC
GGGCGGCGGCCGCCCCTCCCCCGCAGCGGCGGCCCAGGGGGCACACGCCCCCCTCC
CGCCGCGCCATTGGCCTCTCCGCCCCACCGCCCCGCACCCATTGGCCVGCTCGCCGCCAATCAGCGGAAGCCGCCGGG
GCCGGCCTAGAGAAGAGGCTGT

FIG. 26D

SEQ ID NO: 359

Synthetic HLAG1:

AGTGTGGTACTTTGTCTTGAGGAGATGTCCTGGACTCACACGGAAACTTAGGGCTACGGAATGAAGTTCTCACTCCCAT
TAGGTGACAGGTTTTTAGAGAAGCCAATCAGCGTCGCCGCGGTCCTGGTTCTAAAGTCCTCGCTCACCCACCCGGACT
CATTCTCCCCAGACGCCAAGGATGGTGGTCATGGCGCCCCGAACCCTCTTCCTGCTGCTCTCGGGGGCCCTGACCCTG
ACCGAGACCTGGGCGGGCTCCCACTCCATGAGGTATTTCAGCGCCGCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCG
CTTCATCGCCATGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGCGACTCGGCGTGTCCGAGGATGGAGC
CGCGGGCGCCGTGGGTGGAGCAGGAGGGGCCGGAGTATTGGGAAGAGGAGACACGGAACACCAAGGCCCACGCA
CAGACTGACAGAATGAACCTGCAGACCCTGCGCGGCTACTACAACCAGAGCGAGGCCAGTTCTCACACCCTCCAGTG
GATGATTGGCTGCGACCTGGGGTCCGACGGACGCCTCCTCCGCGGGTATGAACAGTATGCCTACGATGGCAAGGATTA
CCTCGCCCTGAACGAGGACCTGCGCTCCTGGACCGCAGCGGACACTGCGGCTCAGATCTCCAAGCGCAAGTGTGAGG
CGGCCAATGTGGCTGAACAAAGGAGAGCCTACCTGGAGGGCACGTGCGTGGAGTGGCTCCACAGATACCTGGAGAA
CGGGAAGGAGATGCTGCAGCGCGCGGACCCCCCCAAGACACACGTGACCCACCACCCTGTCTTTGACTATGAGGCCA
CCCTGAGGTGCTGGGCCCTGGGCTTCTACCCTGCGGAGATCATACTGACCTGGCAGCGGGATGGGGAGGACCAGACC
CAGGACGTGGAGCTCGTGGAGACCAGGCCTGCAGGGGATGGAACCTTCCAGAAGTGGGCAGCTGTGGTGGTGCCTT
CTGGAGAGGAGCAGAGATACACGTGCCATGTGCAGCATGAGGGGCTGCCGGAGCCCCTCATGCTGAGATGGAAGCA
GTCTTCCCTGCCCACCATCCCCATCATGGGTATCGTTGCTGGCCTGGTTGTCCTTGCAGCTGTAGTCACTGGAGCTGCGG
TCGCTGCTGTGCTGTGGAGAAAGAAGAGCTCAGATTGAAAAGGAGGGAGCTACTCTCAGGCTGCAGAGACCAGCCC
ACCCTGTGCCACCATGACCCTCTTCCTCATGCTGAACTGCATTCCTTCCCCAATCACCTTTCCTGTTCCAGAAAAGGGGC
TGGGATGTCTCCGTCTCTGTCTCAAATTTGTGGTCACTGAGCTATAACTTACTTCTGTATTAAAATTAGAATCTGAGTATAA
ATTTACTTTTTCAAATTATTTCCAAGAGAGATTGATGGGTTAATTAAAGGAGAAGATTCCTGAAATTTGAGAGACAAAAT
AAATGGAAGACATGAGAACTTT

FIG. 26E

SEQ ID NO: 360

Right Arm Rosa26:

GCTTTGGGGCTCCGGCTCCTCAGAGAGCCTCGGCTAGGTAGGGGAGCGGGACTCTGGTGGGAGGGVGGGTG
CGGTGCDTTGGCGGGGGATGGGTGGCTGVGGBGGCCGTCTGDCCGVTHGCGGGGGGTYGCCTTTCCYAGTGG
GACAGTCGGGAACATAWYGTTTGTTACGCTGGAAGGGGAAGRGGRGGCGGGAGGCAGGCGGGAGTGCGG
CCCGCCCTGCGGCAACCGGAGGGGGAGAAGGGAGCGGAAAACBCTCGAAWCCGGACGGAGCCATTG
CTCBCGCAGAGGGGGGGCAGCGGAGGAGCGCTTCCGGCTVDCCTCTCTTGTCGCTGATTGGCCGCTTCTCCTCC
CGCCGTCCCGCCGTGTGTGAAAACACACAAATGGCGTGTTTTGGTTGGAGTAAAGCTCCTGTCAGTTACAGCCTC
GGGAGTGCGCAGCCTCCCAGGAACTCTCGCATTGCCCCCCTGGGTGGGGTAGGTAGGTGGGGTGGAGAGAGCT
GCACAGGCGGGGCGCTGTCGGCCTCCTGCGGGGGGAGGGGGAGGGTCAGTGAAAGTGGCTCCCGCGCGGGCG
TCCTGCCACCCTCCCCTCCGGGGGAGTCGGTTTACCCGCCGCCTGCTCGGCTTTGGTATCTGATTGGCTGCTGA
AGTCCTGGGAACGGCCCCCTTGTTATTGGCTTGGGTCCCAAATGAGCGAAACCACTACGCGAGTCGGCAGGGA
GGCGGTCTTTGGTACGGCCCTCCCCGAGGCCAGCGCCGCAGTGTCTGGCCCCCTCGCCCCTGCGCAACGTGGC
AGGAAGCGCGCGCAGGAGGCGGGGGCGGGCCGAGGCTTCTGGGTGGTGACTGCGGCTCC
GCCCTGGGCGTCCGCCGCCTGAAGGACGAGACTAGCTCTCTACCTGCTCTCGGACCCGTGGGGGTGGGGGT
GGAGGAAGGAGTGGGGGGGTCGGTCCTGCTGGCTTGTGGGTGGGAGGCGCAT

FIG. 26F

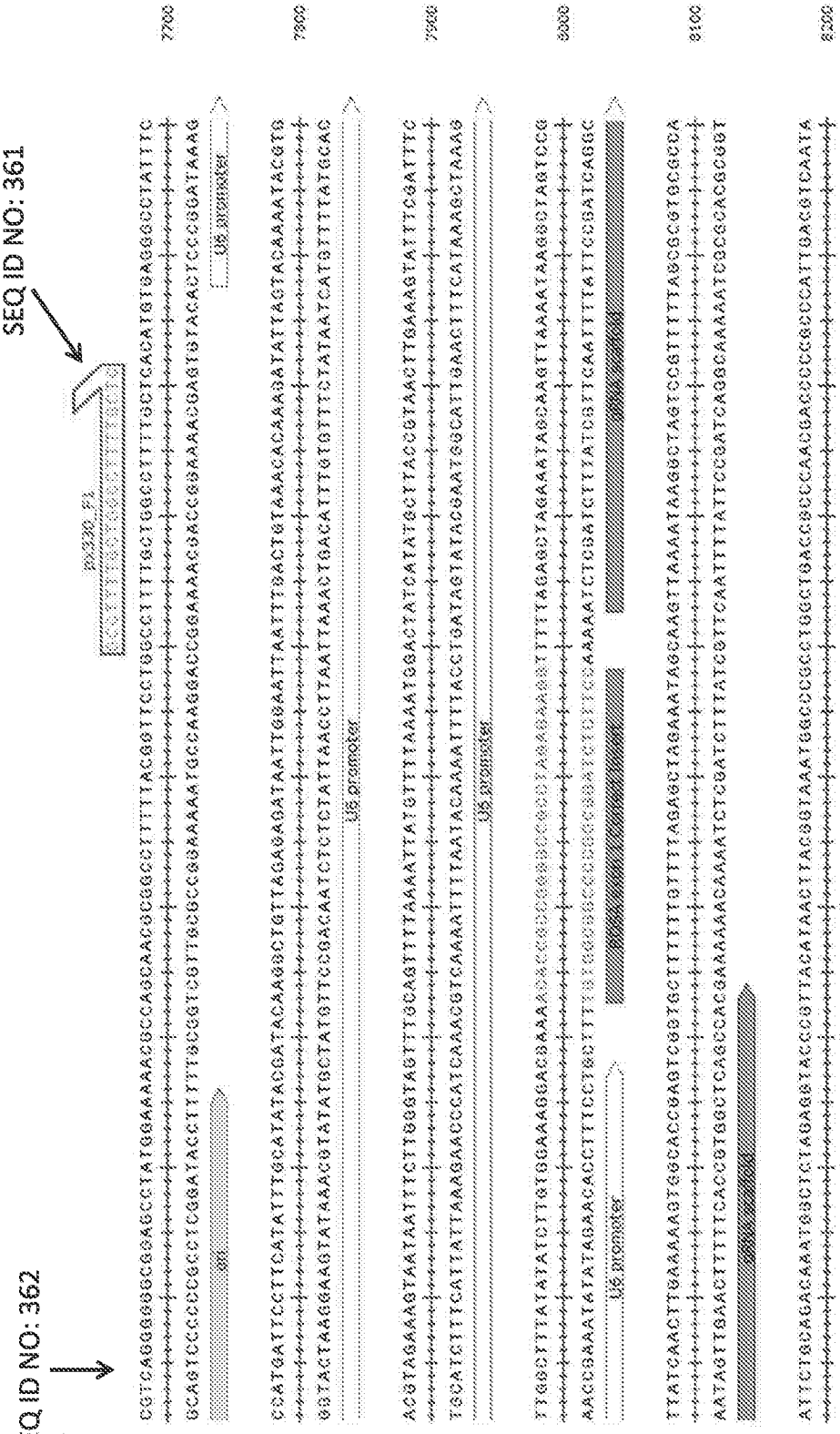

SEQ ID NO: 361
SEQ ID NO: 362
SEQ ID NO: 363
U6 promoter
U6 promoter
U6 promoter
U6 promoter
7700
7800
7900
8000
8100
8200

FIG. 27A

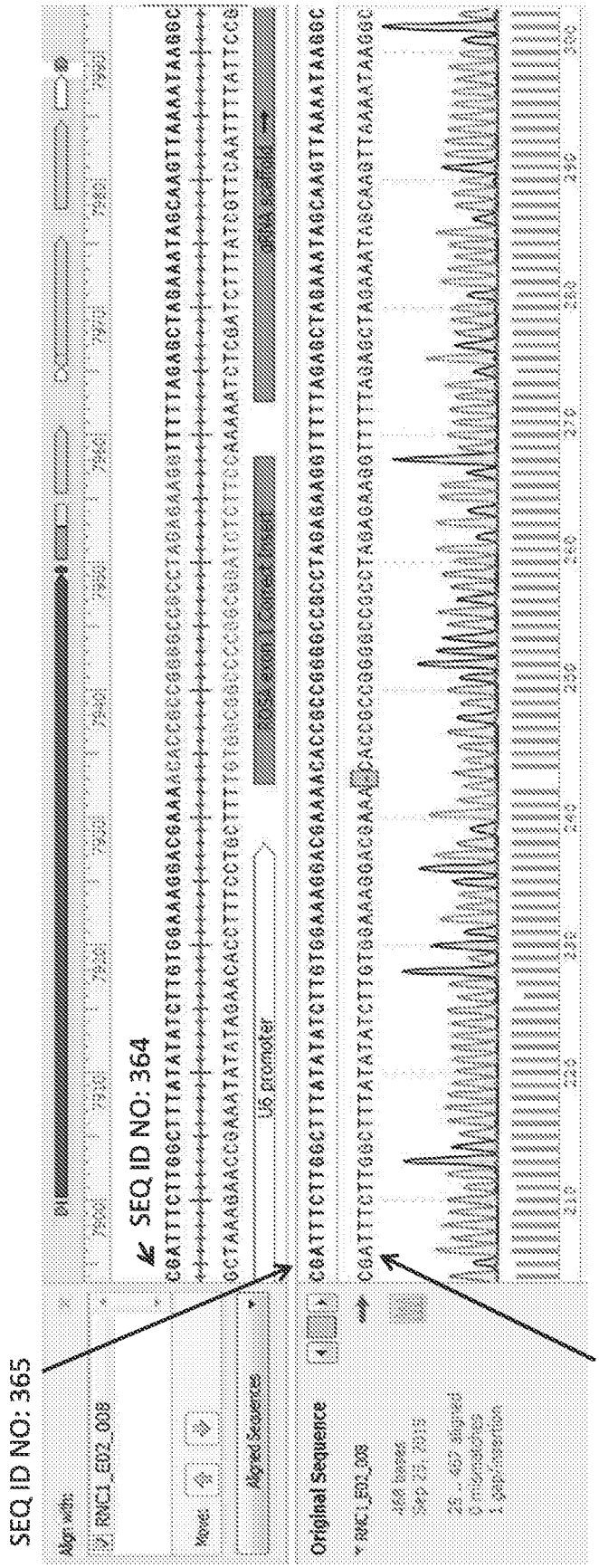

SEQ ID NO: 365
SEQ ID NO: 364
SEQ ID NO: 366
Align with:
RMC1_E02_008
Moves
Aligned Sequences
Original Sequence
RMC1_E02_008
16 promoter

FIG. 27B

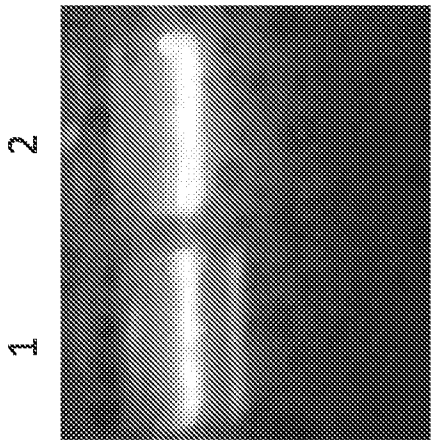


FIG. 27C

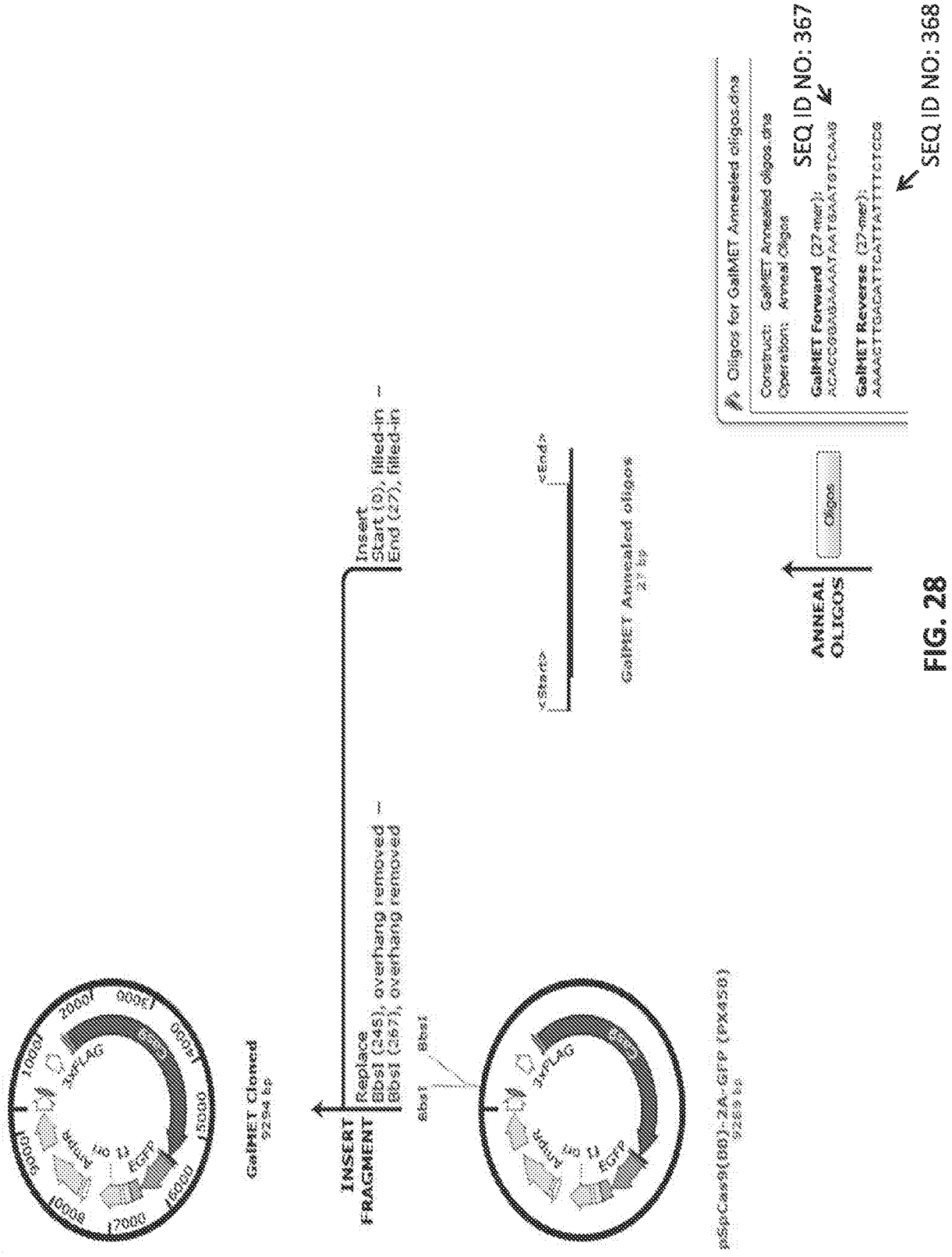

Oligos for GalMET Annealed oligos.dna
Construct: GalMET Annealed oligos.dna
Operation: Anneal Oligos
GalMET Forward (27-mer):
ACACCGGGAAAATAATGAATGTCAAG
SEQ ID NO: 367
GalMET Reverse (27-mer):
AAAAGTTGACATTCATTATTTTCTCCGG
SEQ ID NO: 368
ANNEAL OLIGOS
Oligos
GalMET Annealed oligos
27 bp
<Start>
<End>
INSERT FRAGMENT
Replace
BbsI (246), overhang removed →
BbsI (267), overhang removed
Insert
Start (0), filled-in →
End (27), filled-in
BbsI
BbsI
GalMET Cloned
9254 bp
pXpCas9(GD1)-2A-GFP (PX458)
9269 bp
3xFLAG
EGFP
U6 Promoter
sgRNA
2A
SpCas9
NLS
NLS

FIG. 28

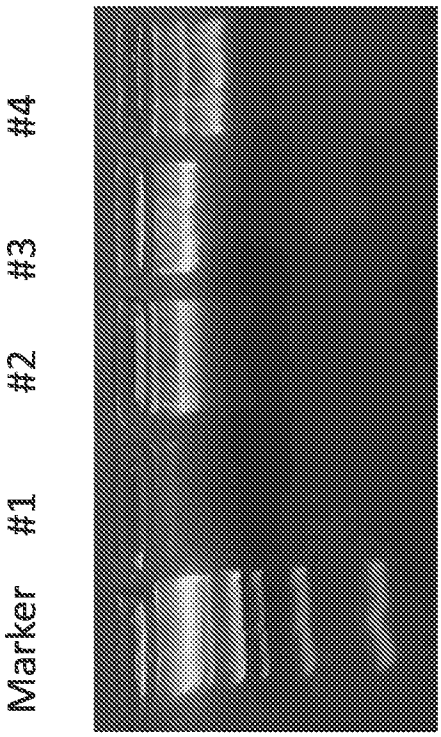


FIG. 29

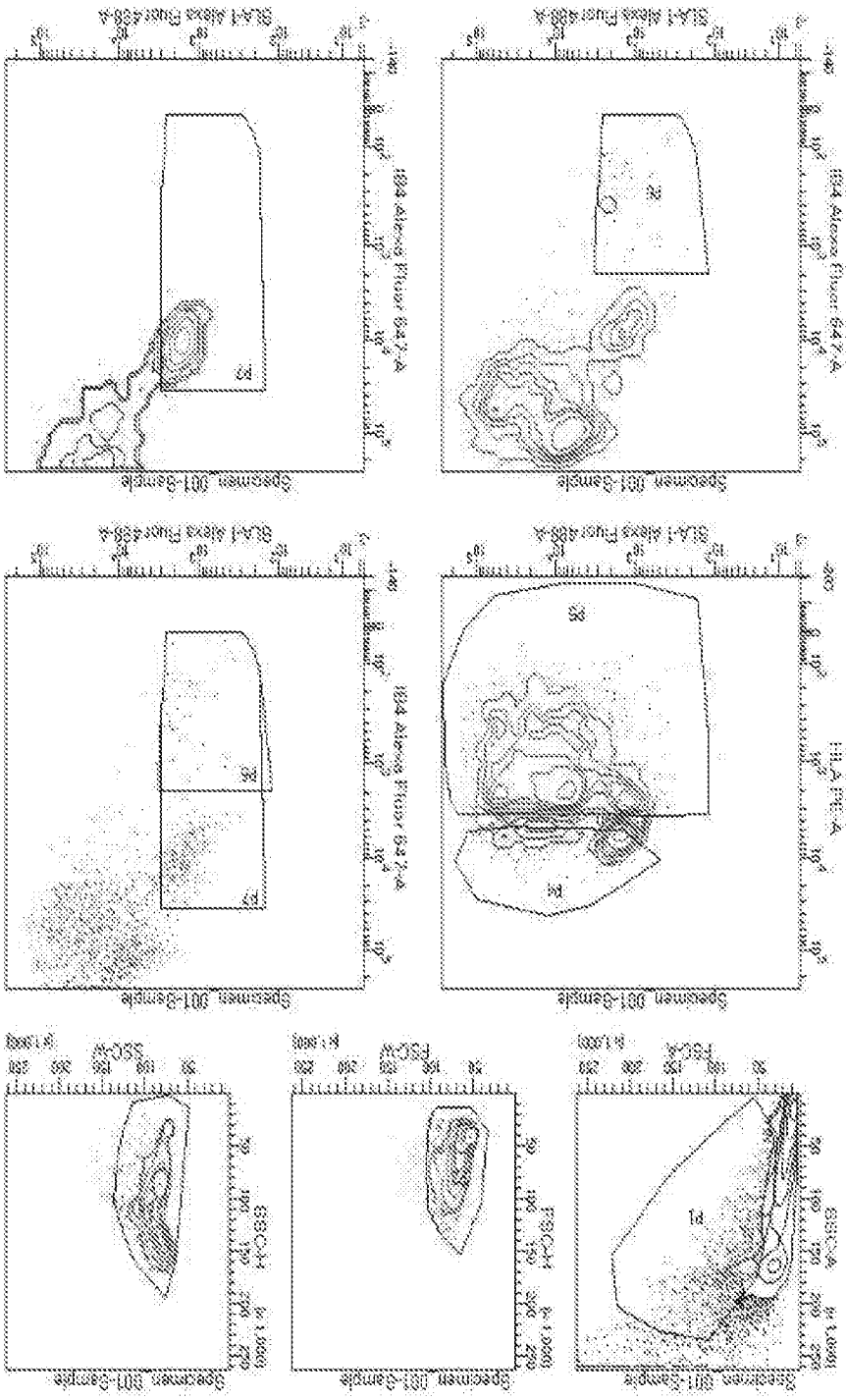


FIG. 30

Left Arm

CD47 codon

Right Arm

ATGTAATGCCCTACTTTATCTTTGTTACATTCTTTGTTATGAGTATTGGCTAGCTGCCACACTTTCTGTCCTTCCATTTGAAAT
AAATATCTTTCTATCTCCACCCAAATTAAAGTACTCCGCAACCTGTTATTCCACCCAGCATCCCTTCCCTCTTCAACTACAATTTCATGCAGCGATCA
AGAAATACGAATGTACCGACTGTTTGCCACTTGTGGGTGCATTGGGGAAAAGCTGGGTGGGAAGTGGCAGAGCCTAGATTATAAAGGACCA
GGGTGAGAGTTCCCACTTGTGGCTCAGCTGAAATGAATCTGACTAGCATCCATGAGGACGAAGGTTTGATCCCTGGCCTCAATCAGTGGGTTAAG
GATCTGGCGTTGCTGTCCGTGAGTTGTGGTAGTTCGCAGACAAGGCGTGGACTTAGTGTGGCTGTGGCTAGTGGCATAGGCTAGTGGCTACAG
CTCTGATTCGACCCCTAGCCTGGGAATCTCTATATGCTGTGAGTGTGGCCCTAAAATTTAAATGAAATTAAATAAAGGACCAGGGTATATTTTTCT
TTGAGGATAAGGTACATAGTCAGTATATCAGGGACAGTAGACCTAGGAAACGGATGCTTCCTCTAGTCTGTGATGCGAGGTGGGGCATCTGAGT
TGGGGGCGGCTGGAGCCCTTAGGGACCATTAACTAAACCCGTCACTCTCCCACATCTCGGTGGACCTTGGGATCAGTCAGGATGCTTCCCCTTTG
AGCCTCAAAATGGCCTTAGTATCCTTCCCAACCCAGACGGCCCTGTCAGTTCATTGACTTGGCTAATTTGCCAGTGTAGGCCTATGCAAATTAAGG
TAGAACGCACTCCTTAGCGCTCGTTGACTATTCATCAACTTTCCTTTTAGAAAAGATATTGGTATAAGCACTTCTTAAAAAACCATATTCCACTCT
GGGTGTATTTAATCTAATTTTCCCTTCTTTCTTTTCCCAGATGTGGCCCCCTTGTCGCTGCCCTTCTTTTGGGCTCTGCATGTTGCGGCTCCGCA
CAGCTCCTTTTCAACAAAACGAAGTCAGTTGAGTTCACCTTCTGTAATGATACCGTTGTGATCCCTTGTTTTGTCACCAACATGGAAGCCCAAAATA
CGACTGAGGTCTACGTCAAGTGGAAATTCAAGGGGAGGGATATTTATACGTTTGATGGTGCTCTGAATAAATCTACGGTTCCGACGGATTTTAGT
TCCGCAAAGATTGAAGTGTCTCAGCTGTTGAAGGGTGACGCTTCCCTGAAAATGGATAAATCCGATGCCGTTAGCCATACGGGGAATTACACCTG
CGAGGTTACCGAACTCACCCGCGAGGGGGAGACGATAATAGAACTTAAGTATATAGGGGTGGTTAGCTGGTTCTCTCCAAACGAGAACATTCTGATA
GTTATTTTCCCAATCTTCGCTATATTGCTGTTCTGGGGTCAATTCGGCATTAAAAACGCTTAAATATAGGAGCGGCGGGATGGACGAGAAAACGAT
CGCCTTGCTTGTCGCAGGTTTGGTTATCACCGTCATTGTGATTGTCGGAGCCATCCTGTTTGTCCCTGGTGAGTATAGCTTGAAAAATGCCACTGG
CCTCGGTCTGATCGTGACGTCCACTGGCATCCTTATACTCCTTCATTATTATGTGTTCAGTACTGCCATTGGTCTTACGTCTTTTGTGATTGCCATCC
TCGTCATTCAGGTCATCGCATACATACTCGCAGTCGTCGGTTTGAGCCTGTGCATCGCAGCGTGCATTCCCATGCGGACCTCTCTTGATCTCTG
GTCTTTCTATATTGGGCGCTGGCACAACTCTTGGCTTGGTTTACATGAAGTTTGTCGCCTCTAATCAGAAGACGATCCAACCCCCGCGCAACAACT
GATGGTTCTGTCAATGCTGCTTGTCTCAACTGTAATGGTTGTTTTGGGAATACATCAACAGGTAATTATGAAACATGATGAAATGATGTTGATG
AAAGTCTCCTCTAATCTCCTAGTTATCAGCCAAGTTCACCAGCTTGCATTAAAAGTAGGATTCACTGACACCGTAAAGAAAGCATTCCAGAGAGTTG
CCGTTGTGGCTCAGGGGCAGCAAACCCAATTAGGATCCAAGAGGAGGTGGGTTTGATCCCTGGCCTTGCTCTTTGGCTTAAGGATCCGGCATTG
CCGTGACCTGTGGTGTAGGTTGCAGATGCAGCTCGGATCTGGCATTGCTGTGGCTGTGGCGTAGGCTGGTGGCTTCAGCTCCAGTTTGACCCCTA
GCCTGGGAACTTCCATATCCCACACTTGCGGCCCTAAAAAGCAAAGAAAGAAAGAAAATATTCTACCCTTCCTGTATCCCTGAGCCCTTAAATACC
GTCTTTAAAGTCATTAGATCTTCAAGTACCTTCCAGCTAATTAATTATCTTCCTTCCTGATGTCCTGATTTTTATACCTCTGCAGTTC
TGGGTAGGCTAGAGCCAGAAATAATAAGGTCATGTTAAGACCAAGATATAATTATTATATGACCAGATATGGAAGTTACCTTGAGAA
CTTTCAGACAGGAATTCCATGAGAAATACACCCTGATTTTTTGCAATCCTAAAATATTTGCAGAGTTTAAAGGAACAACTCAAGTTGTTGACTTTTG
CTGCAAAACACACTGAGTCGCTGGTGATTCATTTGTGCCTGGCTAAACTTTTGGGTGTTTTGTCTTTTTTTTTTAACTCTGGAAAGCAAAATGAATT
AAACATTTCTGAGTTTTCAAATTCATCAGTGGATTCACCCCAAATATTTGACGCTGCTTCTTTTGCTTTTGGAAACTACGATGCCTTGGAGATTCCAG
CTGGAGACGCTTCTGACAGAAAGAAATGTCTGCAAGCAGCT

SEQ ID NO: 369

FIG. 31

SEQ ID NO: 370

Sequence confirmation for Gibson assembly of right arm:
CTCTCTTTCATCTCTGGTCTTTCTATATTGGCGCTGGCACAACTTCTTGGCTTGGTTTACATG
AAGTTTGTCGCCTCTAATCAGAAGACGATCCAACCCCCGCGCAACAACTGATGGTTCTGTC
AATGCTGCTTGTCTCAACTGTAATGGTTGTGTTTTGGGAATACATCAACAGGTAATTATGAA
ACATGATGAAATGATGTTGATGAAAGTCTCCTCTAATCTCCTAGTTATCAGCCAAGTCACCA
GCTTGATTAAAAGT

FIG. 32A

SEQ ID NO: 371

Sequence confirmation for Gibson assembly of left arm:
AGAAAAGATATTGGGTATAAGCACTTACTTAAAAAACCATATTCCACTCAGGGTGTATTTA
ATCTAATTCTTCCCTTCTCCTTTTCTTTTCCCAGATGTGGCCCCTTGTCGCTGCCCTTCTTT
TGGGCTCTGCATGTTGCGGCTCCGCACAGCTCCTTTTCAACAAAACGAAGTCAGTTGAG
TTCACCTTCTGTAATGATACCGTTGTGATCCCTTGTTTTGTCACCAACATGGAGCCCAAAA

FIG. 32B

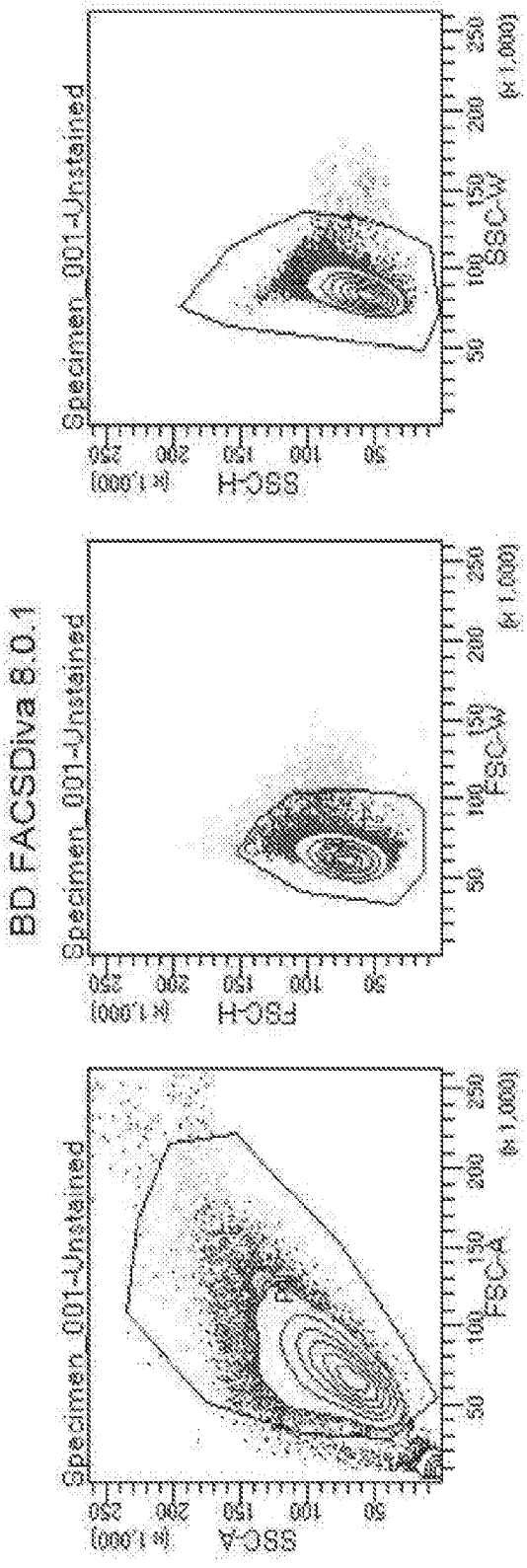

BD FACSDiva 8.0.1
Specimen_001-Unstained
SSC-A
FSC-A
FSC-H
FSC-W
SSC-H
SSC-W
(x 1,000)

FIG. 33A

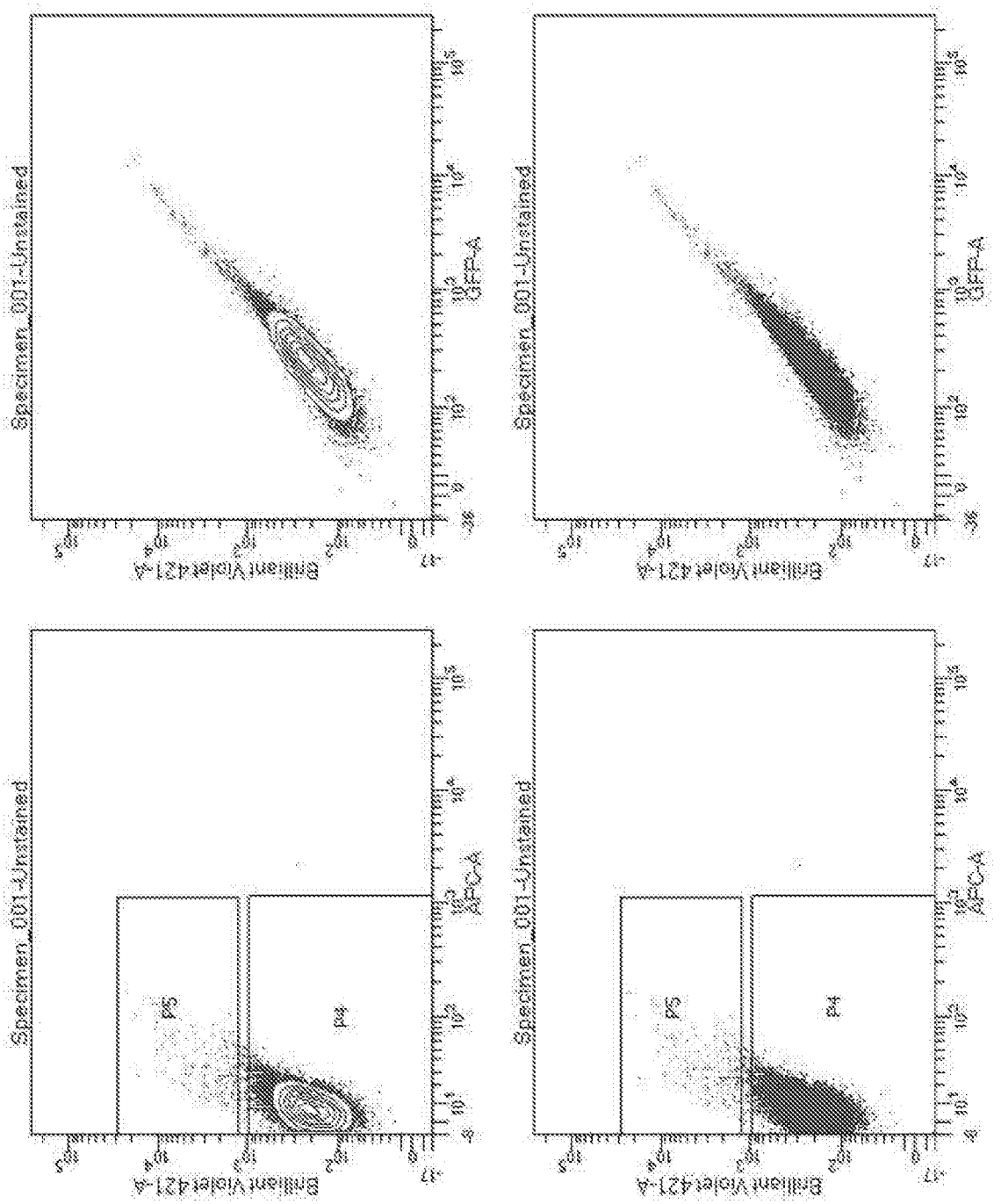

Specimen_001-Unstained
Brilliant Violet 421-A
GFP-A
APC-A
P5
P4

FIG. 33B

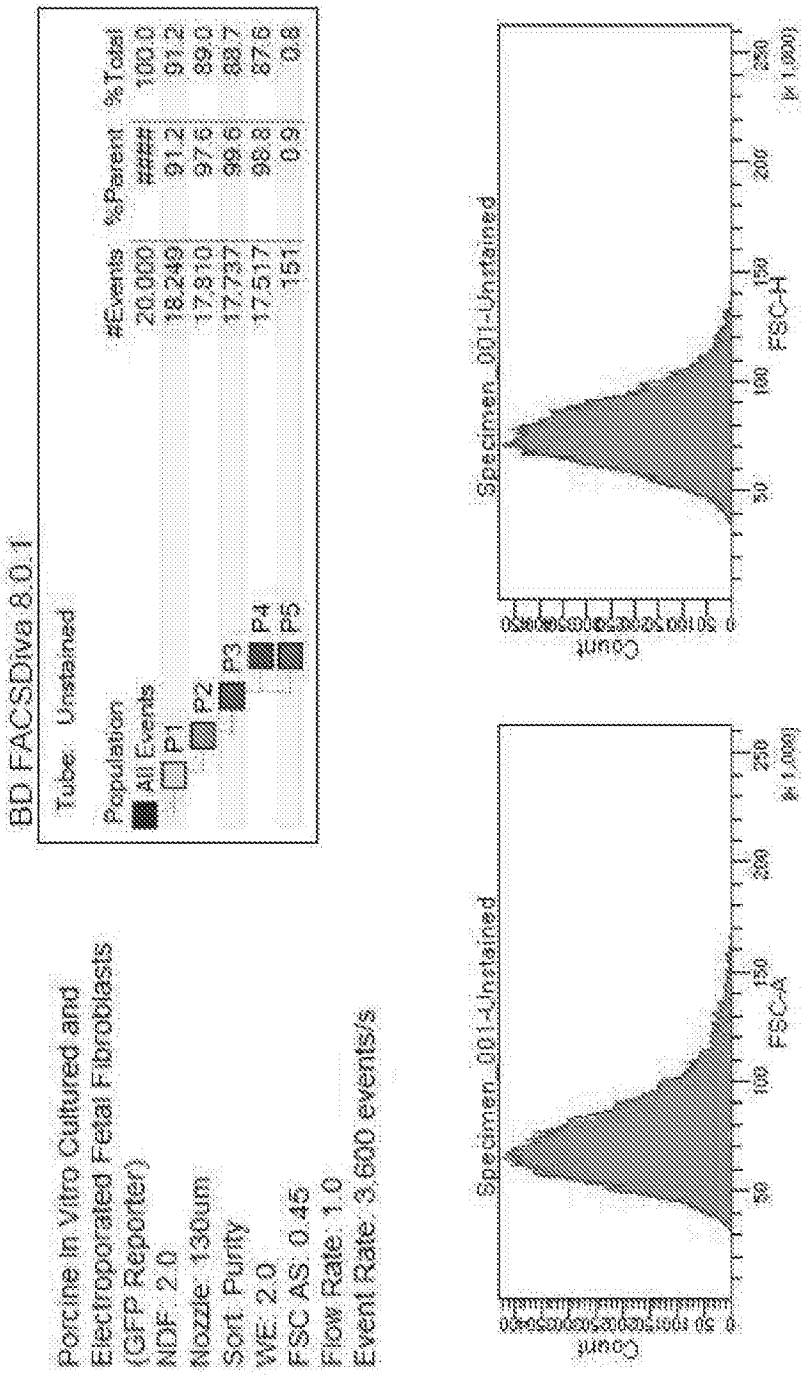

BD FACSDiva 8.0.1
Tube: Unstained
Population
All Events
P1
P2
P3
P4
P5
#Events
20,000
18,249
17,910
17,737
17,517
151
%Parent
####
91.2
97.6
99.6
98.8
0.9
%Total
100.0
91.2
89.0
88.7
87.6
0.8
Porcine In Vitro Cultured and Electroporated Fetal Fibroblasts (GFP Reporter)
NDF: 2.0
Nozzle: 130um
Sort Purity
WE: 2.0
FSC AS: 0.45
Flow Rate: 1.0
Event Rate: 3,600 events/s
Specimen_001-Unstained
Count
FSC-A
Specimen_001-Unstained
Count
FSC-A

FIG. 33C

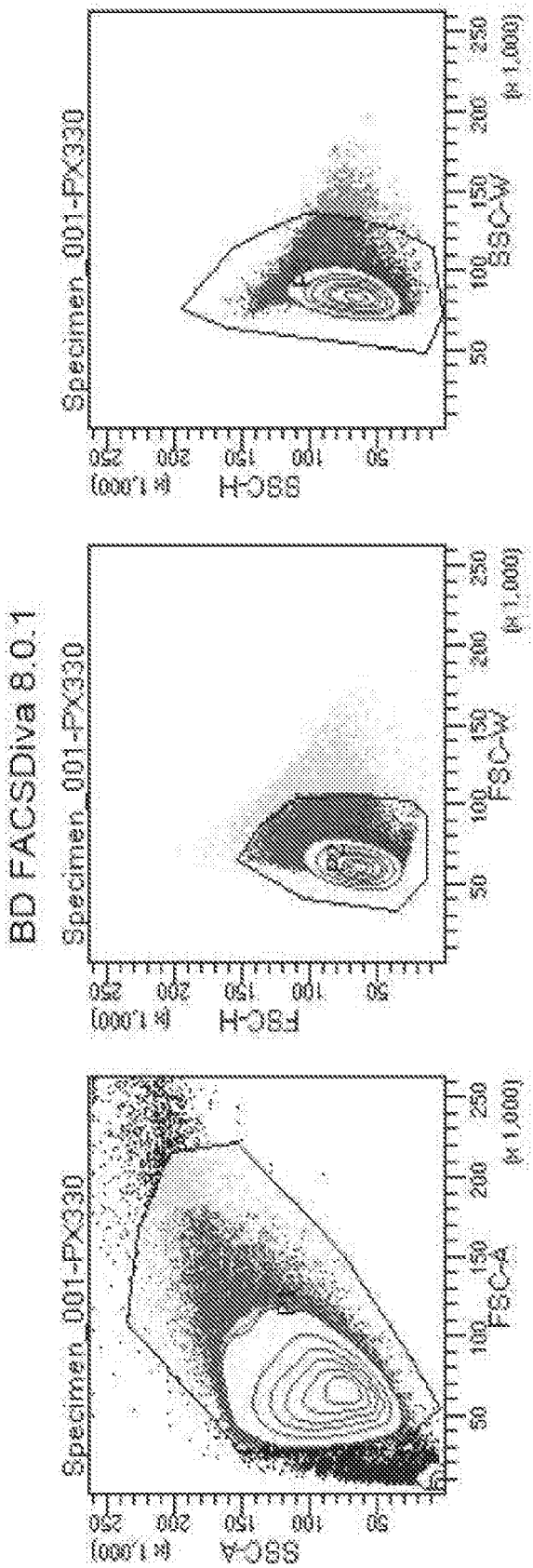

BD FACSDiva 8.0.1
Specimen_001-PX330
SSC-A
FSC-A
FSC-W
SSC-W
(x 1,000)

FIG. 34A

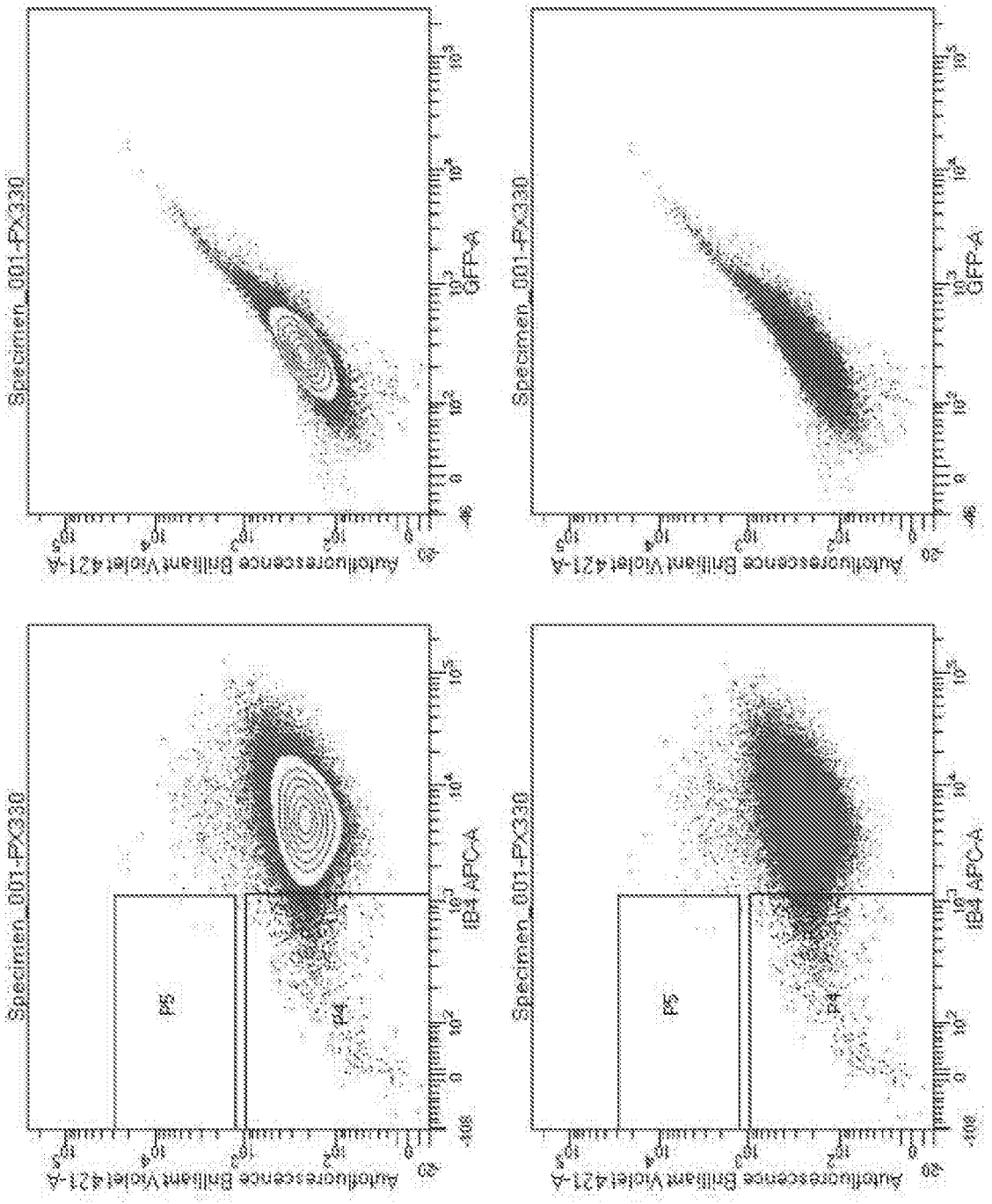

Specimen_001-FX330
Specimen_001-FX330
Specimen_001-FX330
Specimen_001-FX330
Autofluorescence Brilliant Violet 421-A
IB4 APC-A
GFP-A
P4
P5

FIG. 34B

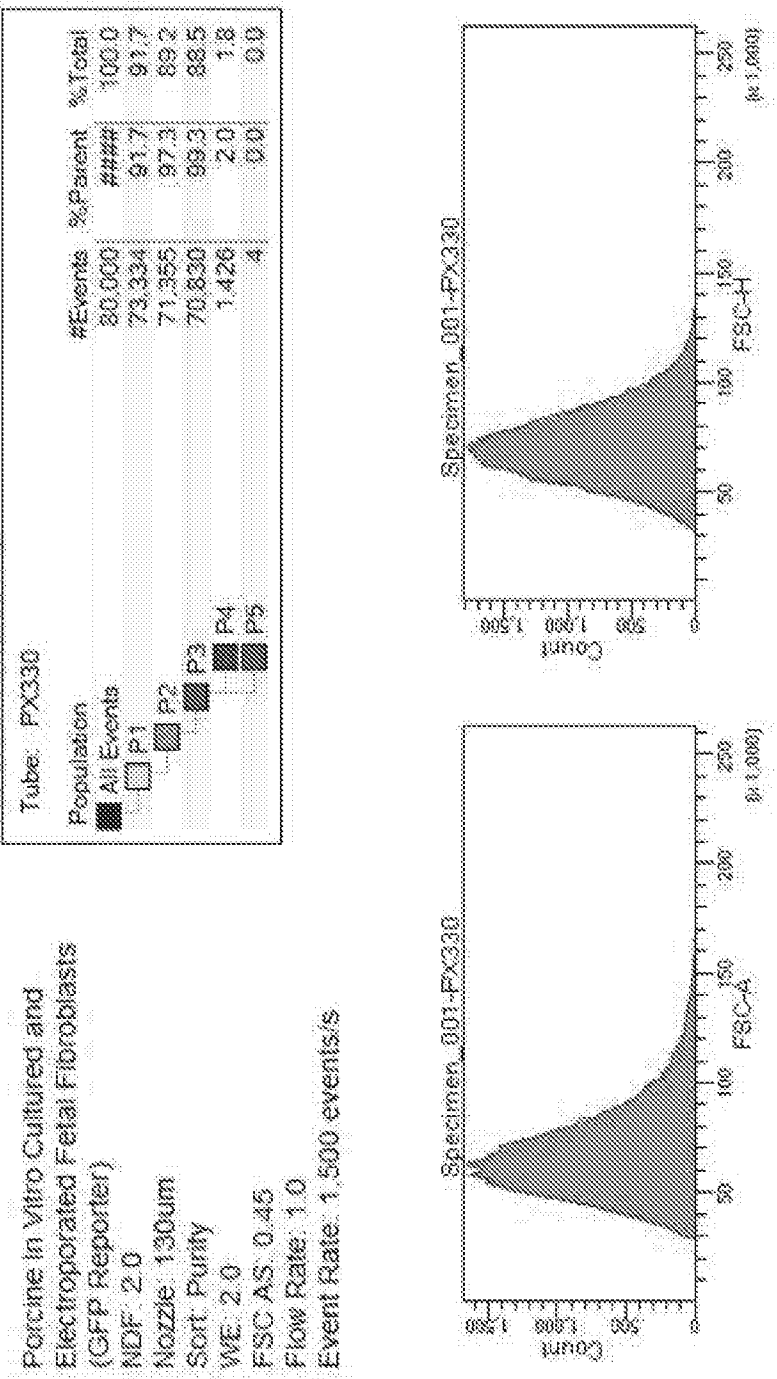

BD FACSDiva 8.0.1
Tube: PX330
Population
All Events
P1
P2
P3
P4
P5
#Events
80,000
73,334
71,355
70,830
1,428
4
%Parent
#####
91.7
97.3
99.3
2.0
0.0
%Total
100.0
91.7
89.2
88.5
1.8
0.0
Porcine In Vitro Cultured and Electroporated Fetal Fibroblasts (GFP Reporter)
NDF: 2.0
Nozzle: 130um
Sort: Purity
WE: 2.0
FSC AS: 0.45
Flow Rate: 1.0
Event Rate: 1,500 events/s
Specimen_001-PX330
Count
FSC-A
FSC-H

FIG. 34C

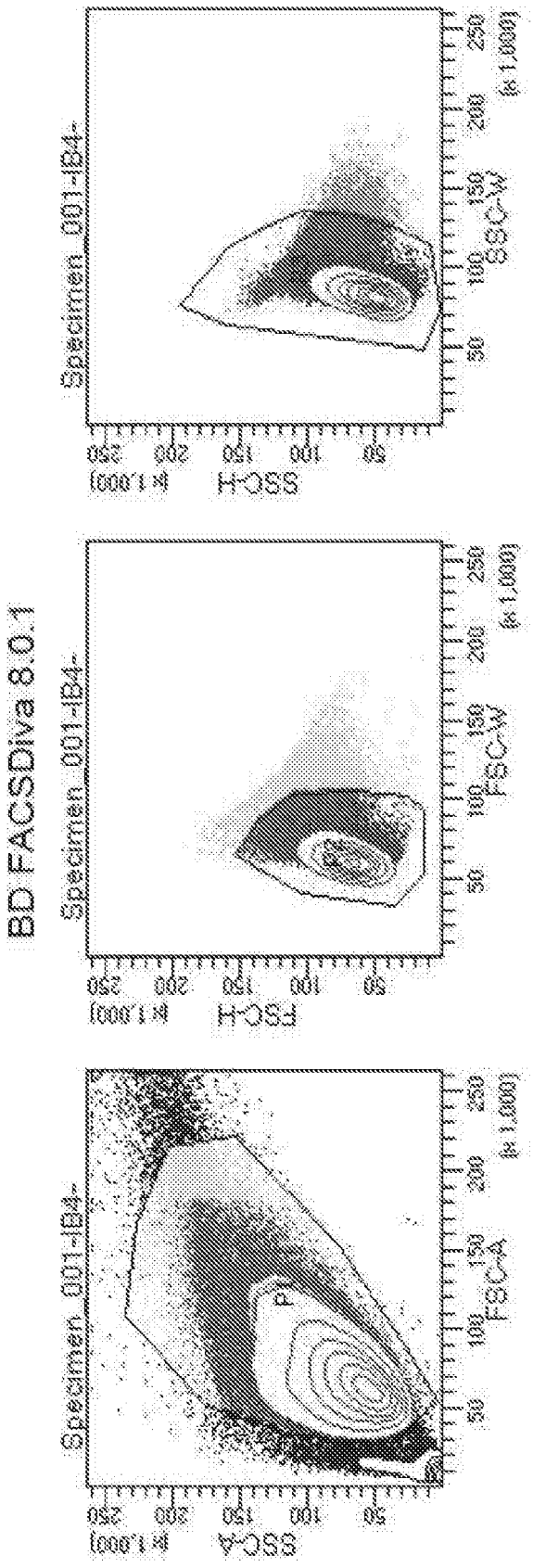

BD FACSDiva 8.0.1
Specimen_001-IB4-
SSC-H
SSC-W
FSC-H
FSC-W
FSC-A
SSC-A
P1
50
100
150
200
250
(x 1,000)

FIG. 35A

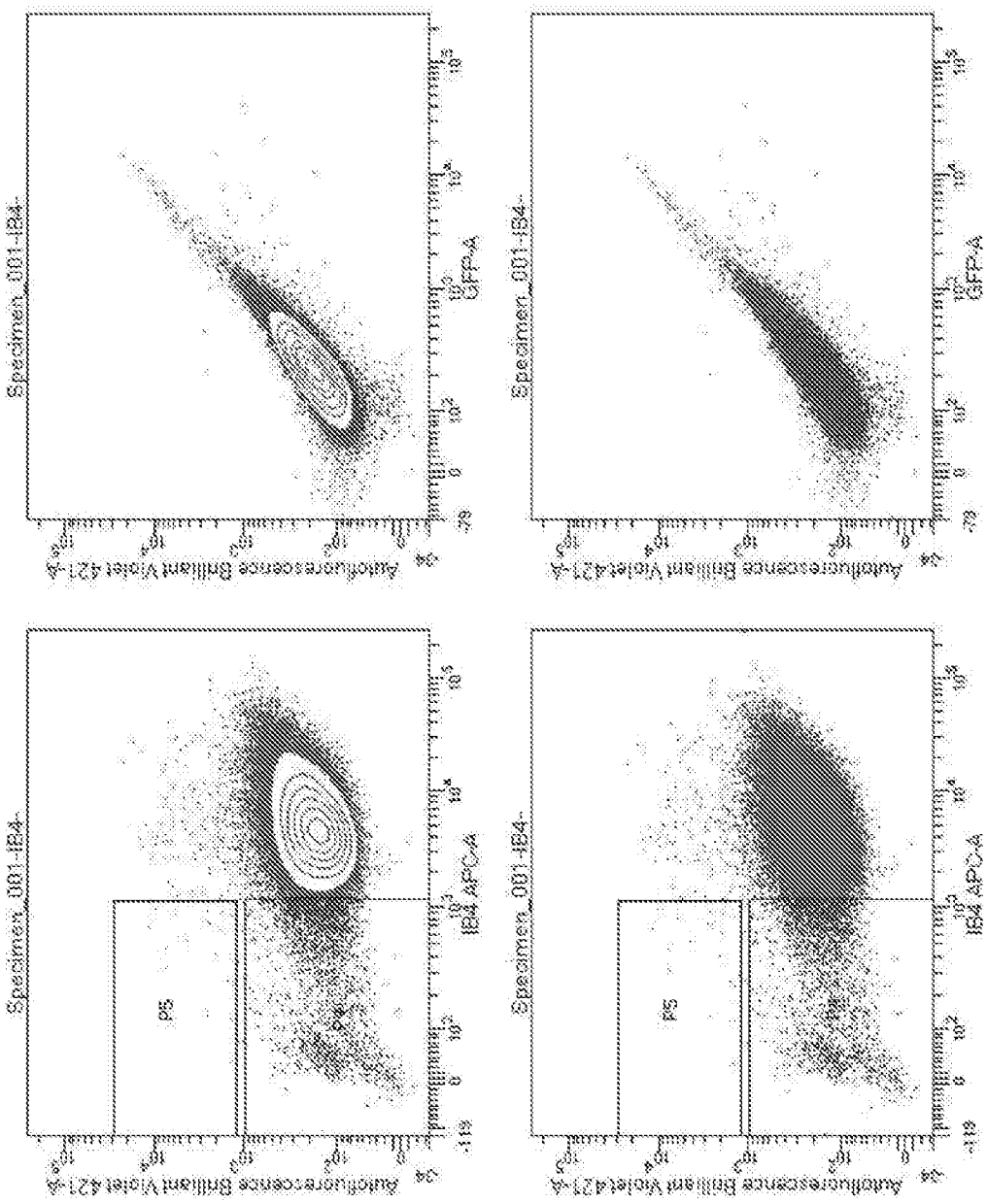

Specimen_001-IB4-
Autofluorescence Brilliant Violet 421-A
GFP-A
IB4 APC-A
P8

FIG. 35B

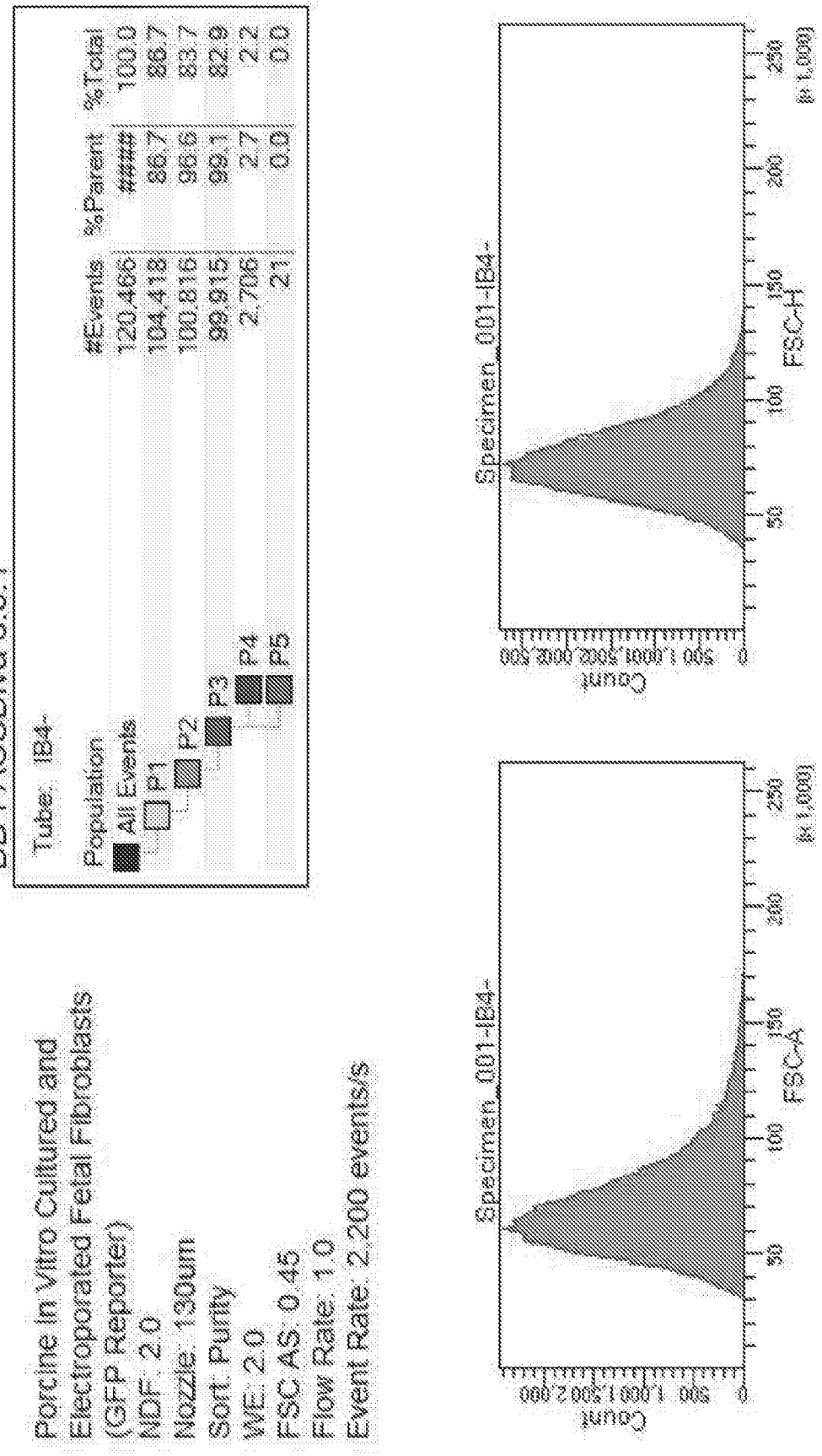

BD FACSDiva 8.0.1
Tube: IB4-
Population
#Events
%Parent
%Total
All Events
120,466
####
100.0
P1
104,418
86.7
86.7
P2
100,816
96.6
83.7
P3
99,915
99.1
82.9
P4
2,706
2.7
2.2
P5
21
0.0
0.0
Porcine In Vitro Cultured and Electroporated Fetal Fibroblasts (GFP Reporter)
NDF: 2.0
Nozzle: 130um
Sort: Purity
WE: 2.0
FSC AS: 0.45
Flow Rate: 1.0
Event Rate: 2,200 events/s
Specimen_001-IB4-
Count
FSC-A
FSC-H
(x 1,000)

FIG. 35C

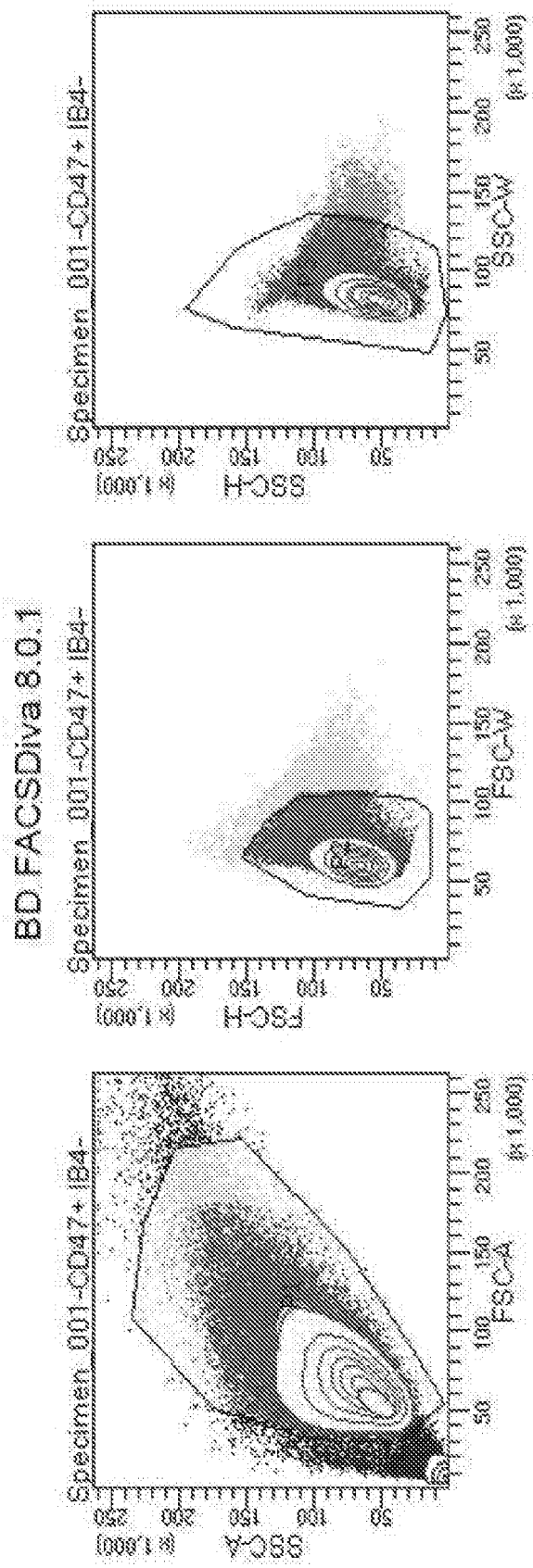

BD FACSDiva 8.0.1
Specimen_001-CD47+ IB4-
SSC-A
FSC-A
FSC-H
SSC-H
FSC-W
SSC-W
(x 1,000)

FIG. 36A

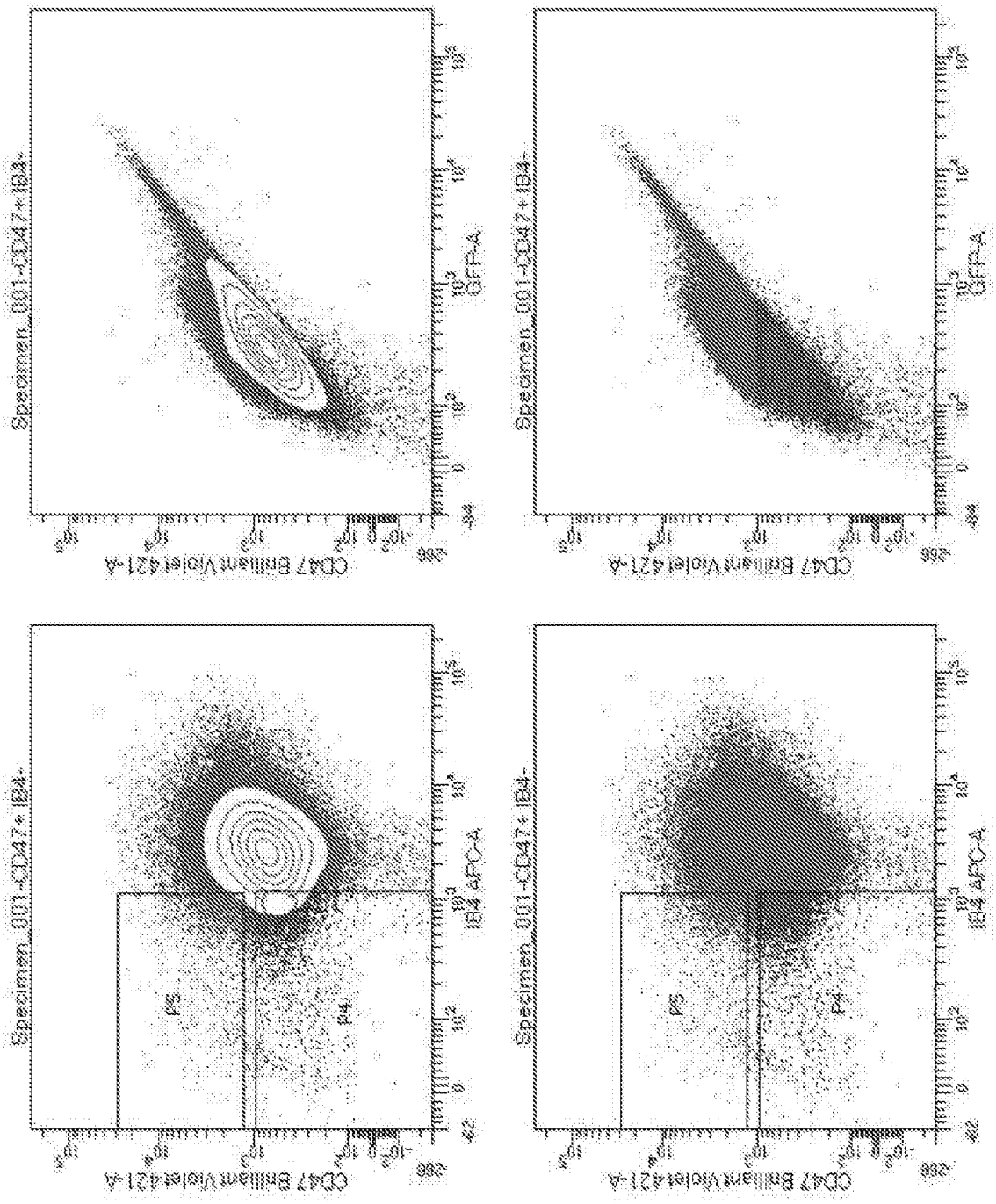

Specimen_001-CD47+ IB4-
CD47 Brilliant Violet 421-A
GFP-A
IB4 AFC-A
P5
P4

FIG. 36B

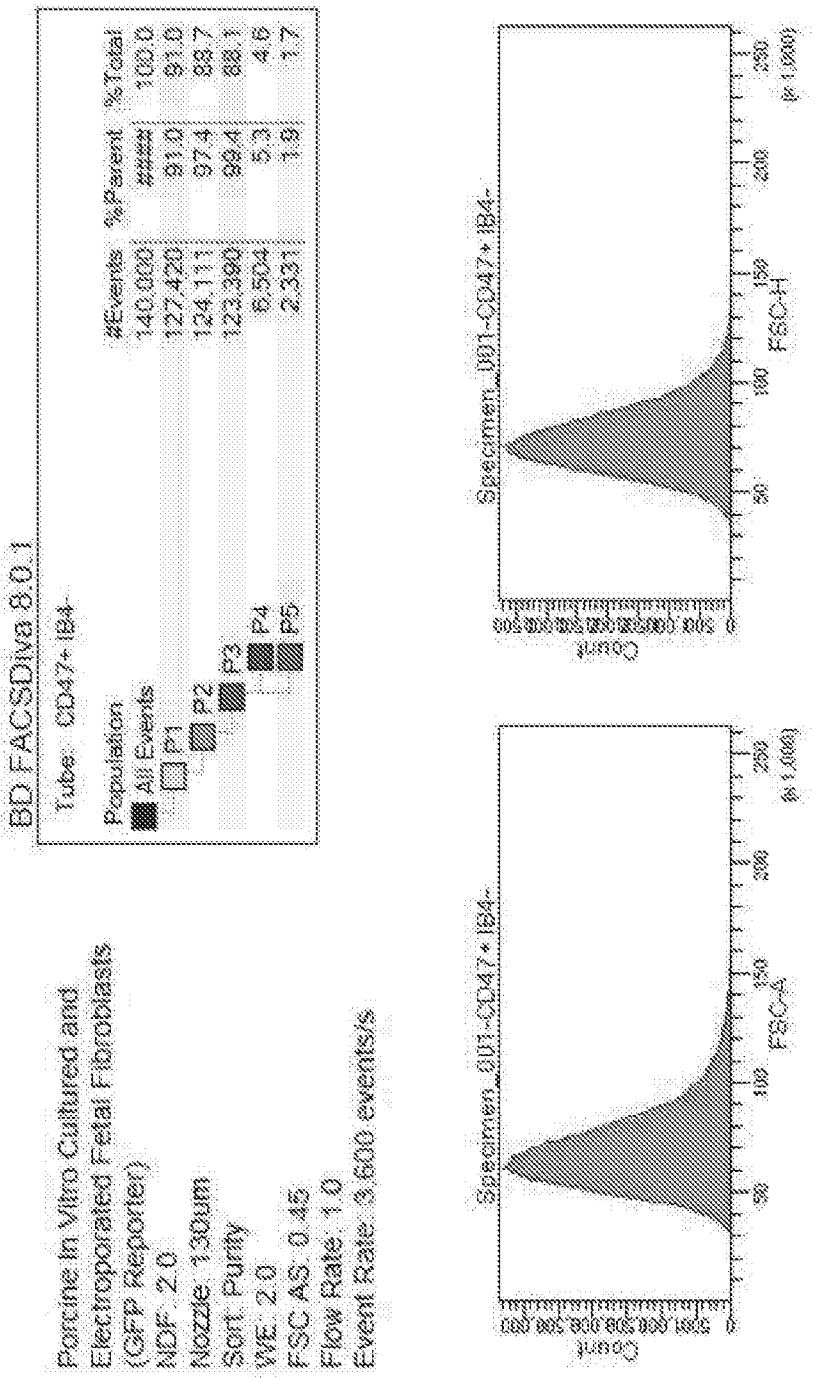

BD FACSDiva 8.0.1
Tube: CD47+ IB4-
Population
All Events
P1
P2
P3
P4
P5
#Events
140,000
127,420
124,111
123,380
6,504
2,331
%Parent
####
91.0
97.4
99.4
5.3
1.9
%Total
100.0
91.0
88.7
88.1
4.6
1.7
Porcine In Vitro Cultured and
Electroporated Fetal Fibroblasts
(GFP Reporter)
NDF: 2.0
Nozzle: 130um
Sort Purity
VIE: 2.0
FSC AS: 0.45
Flow Rate: 1.0
Event Rate: 3,600 events/s
Specimen_001-CD47+ IB4-
Count
FSC-A
FSC-H
(x 1,000)

FIG. 36C

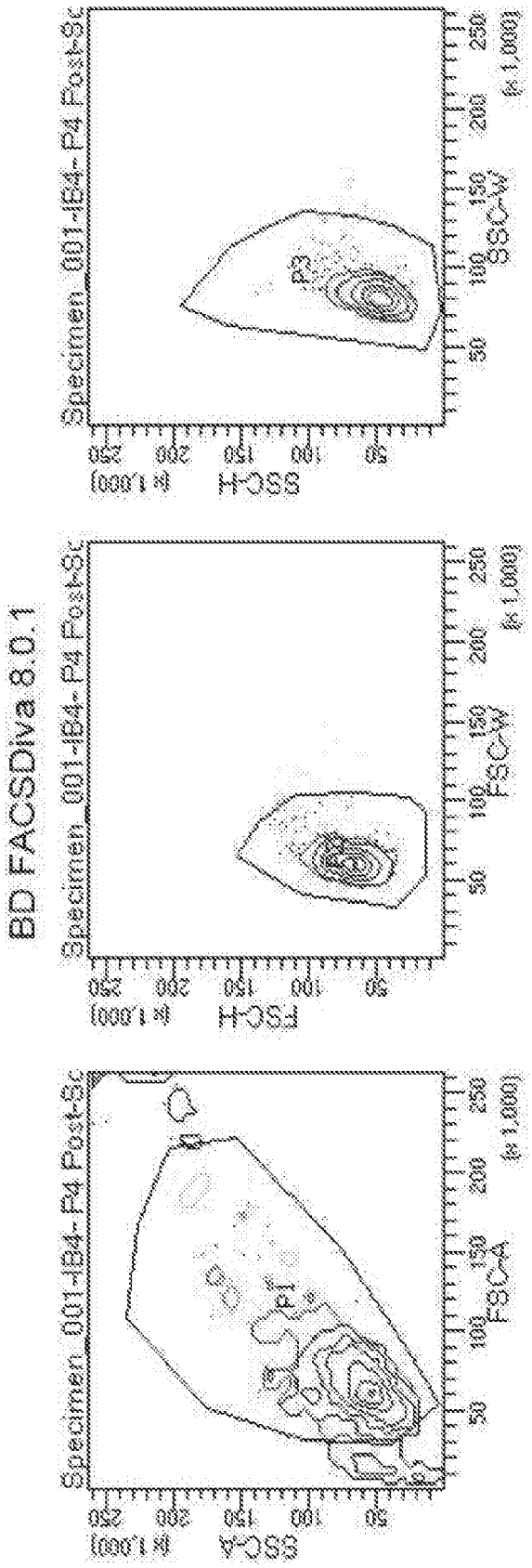

BD FACSDiva 8.0.1
Specimen_001-4B4- P4 Fixat-Sc
SSC-A
FSC-A
FSC-H
FSC-W
SSC-H
SSC-W
P1
P3
(x 1,000)

FIG. 37A

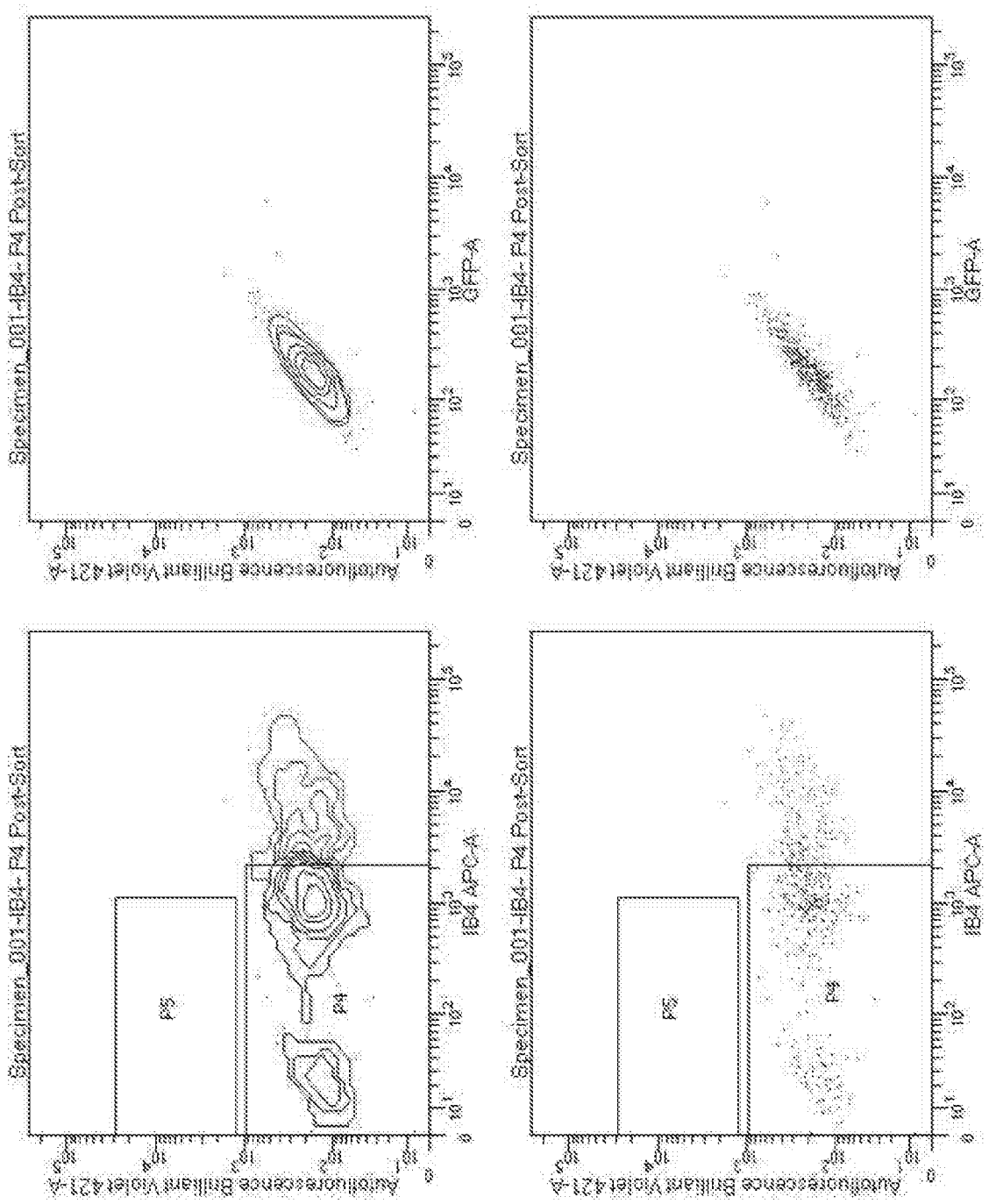

Specimen_001-IB4- P4 Post-Sort
Autofluorescence Brilliant Violet 421-A
GFP-A
IB4 APC-A
P5
P4

FIG. 37B

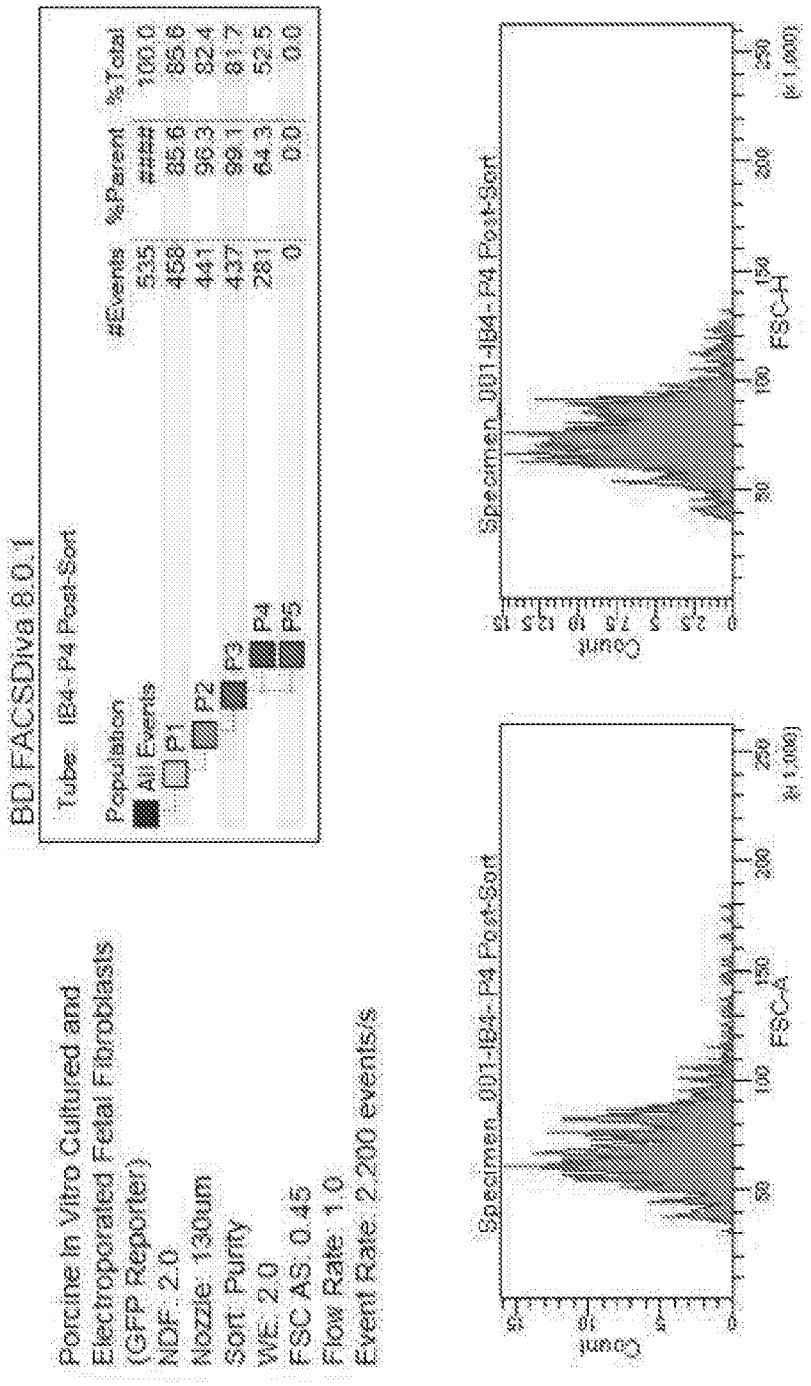

BD FACSDiva 8.0.1
Tube: IE4- P4 Post-Sort
Population
All Events
P1
P2
P3
P4
P5
#Events
535
458
441
437
281
0
%Parent
###
85.6
96.3
99.1
64.3
0.0
%Total
100.0
85.6
82.4
81.7
52.5
0.0
Porcine In Vitro Cultured and Electroporated Fetal Fibroblasts (GFP Reporter)
NDF: 2.0
Nozzle: 130um
Sort: Purity
PE: 2.0
FSC AS: 0.45
Flow Rate: 1.0
Event Rate: 2,200 events/s
Specimen_001-IE4- P4 Post-Sort
Count
FSC-A
(x 1,000)
Specimen_001-IE4- P4 Post-Sort
Count
FSC-A
(x 1,000)

FIG. 37C

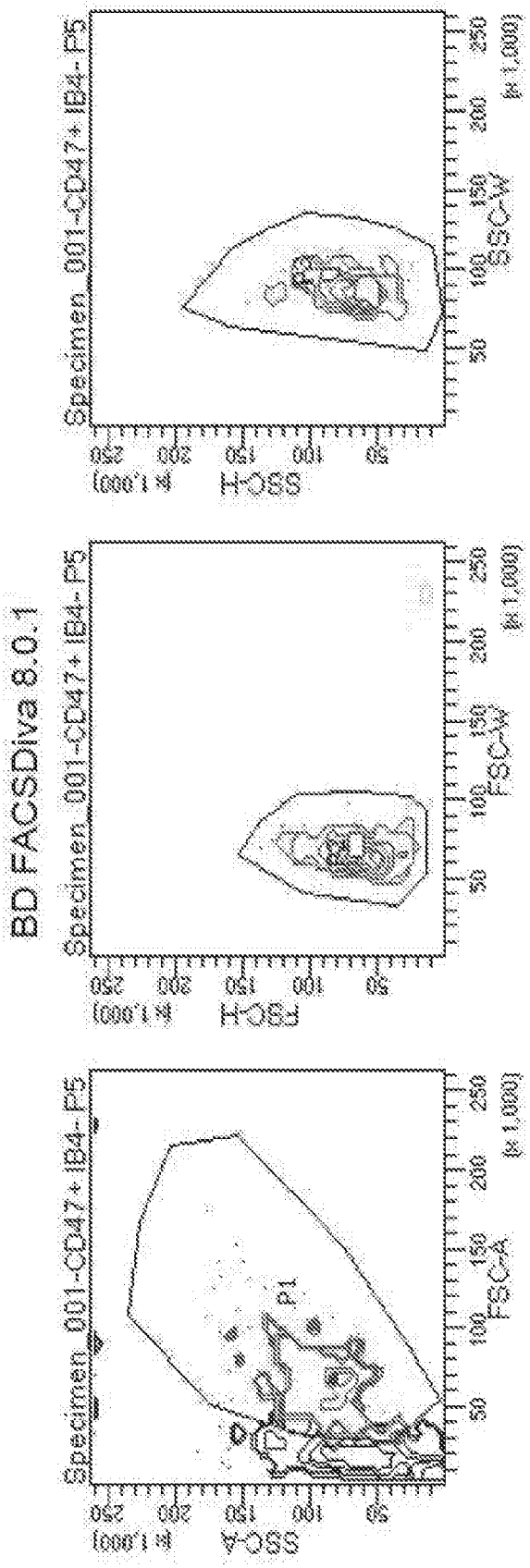

BD FACSDiva 8.0.1
Specimen_001-CD47+IB4-P5
SSC-A
FSC-A
SSC-W
FSC-H
P1

FIG. 38A

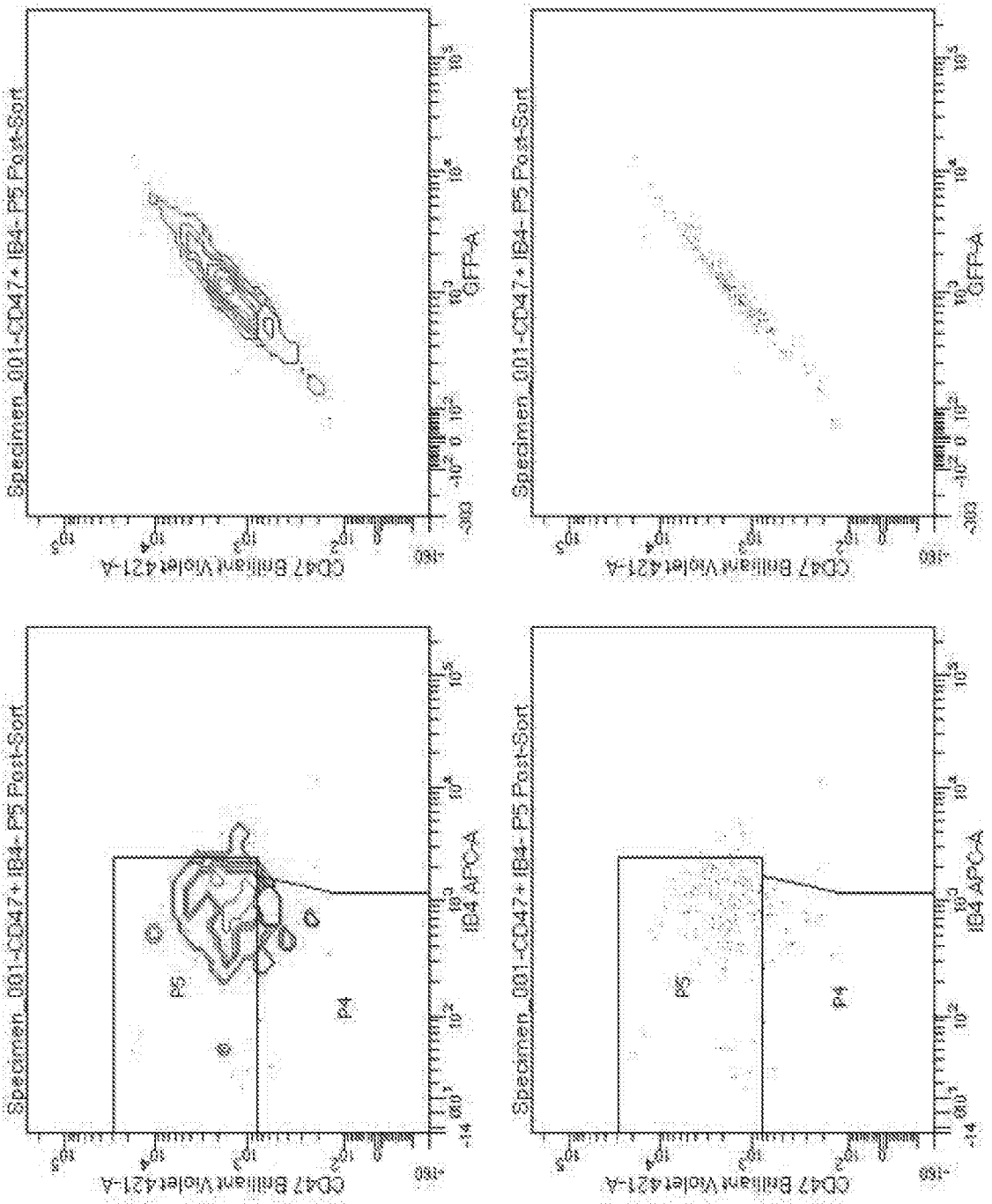

Specimen_001-CD47+ IB4- P5 Post-Sort
CD47 Brilliant Violet 421-A
GFP-A
Specimen_001-CD47+ IB4- P5 Post-Sort
CD47 Brilliant Violet 421-A
IB4 APC-A
P5
P4

FIG. 38B

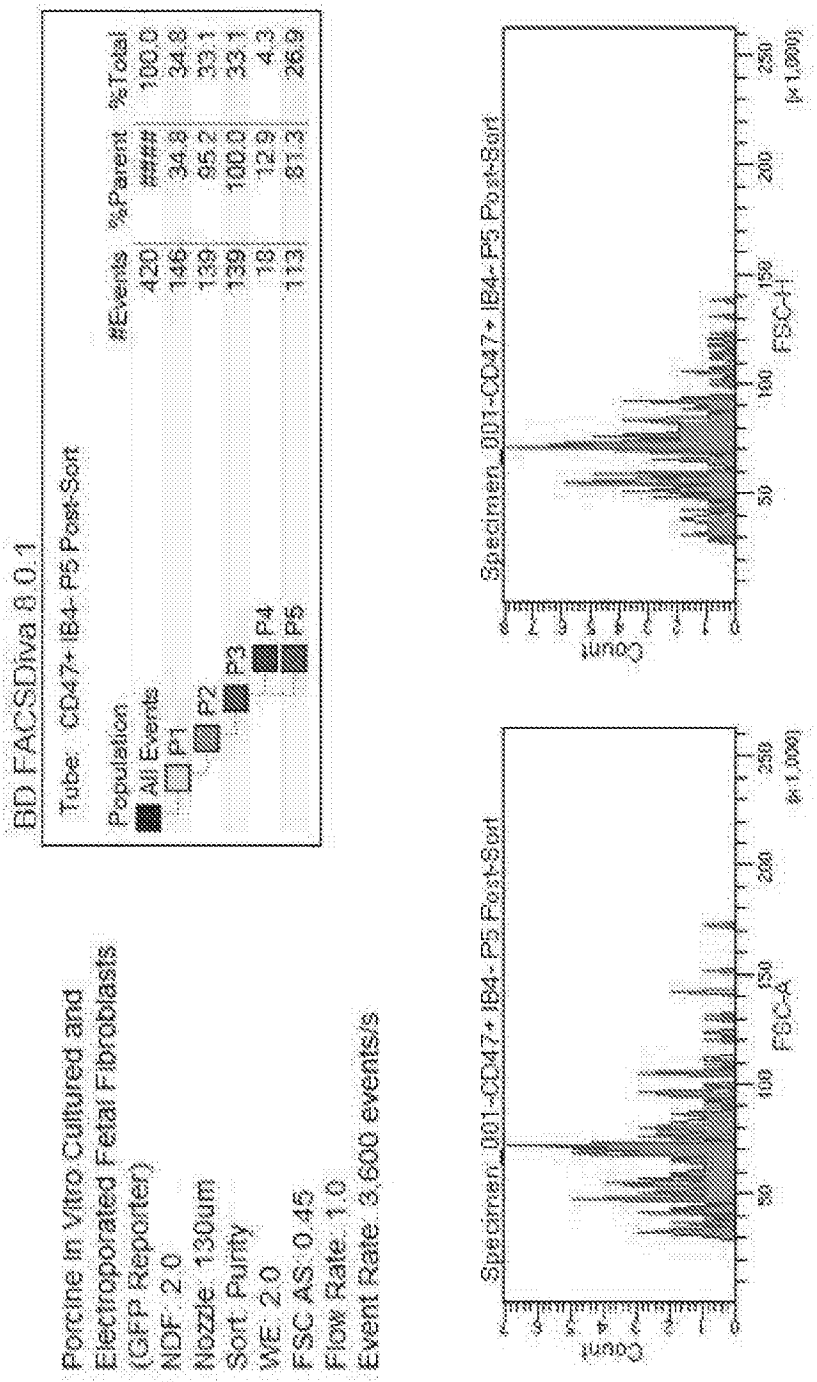

BD FACSDiva 8.0.1
Tube: CD47+ IB4- P5 Post-Sort
Population
All Events
P1
P2
P3
P4
P5
#Events
420
146
139
139
18
113
%Parent
####
34.8
95.2
100.0
12.9
81.3
%Total
100.0
34.8
33.1
33.1
4.3
26.9
Porcine In Vitro Cultured and
Electroporated Fetal Fibroblasts
(GFP Reporter)
NDF 2.0
Nozzle 130um
Sort Purity
WE 2.0
FSC AS 0.45
Flow Rate 1.0
Event Rate 3,600 events/s
Specimen_001-CD47+ IB4- P5 Post-Sort
Count
FSC-A
FSC-H

FIG. 38C

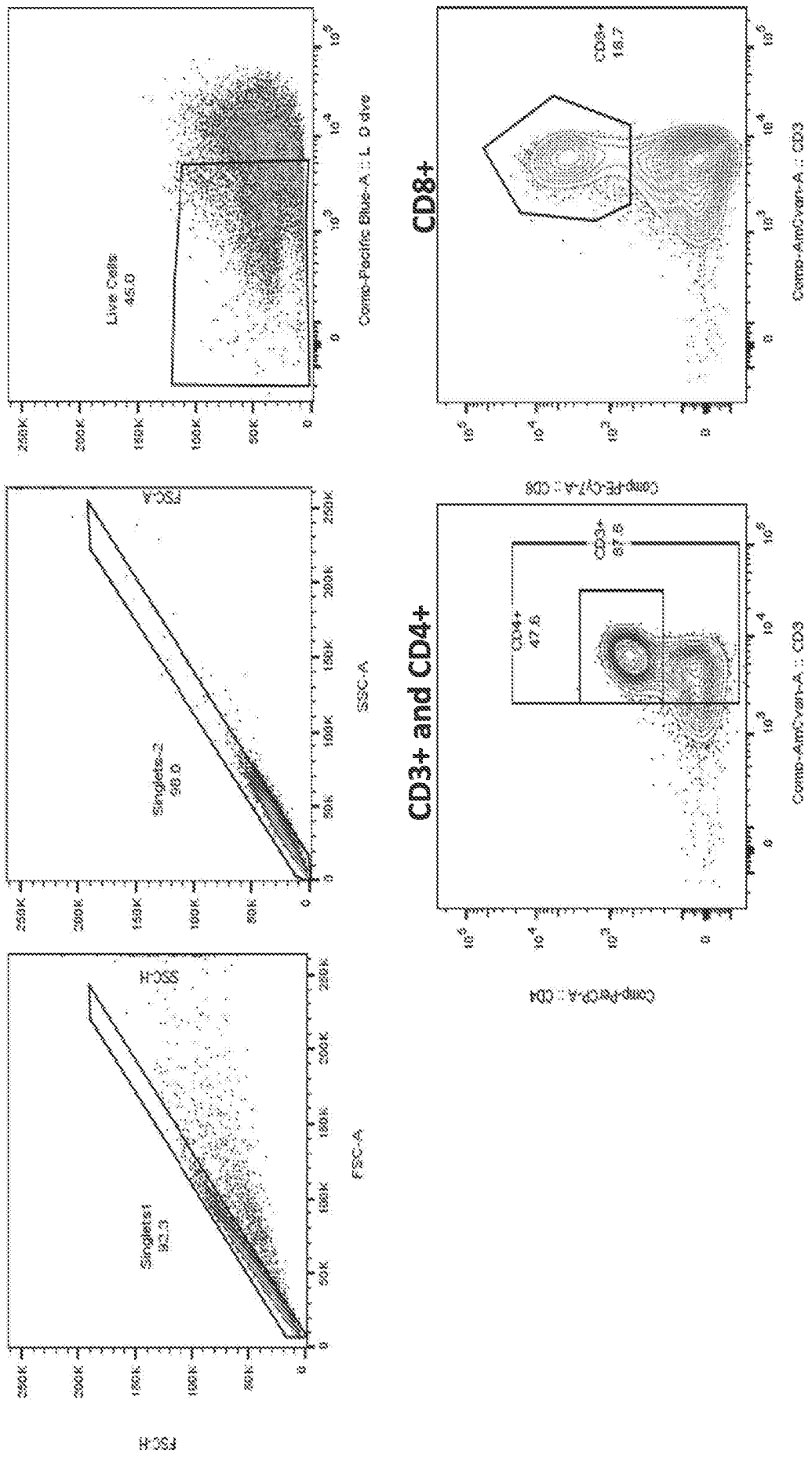

FSC-H
FSC-A
Singlets1
92.3
SSC-H
SSC-A
Singlets2
98.0
SSC-A
Live Cells
46.0
Comp-Pacific Blue-A :: L D dye
CD3+ and CD4+
Comp-PerCP-A :: CD4
Comp-APC-Cy7-A :: CD8
CD4+
47.6
CD3+
87.6
Comp-AmCyan-A :: CD3
CD8+
CD8+
18.7
Comp-AmCyan-A :: CD3

FIG. 39

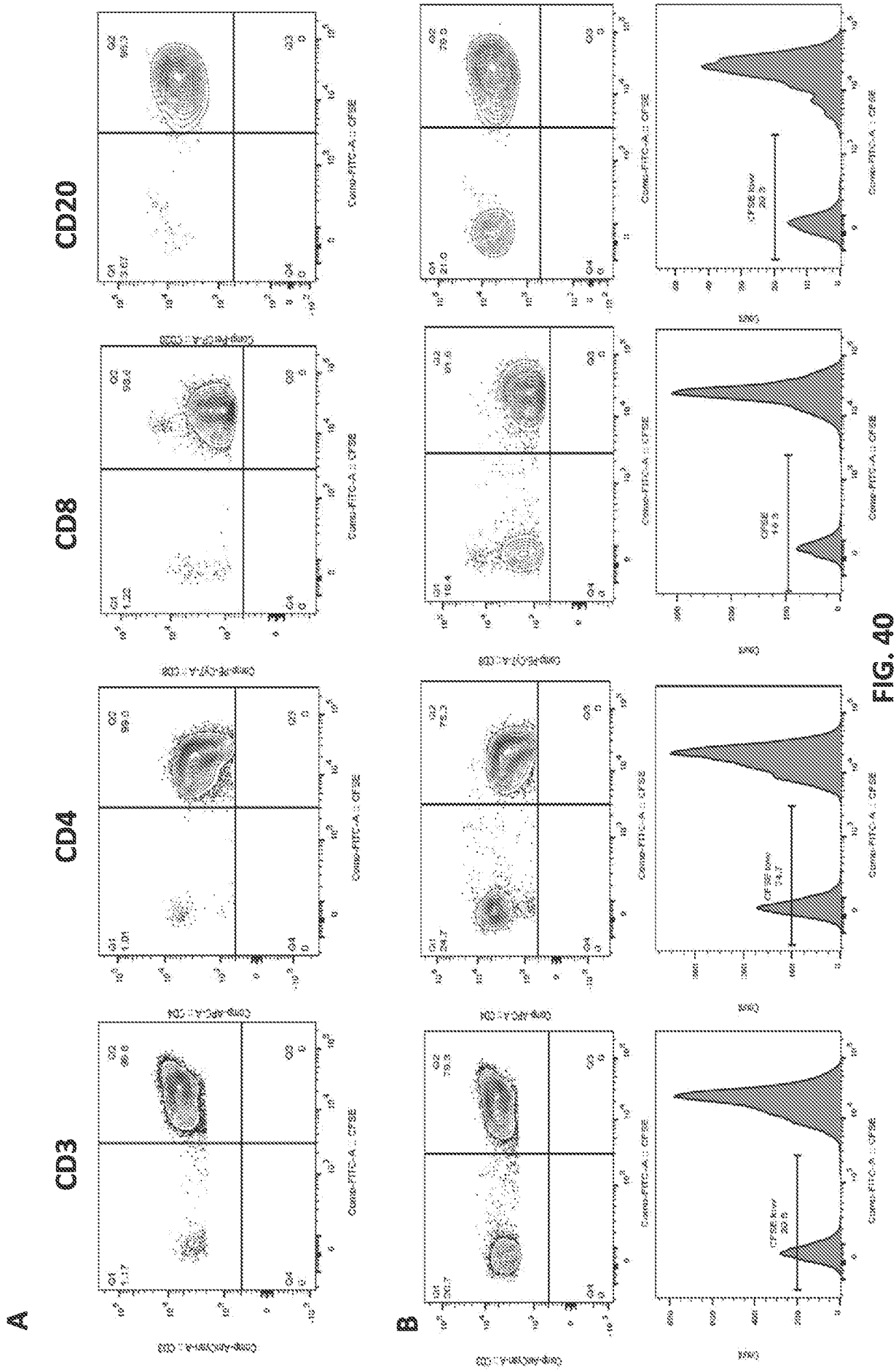

A
B
CD3
CD4
CD8
CD20
Comp-FITC-A :: CFSE
Comp-APC-A :: CD3
Comp-PE-CY7-A :: CD4
Comp-PE-CY7-A :: CD8
Comp-PE-A :: CD20
Q1
Q2
Q3
Q4
CFSE low
CFSE
Count

FIG. 40

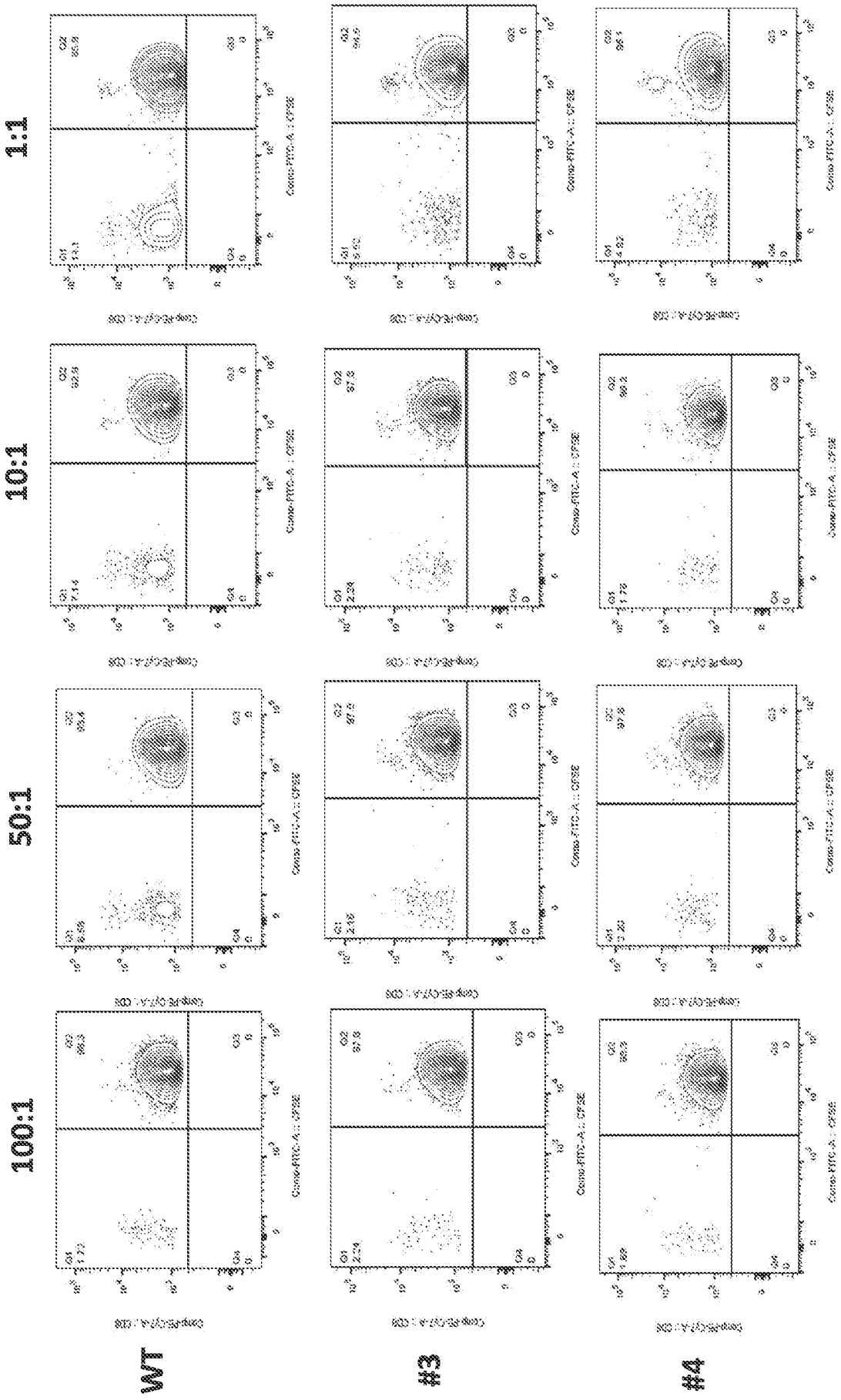


FIG. 41

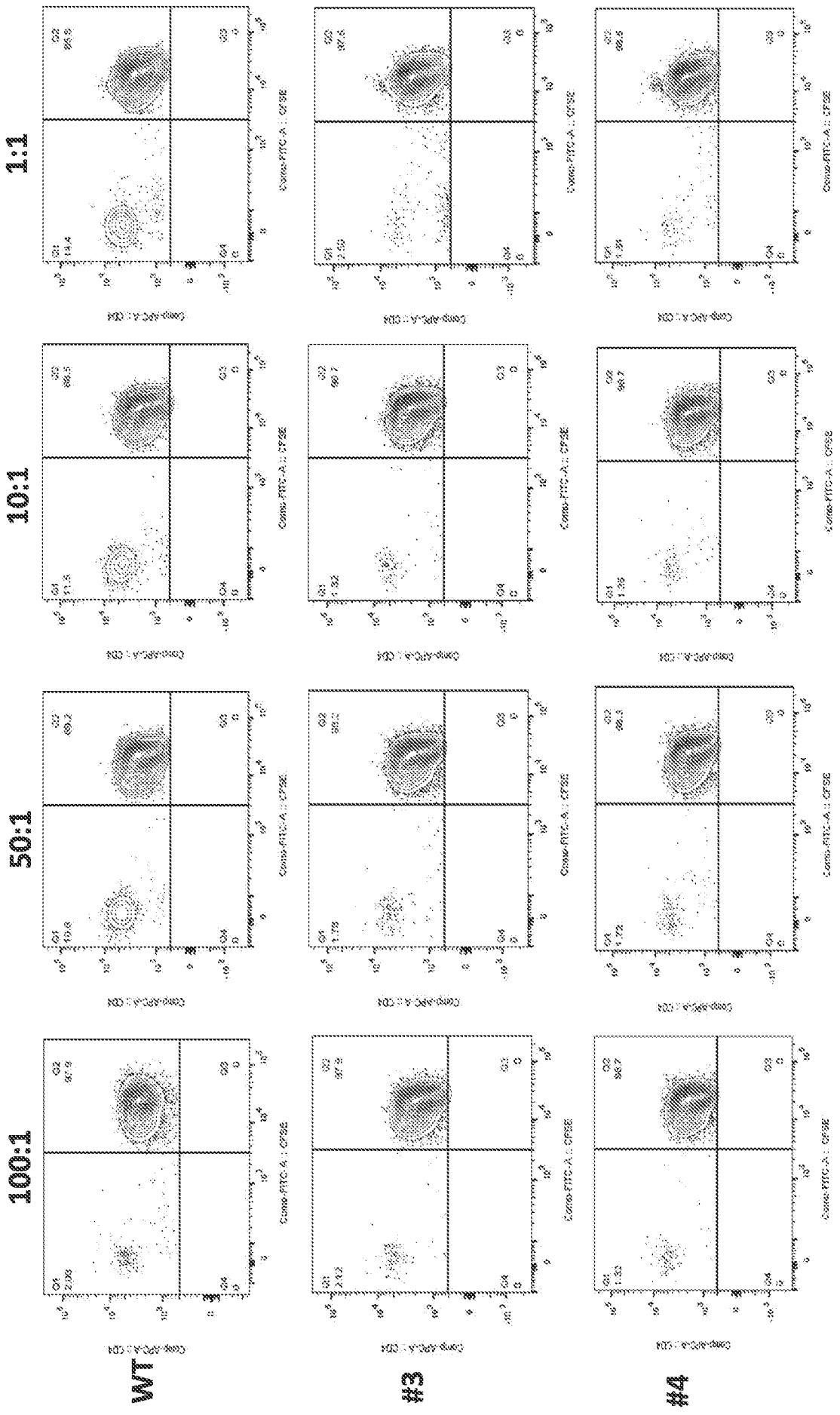


FIG. 42

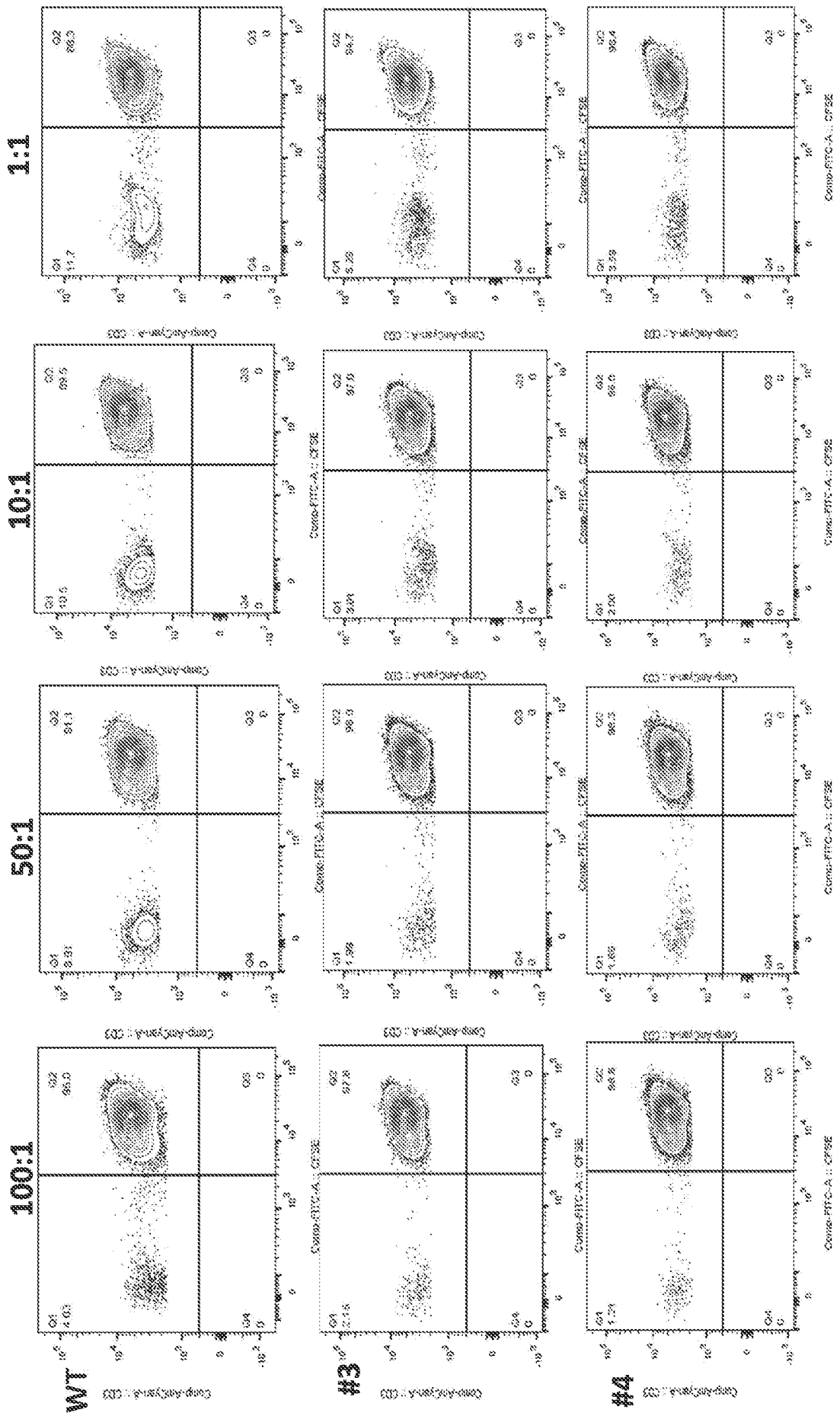


FIG. 43

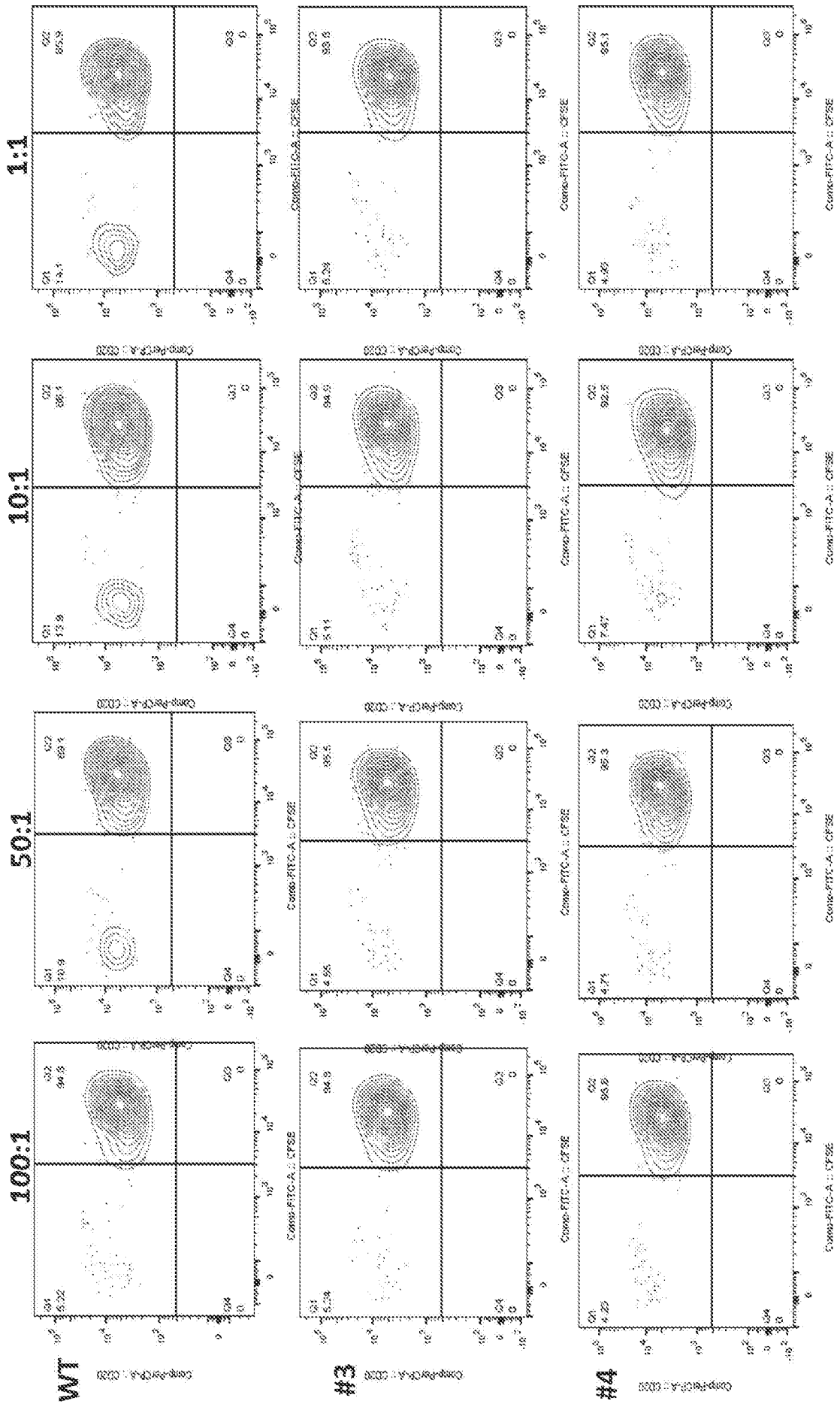


FIG. 44

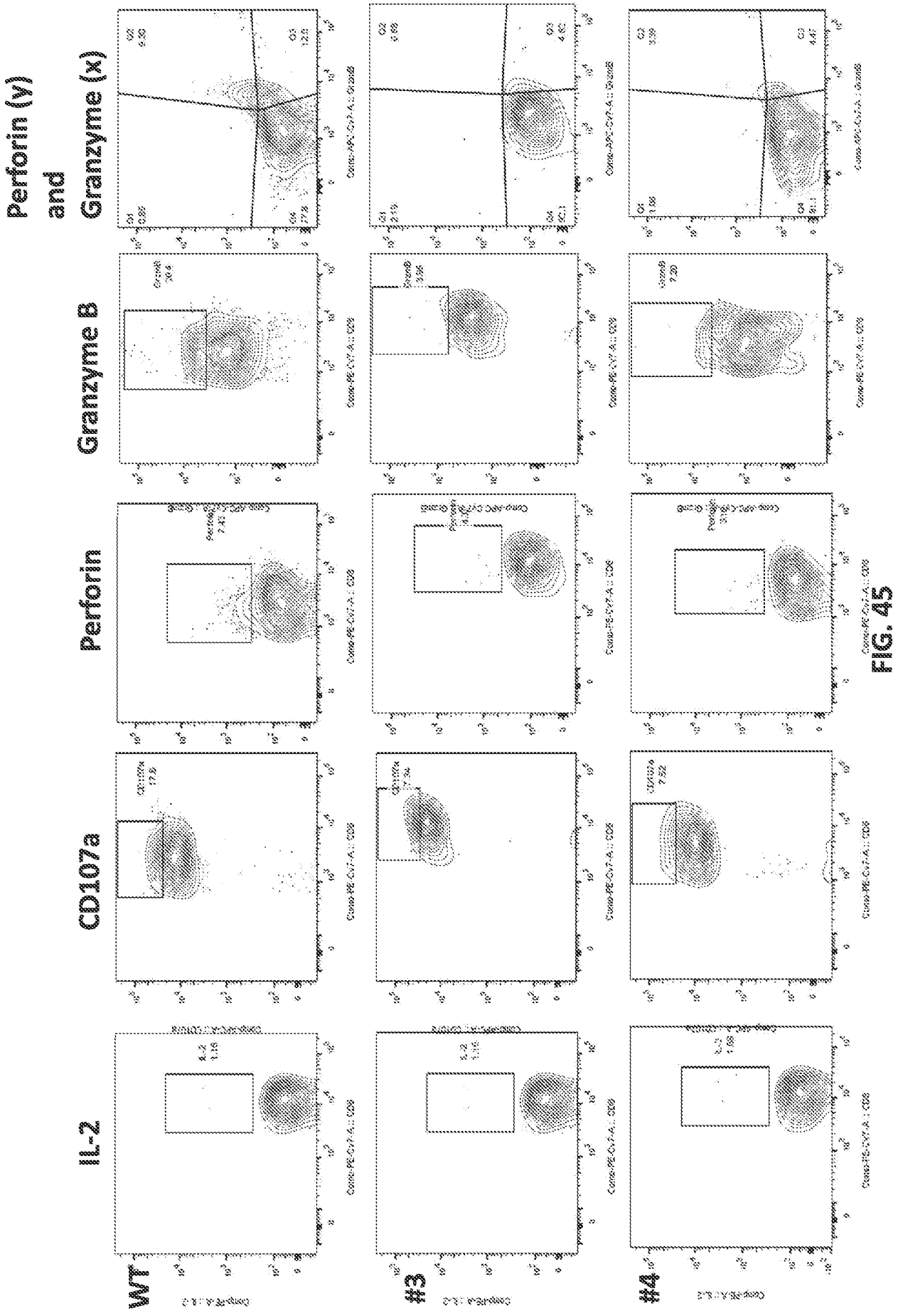

IL-2
CD107a
Perforin
Granzyme B
Perforin (y) and Granzyme (x)
WT
#3
#4

FIG. 45

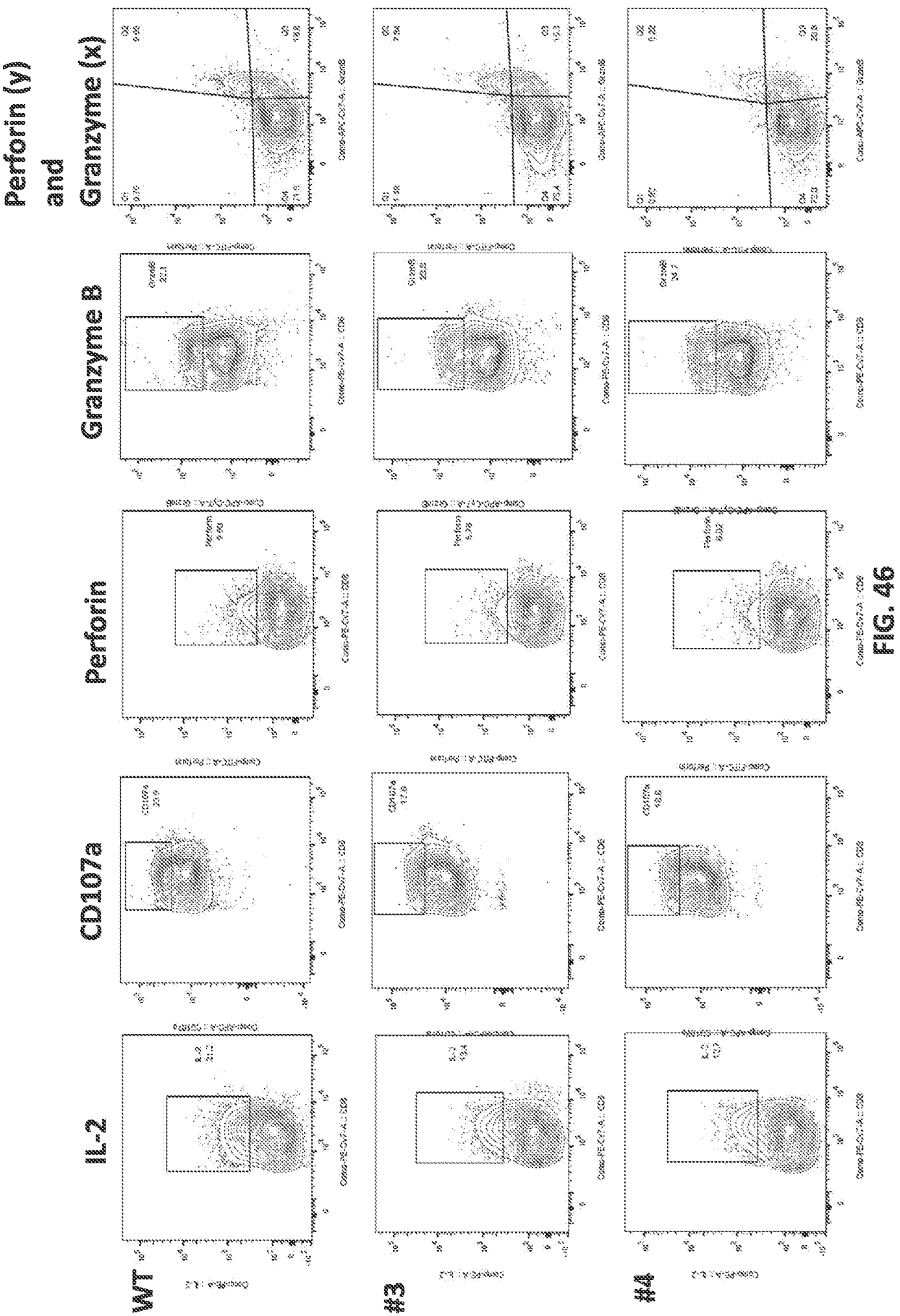

Perforin (y) and Granzyme (x)
Granzyme B
Perforin
CD107a
IL-2
WT
#3
#4

FIG. 46

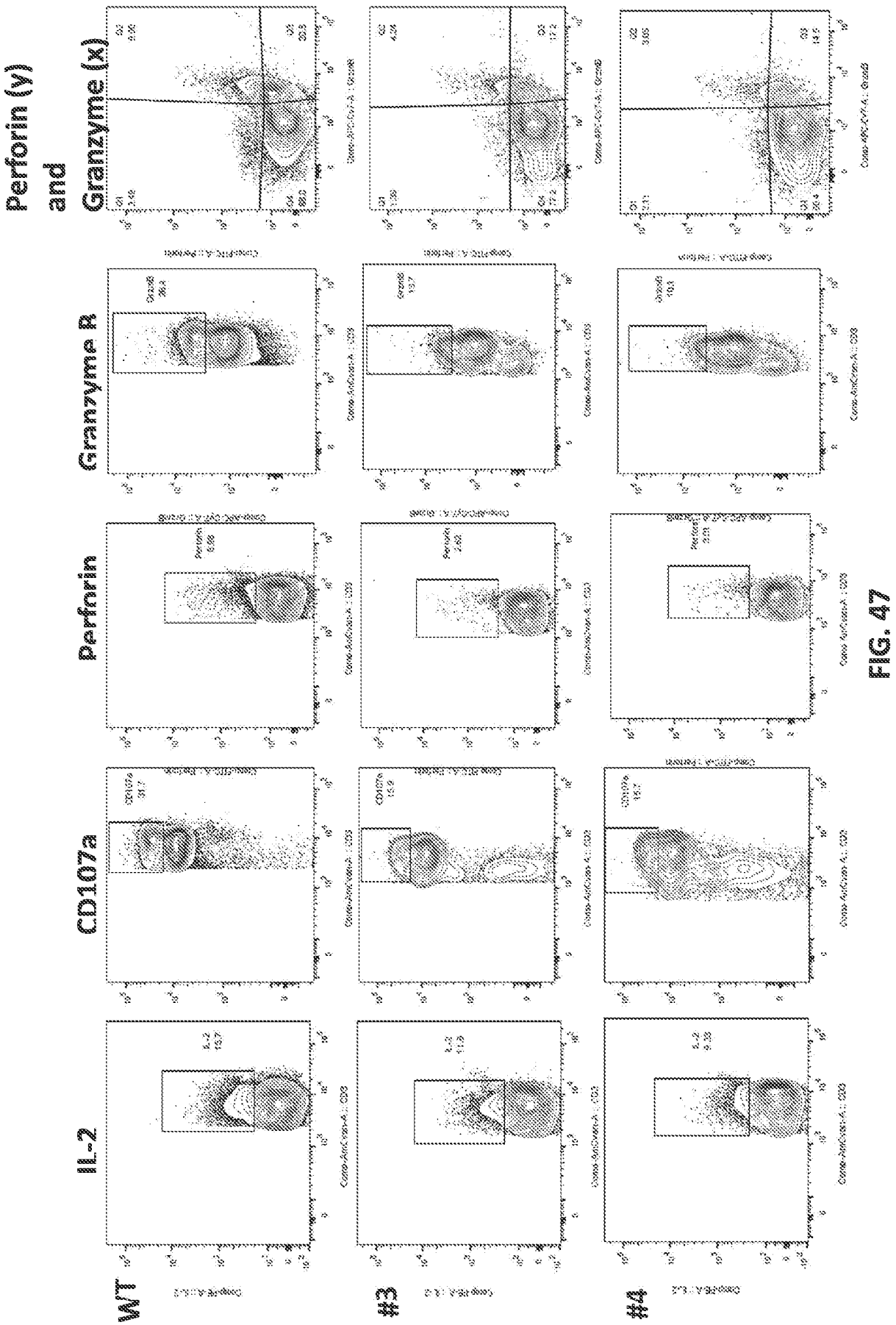

IL-2
CD107a
Perforin
Granzyme R
Perforin (y) and Granzyme (x)
WT
#3
#4

FIG. 47

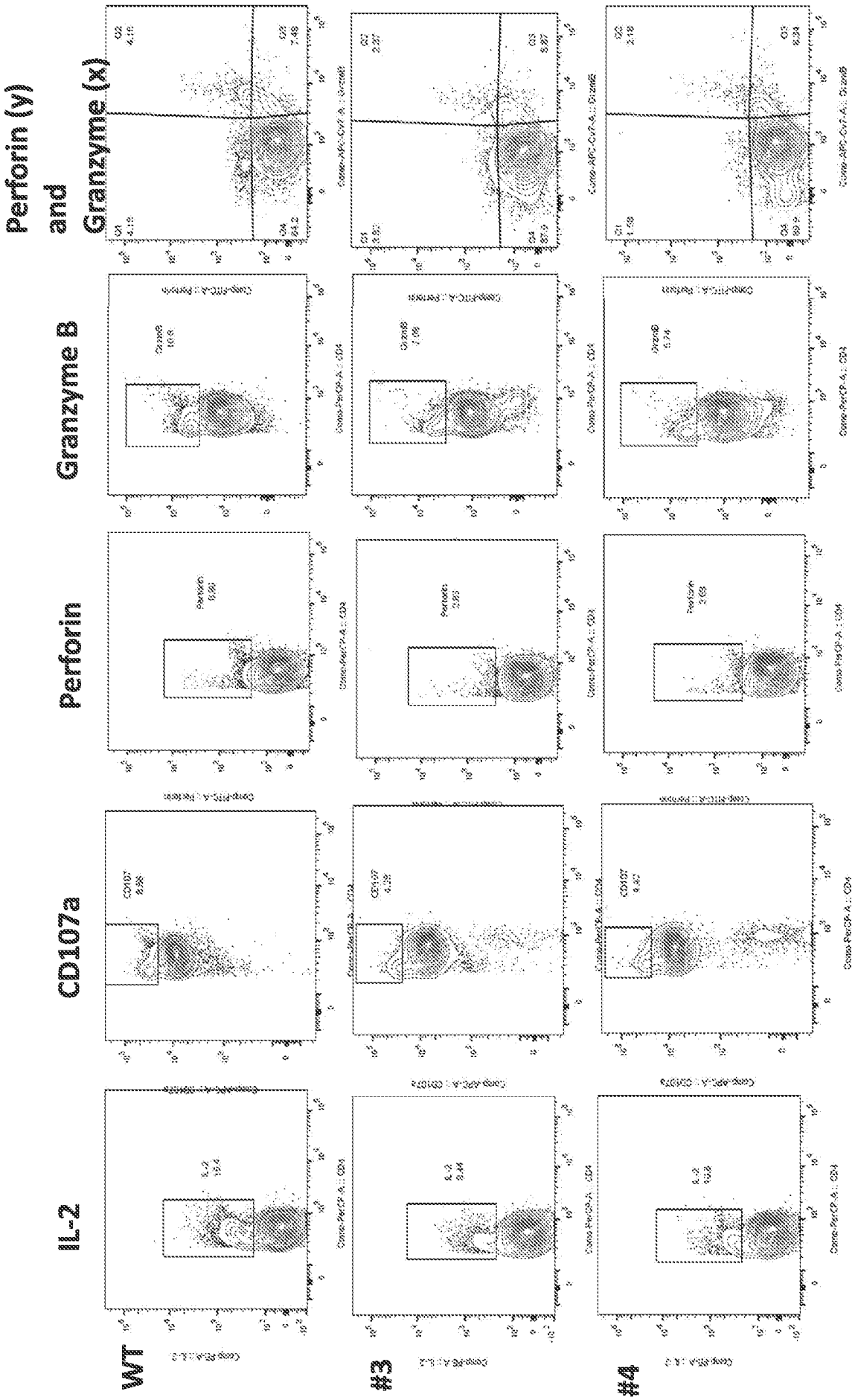

IL-2
CD107a
Perforin
Granzyme B
Perforin (y) and Granzyme (x)
WT
#3
#4

FIG. 48

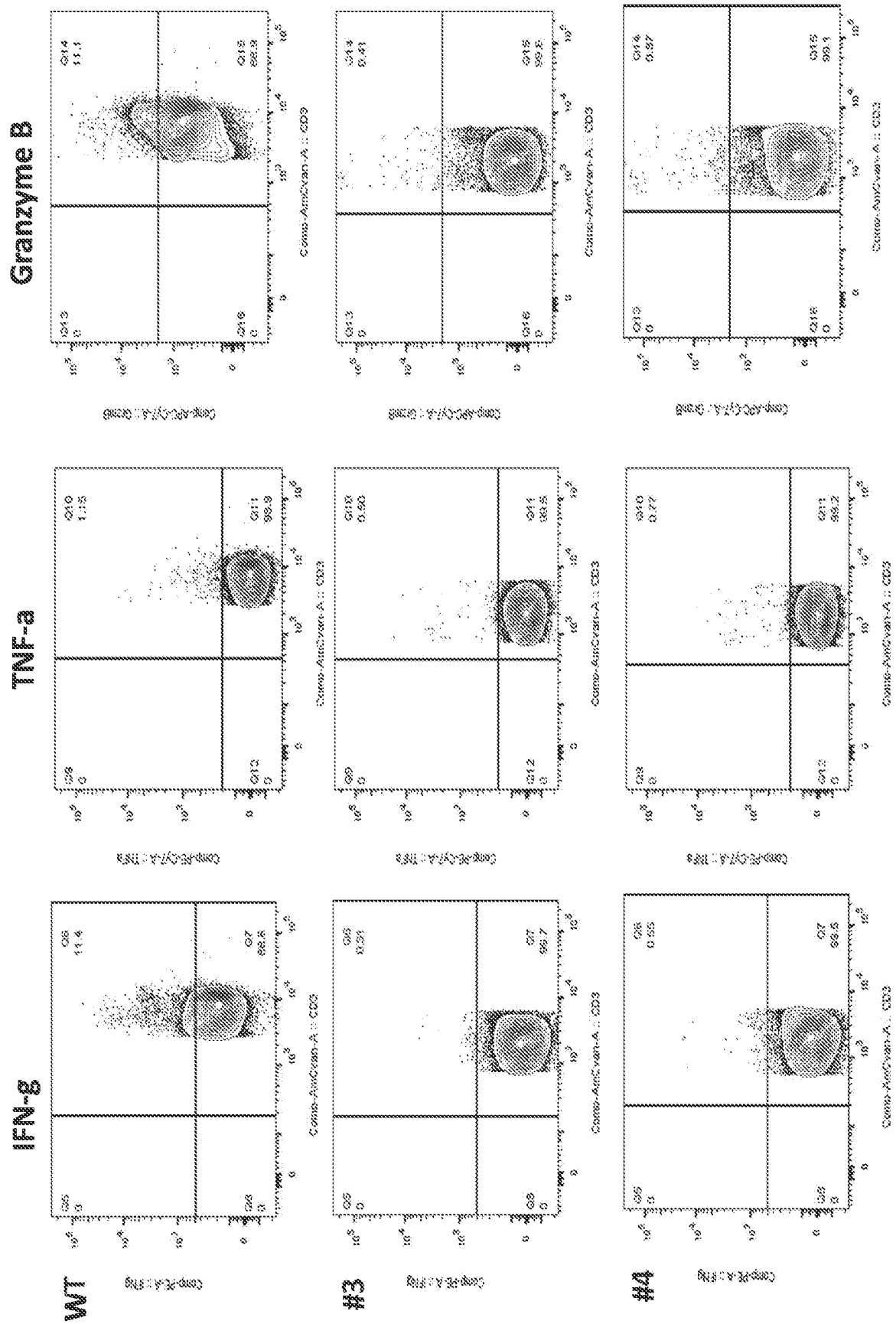


FIG. 49

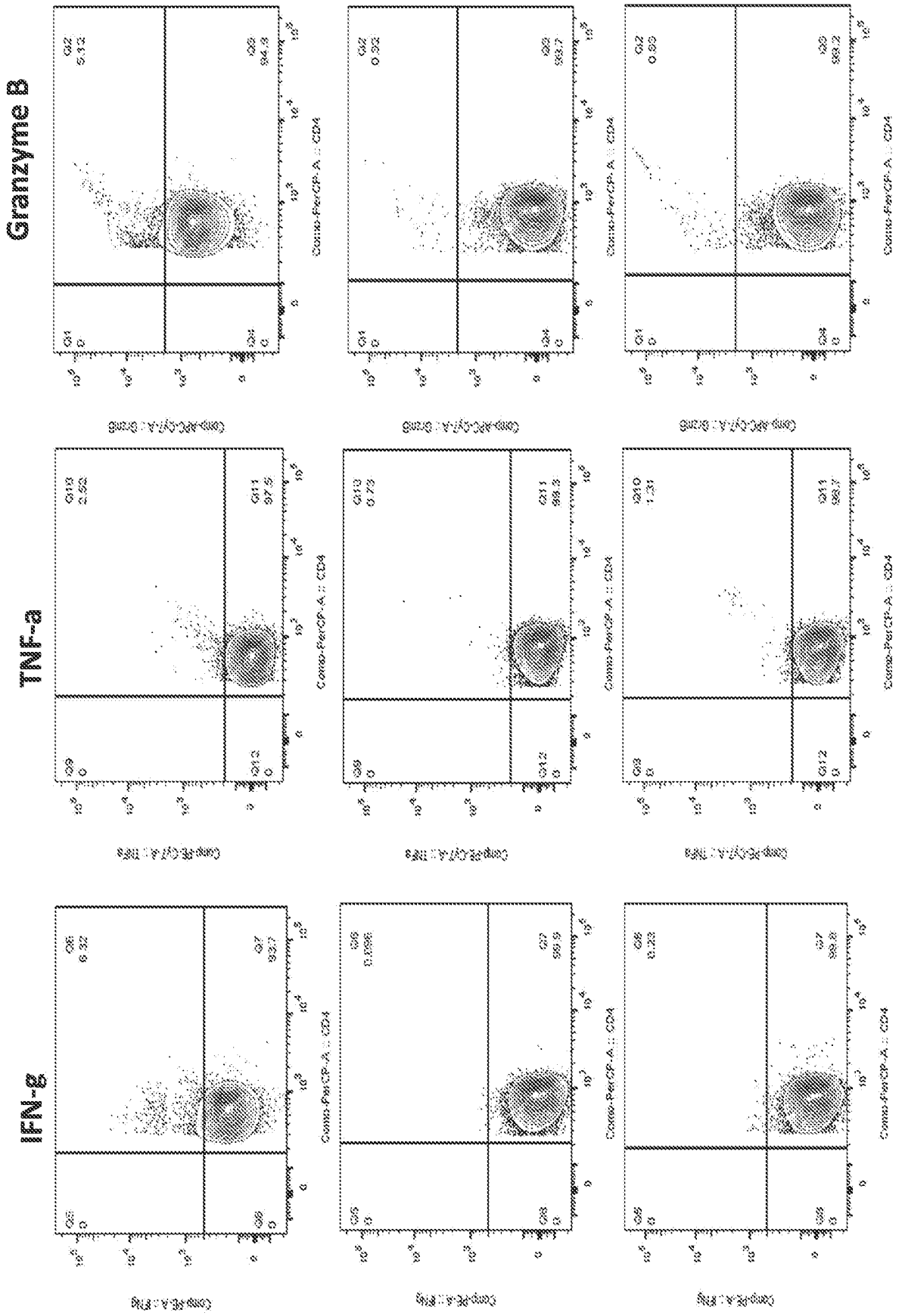

Granzyme B
TNF-a
IFN-g
Comp-PerCP-A :: CD4
Comp-APC-Cy7-A :: Grnzb
Comp-PE-Cy7-A :: TNFa
Comp-PE-A :: IFNg

FIG. 50

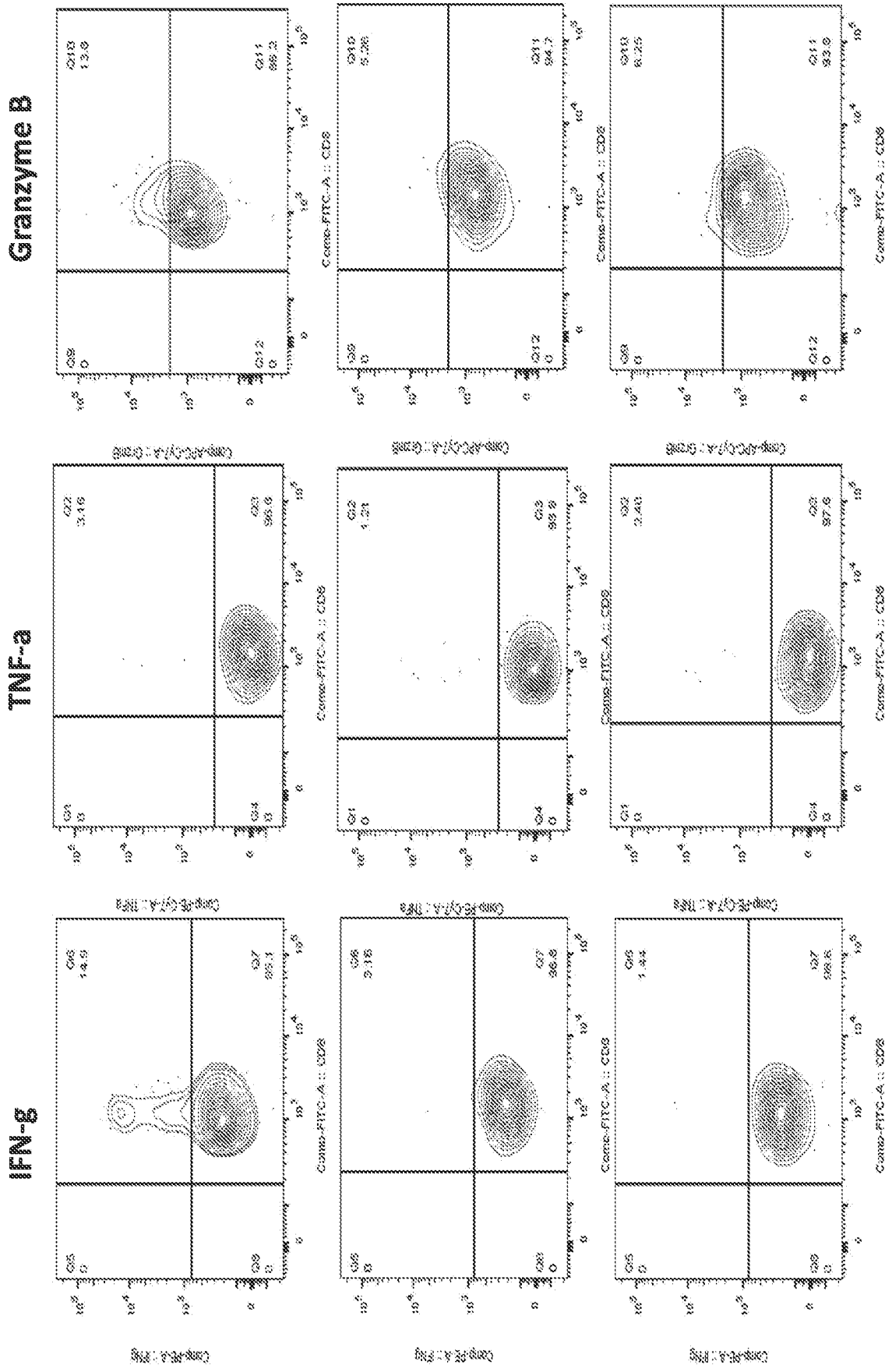

Granzyme B
TNF-a
IFN-g
Comp-FITC-A :: CD8
Comp-PE-A :: IFNg
Comp-APC-Cy7-A :: Granzyme B
Comp-APC-Cy7-A :: TNFa
Q10
13.8
Q11
86.2
Q12
Q9
Q2
3.16
Q3
96.8
Q4
Q1
Q6
14.9
Q7
85.1
Q5
Q8
Q10
6.26
Q11
94.7
Q12
Q9
Q2
1.31
Q3
98.6
Q4
Q1
Q6
9.16
Q7
90.8
Q5
Q8
Q10
6.25
Q11
93.8
Q12
Q9
Q2
2.43
Q3
97.6
Q4
Q1
Q6
1.44
Q7
98.6
Q5
Q8

FIG. 51

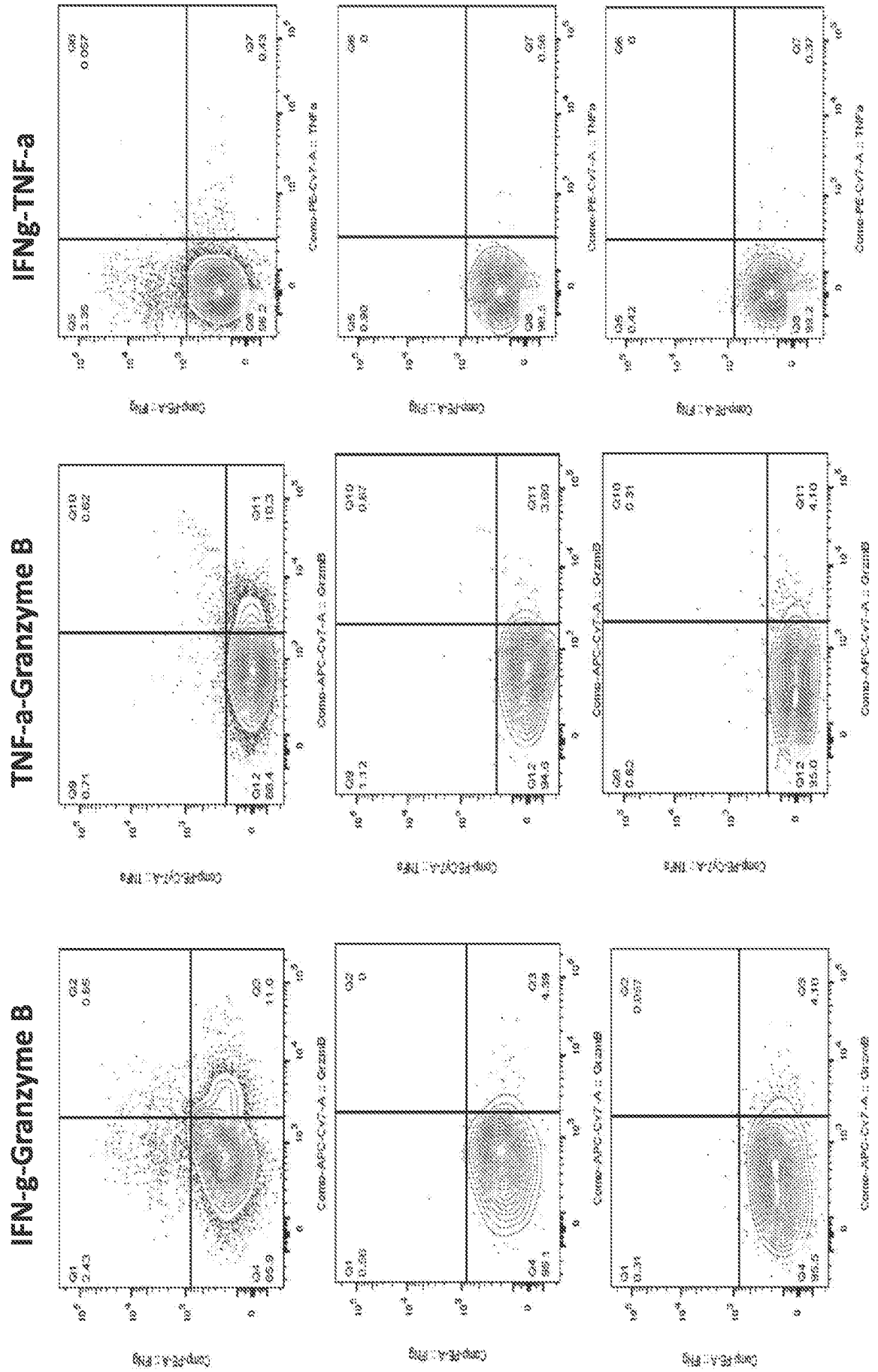


FIG. 52

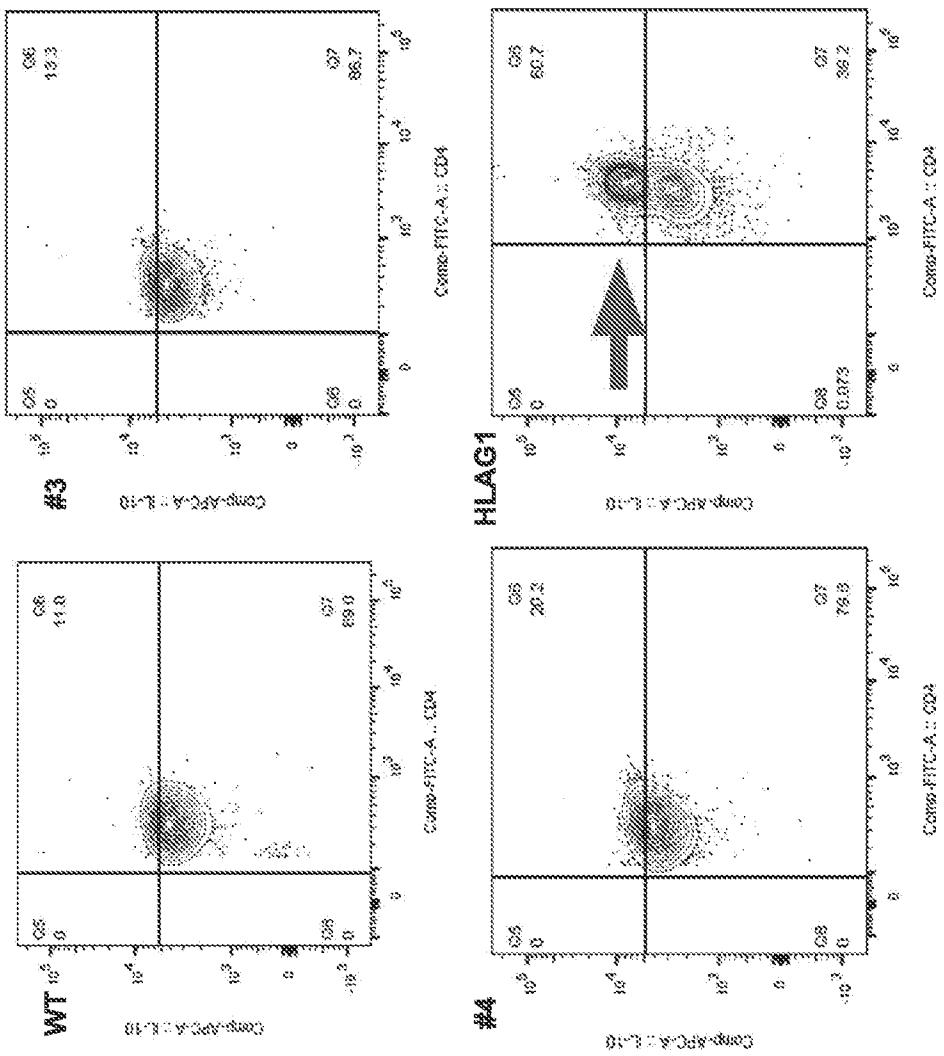

#3
HLAG1
WT
#4
Comp-APC-A :: IL-10
Comp-FITC-A :: CD4
Q6
19.3
Q7
80.7
Q5
0
Q8
0
Q6
60.7
Q7
39.2
Q8
0.073
Q6
11.8
Q7
88.0
Q6
20.2
Q7
79.8

FIG. 53

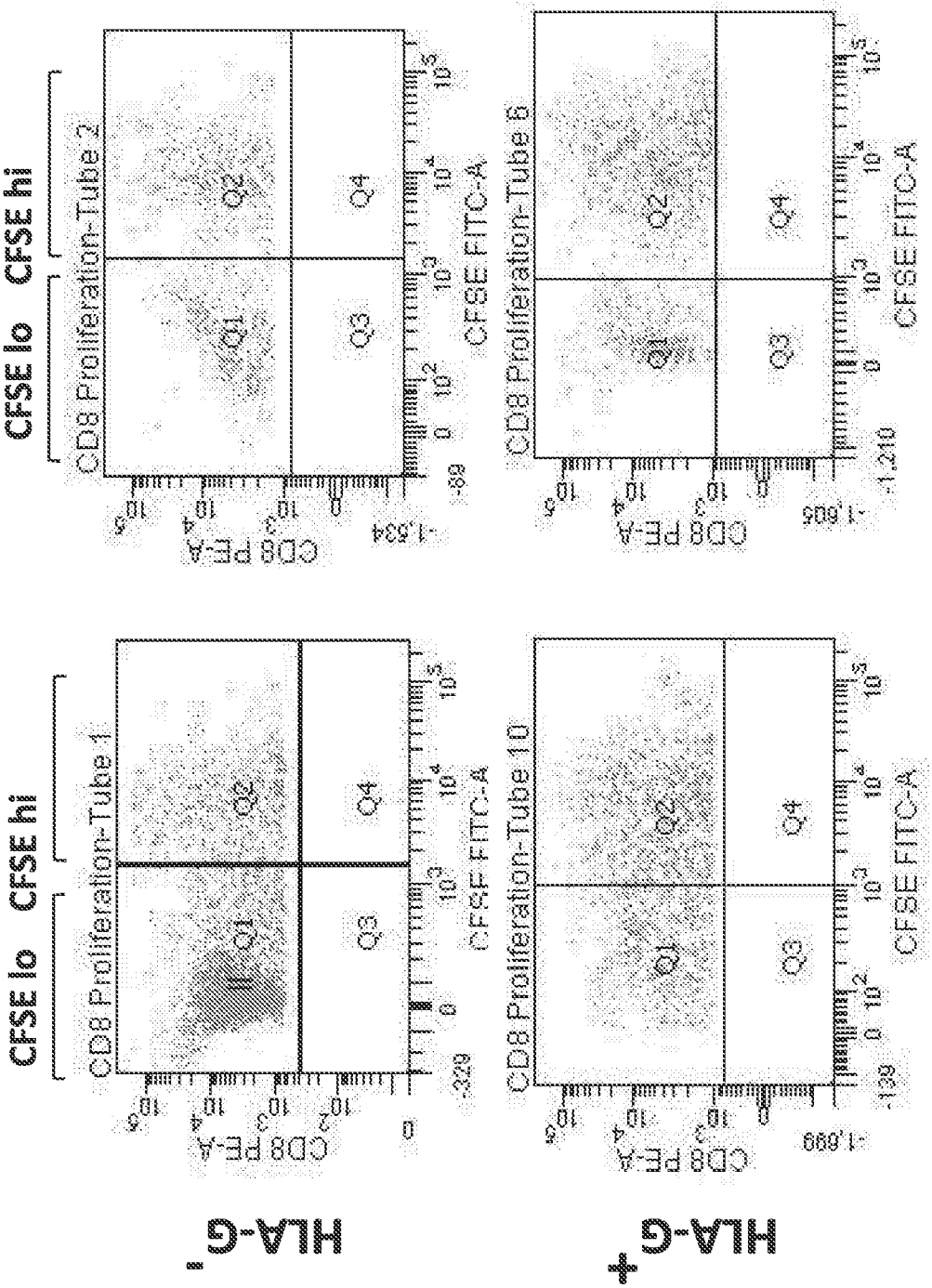

HLA-G-
HLA-G+
CFSE lo CFSE hi
CD8 Proliferation-Tube 1
CD8 Proliferation-Tube 2
CD8 Proliferation-Tube 10
CD8 Proliferation-Tube 6
CD8 PE-A
CFSE FITC-A
Q1
Q2
Q3
Q4

FIG. 54

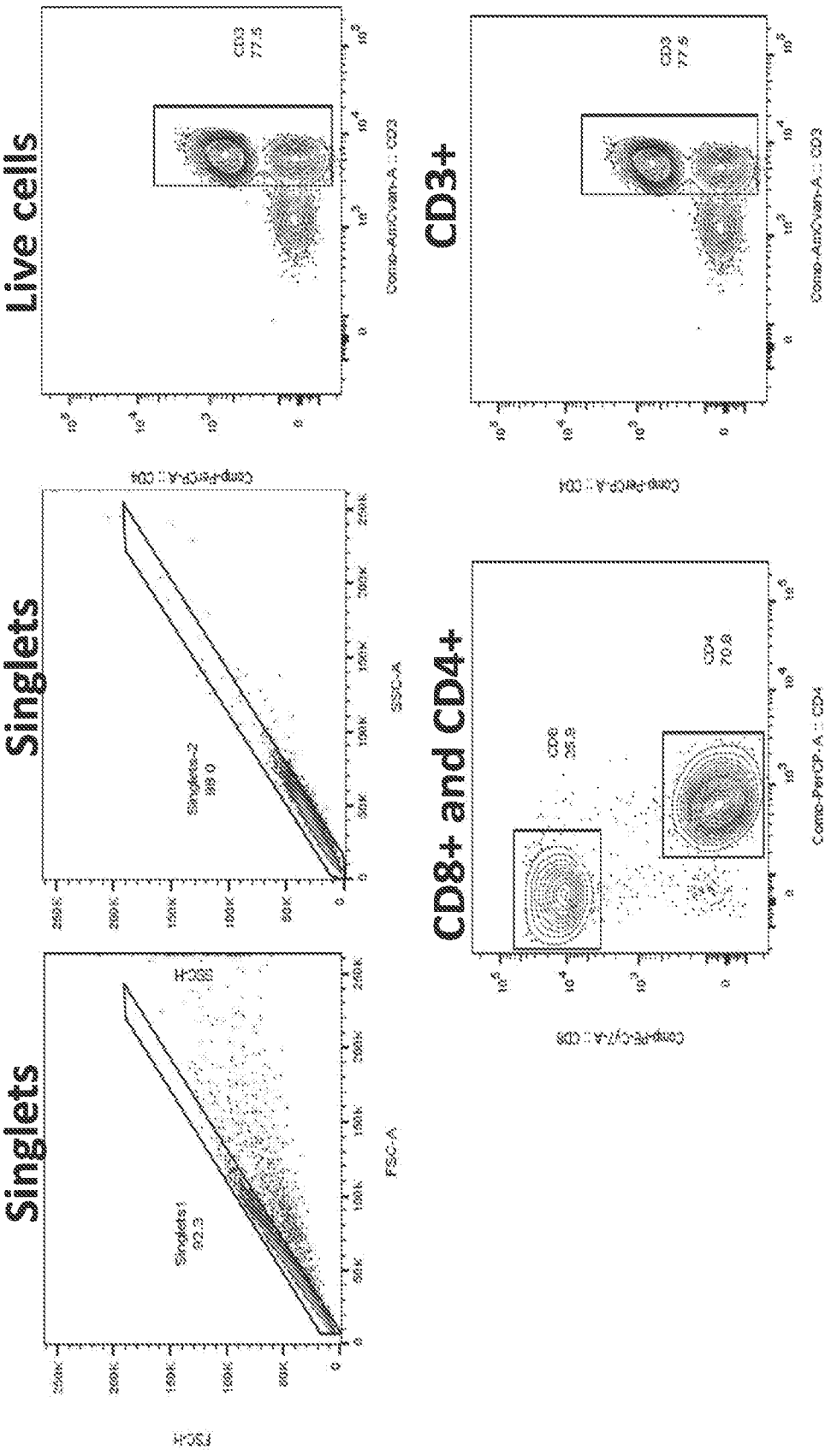

Singlets
FSC-H
FSC-A
Singlets
SSC-H
SSC-A
Live cells
CD3
77.5
Comp-AmCyan-A :: CD3
CD3+
CD3
77.5
Comp-AmCyan-A :: CD3
Comp-PerCP-A :: CD4
CD8+ and CD4+
CD8
35.6
CD4
70.6
Comp-PerCP-A :: CD4
Comp-PE-Cy7-A :: CD8

FIG. 55

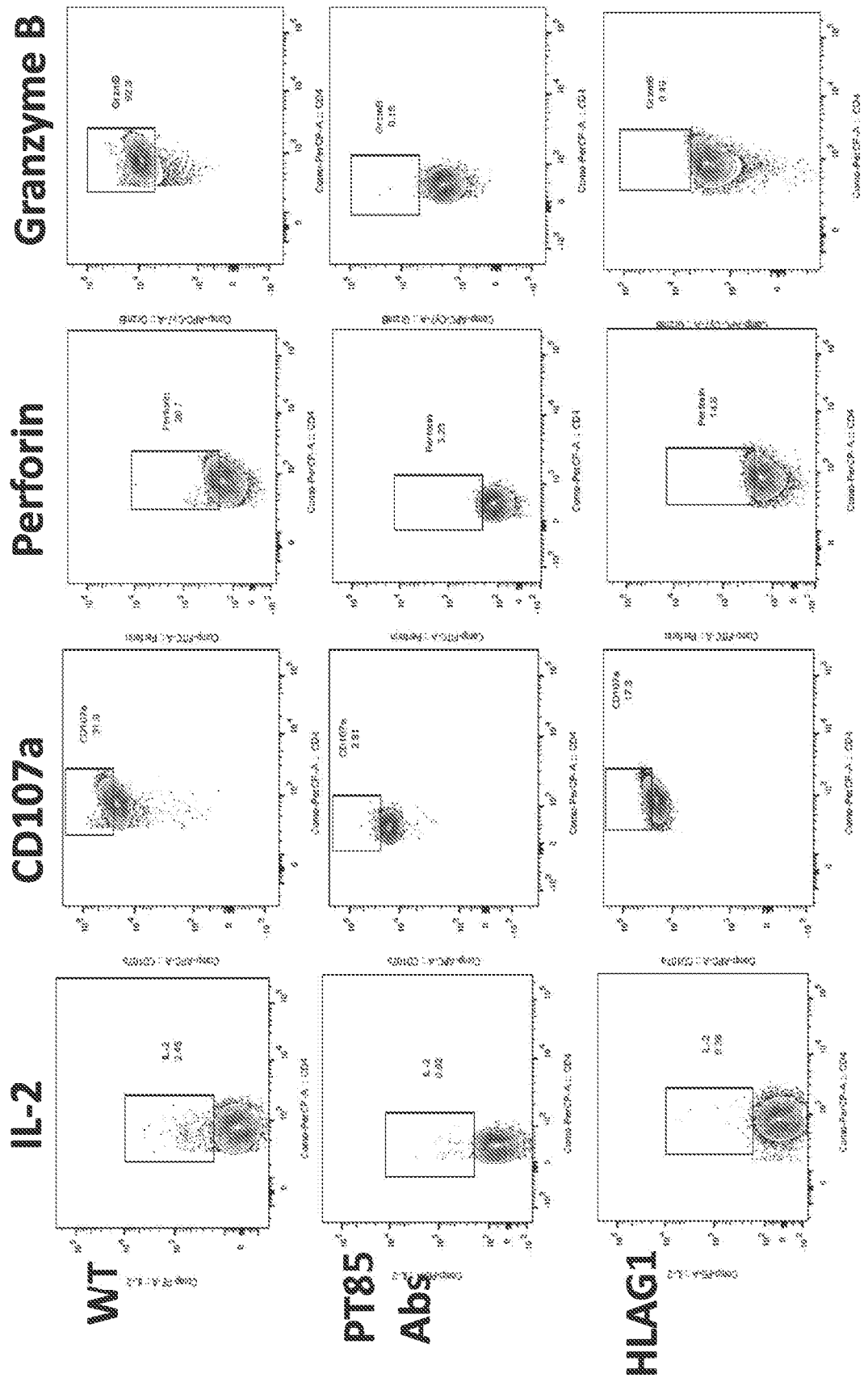


FIG. 56

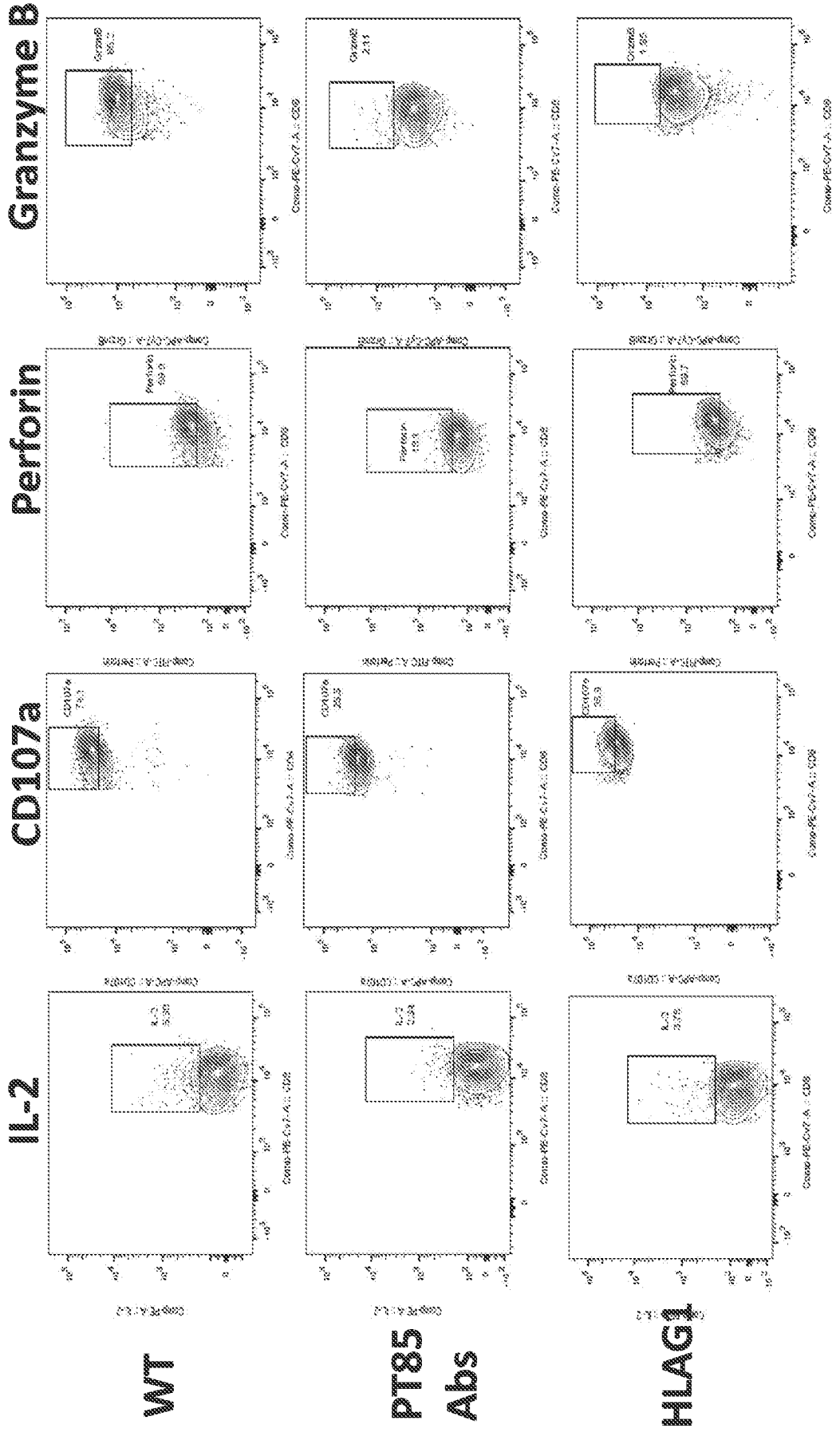


FIG. 57

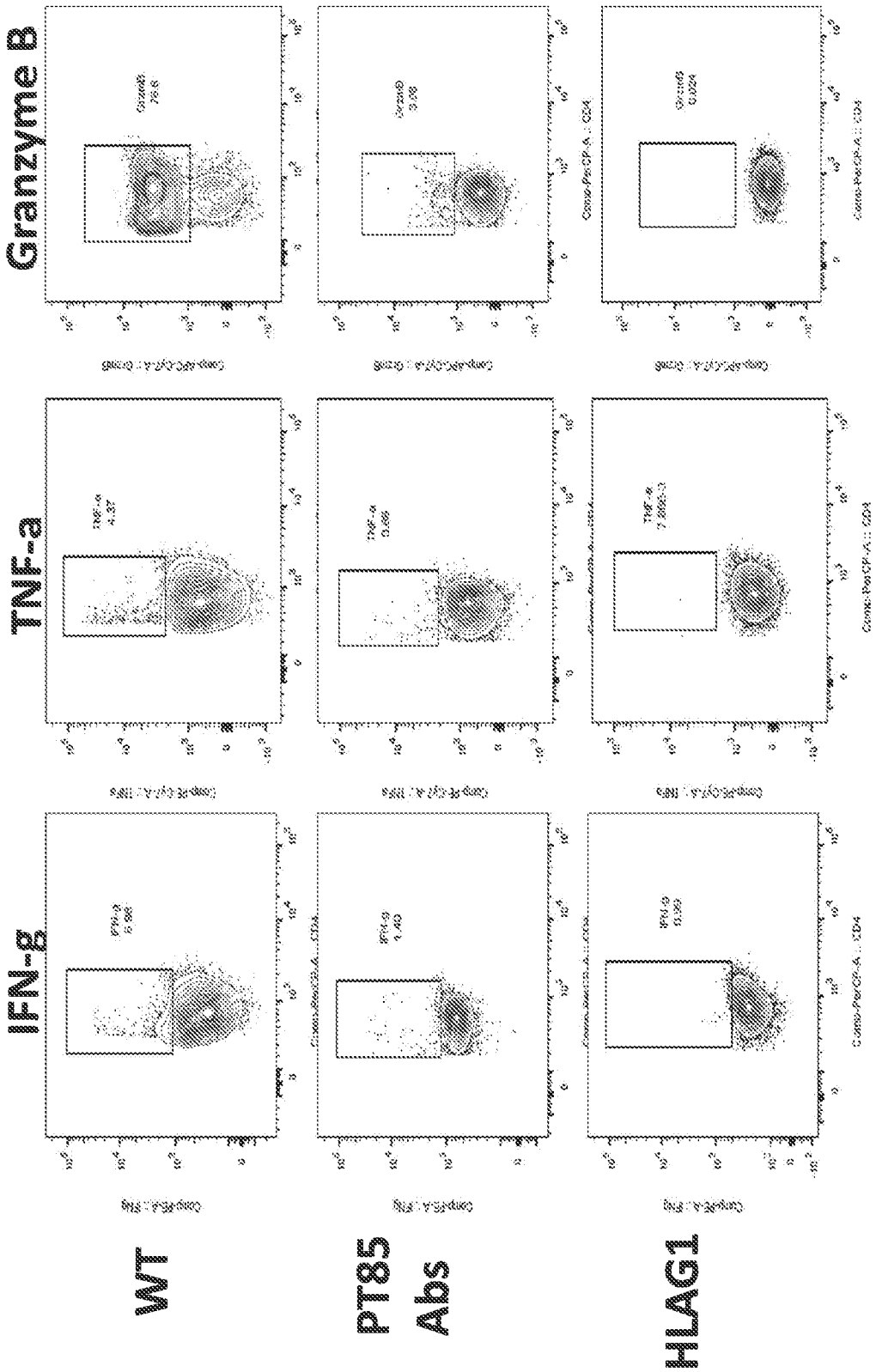


FIG. 58

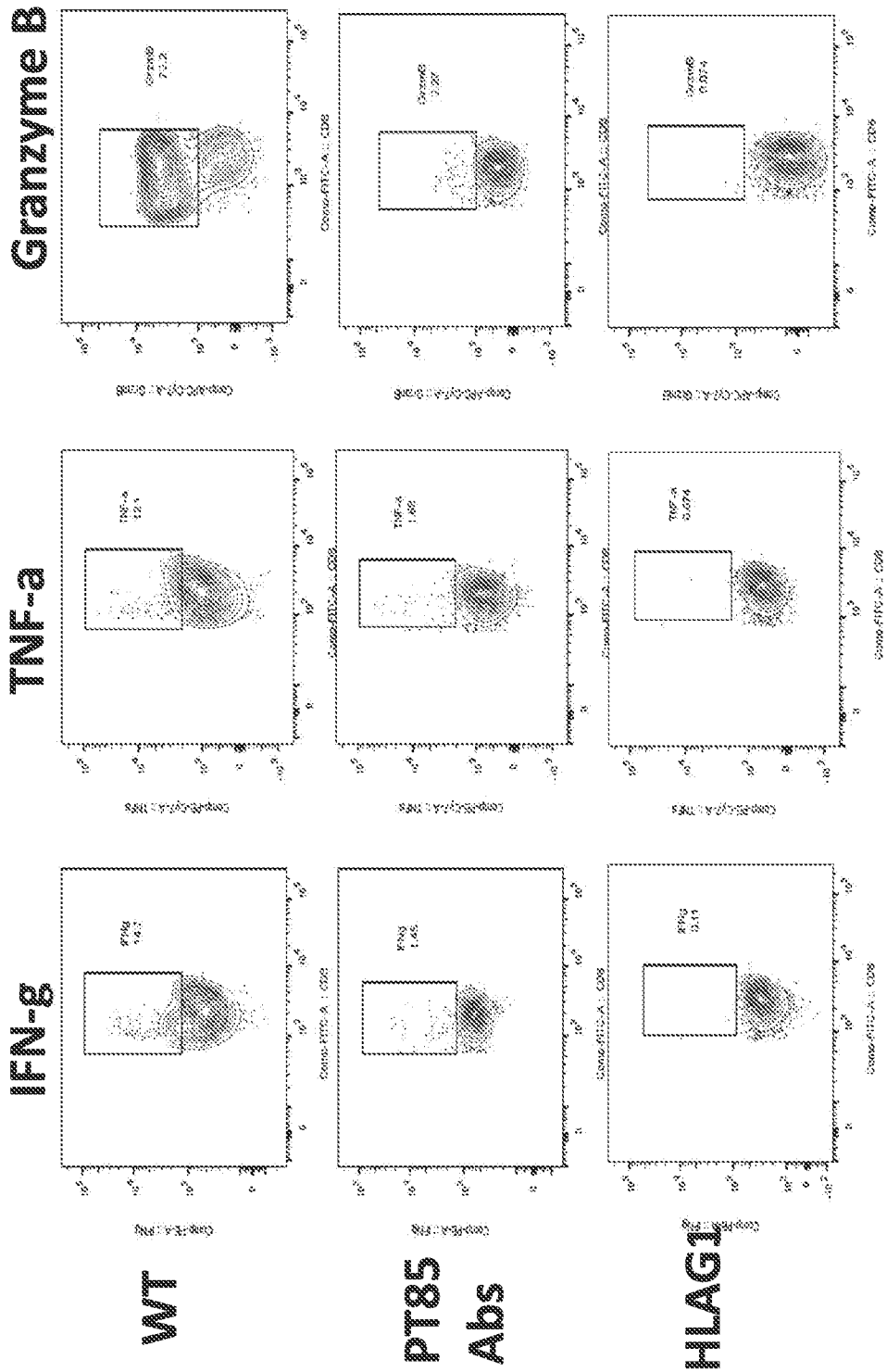


FIG. 59

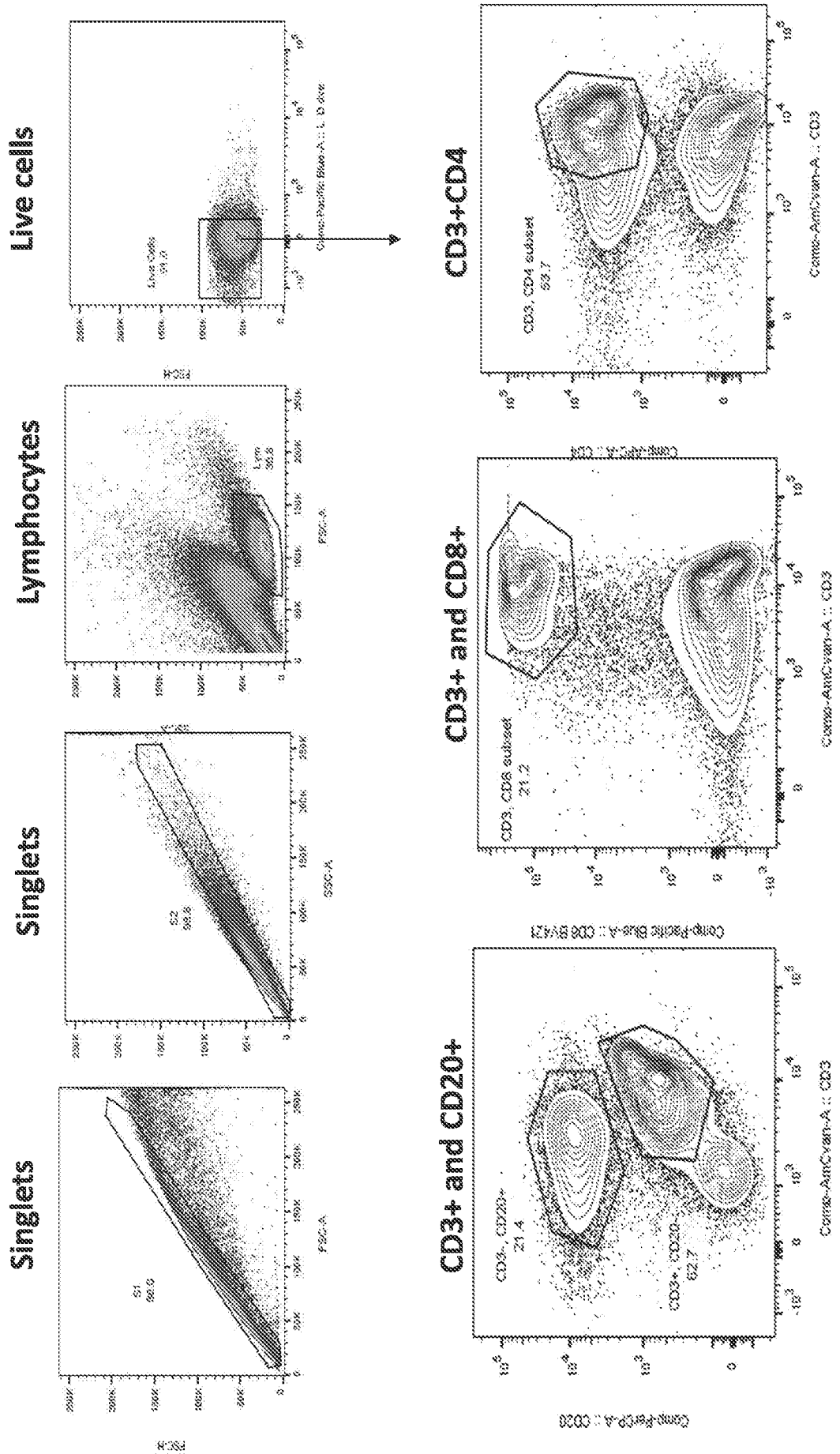

Singlets
Singlets
Lymphocytes
Live cells
CD3+ and CD20+
CD3+ and CD8+
CD3+CD4

FIG. 60

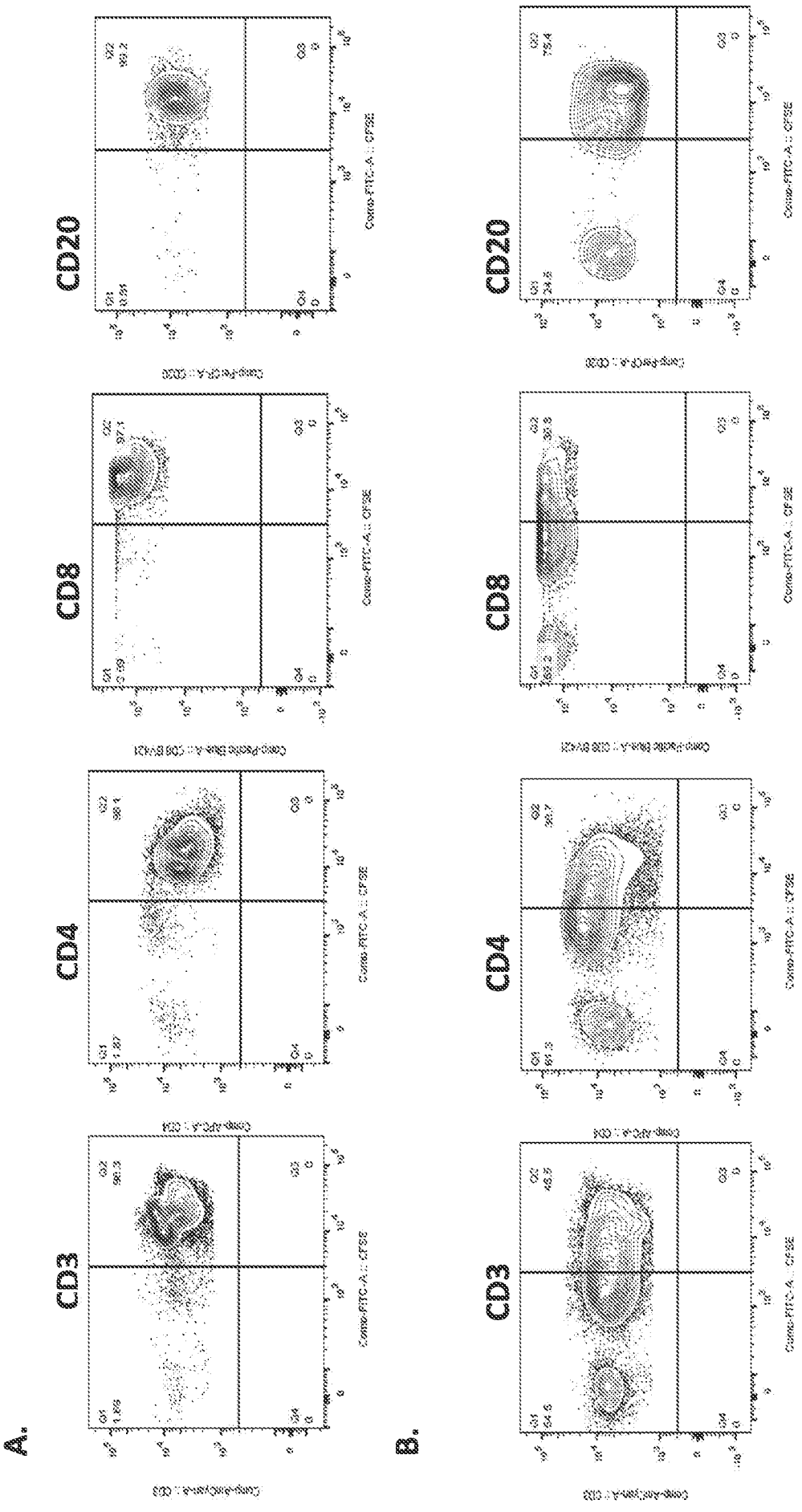

A.
B.
CD3
CD4
CD8
CD20
Comp-FITC-A :: CFSE
Comp-APC-A :: CD4
Comp-Pacific Blue-A :: CD8 BV421
Comp-PerCP-Cy5-5-A :: CD20
Q1
Q2
Q3
Q4

FIG. 61

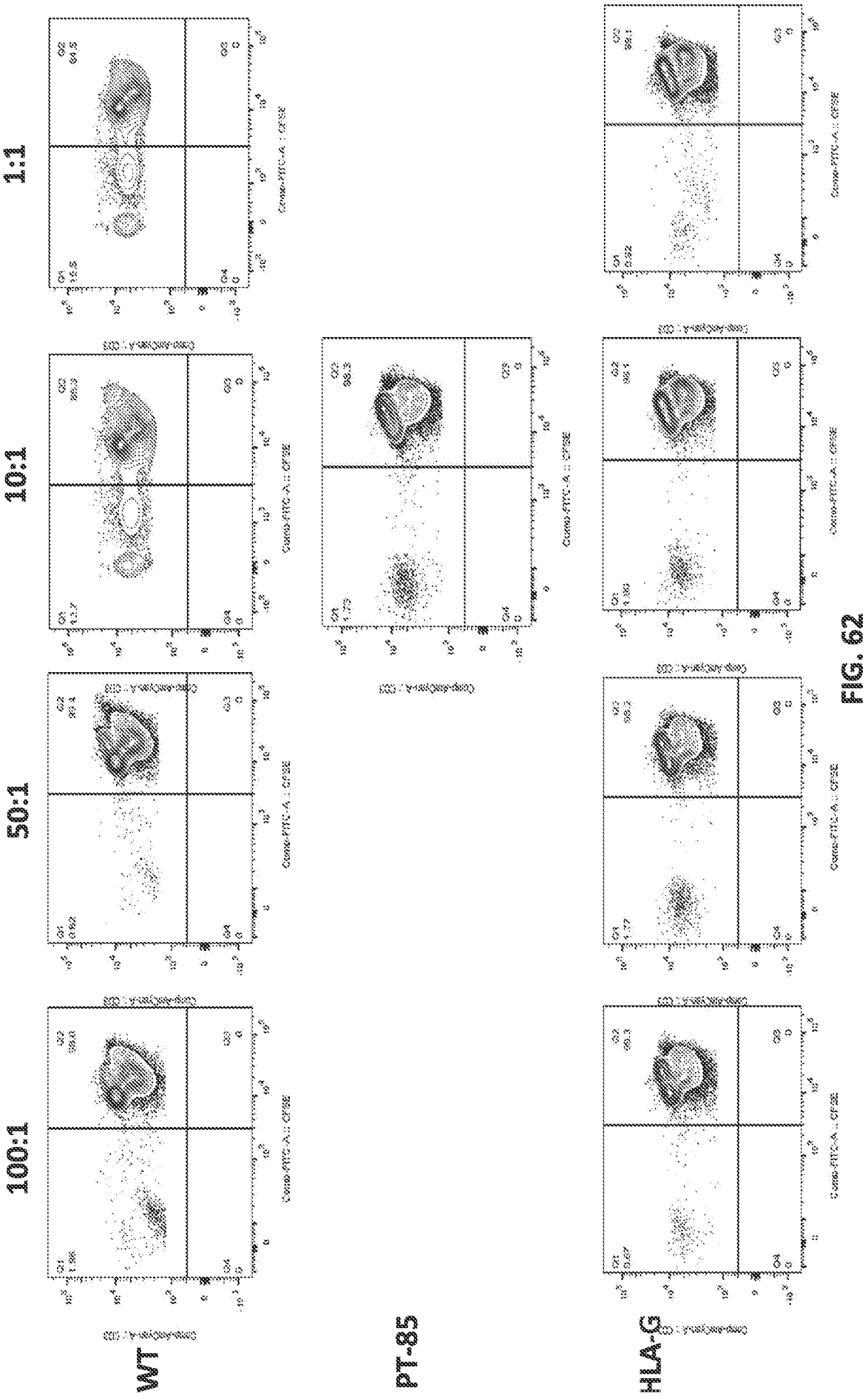


FIG. 62

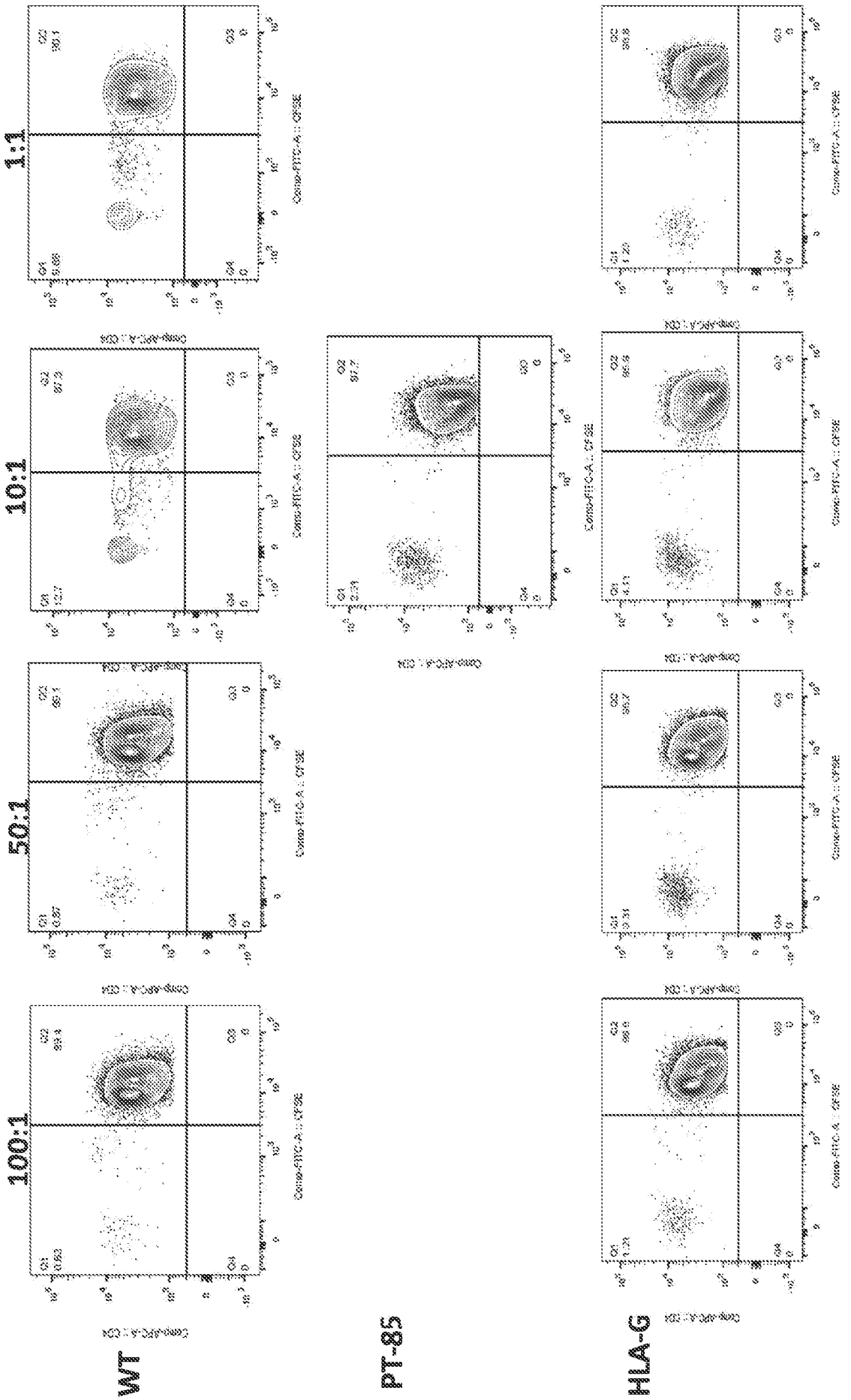


FIG. 63

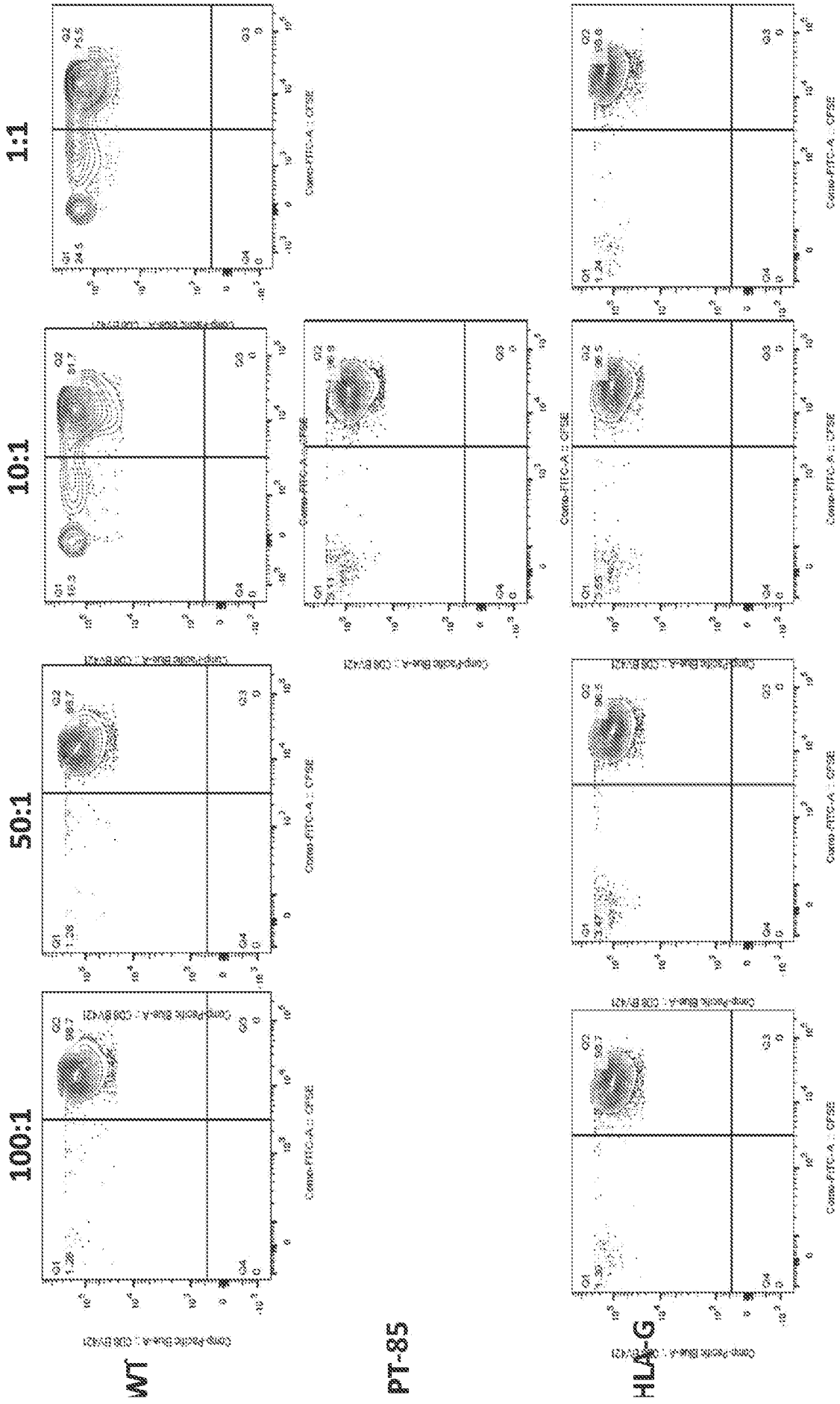

100:1
50:1
10:1
1:1
WT
PT-85
HLA-G
Comp-Pacific Blue-A :: CD8 BV421
Comp-FITC-A :: CFSE
Q1
Q2
Q3
Q4

FIG. 64

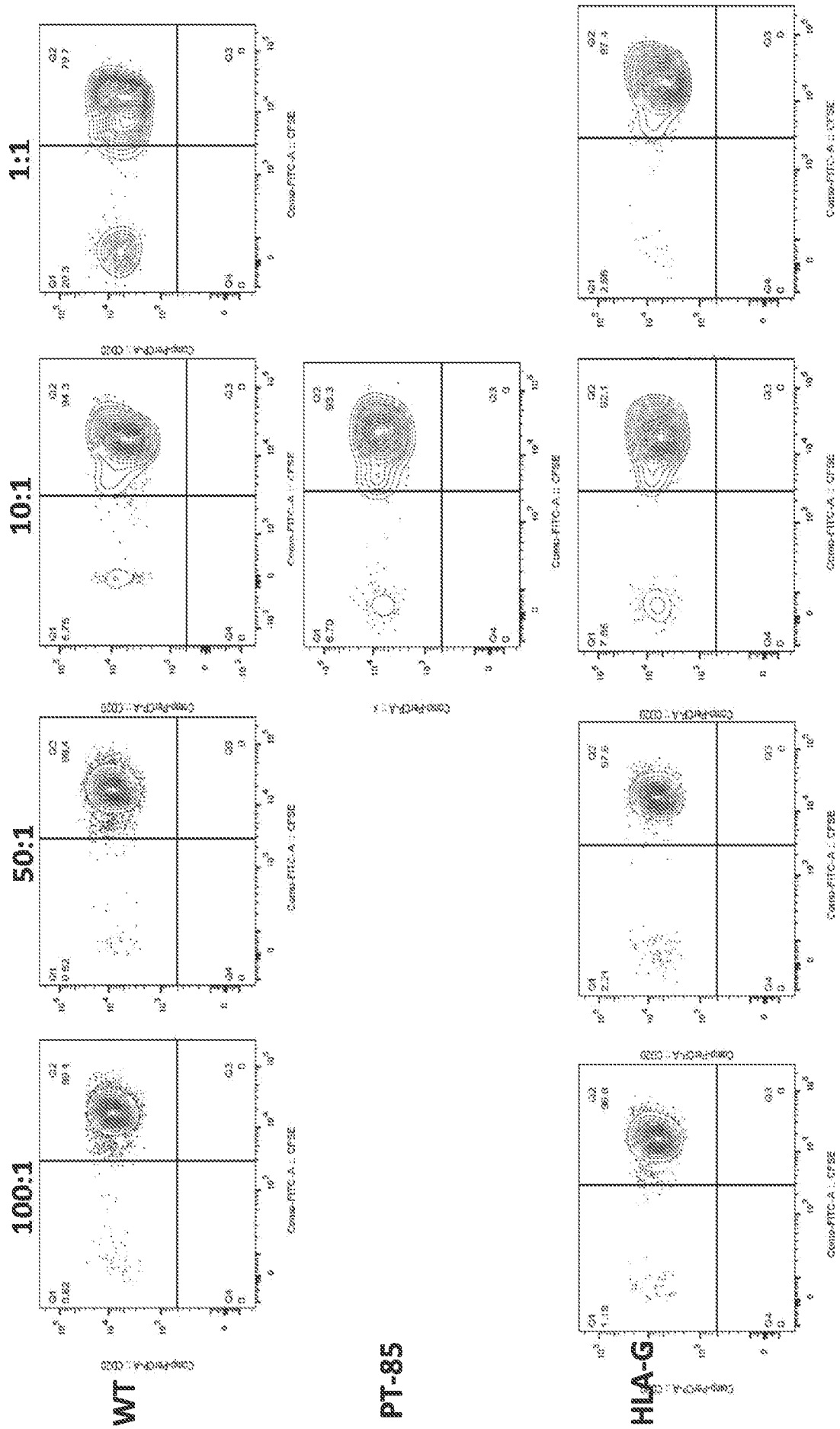


FIG. 65

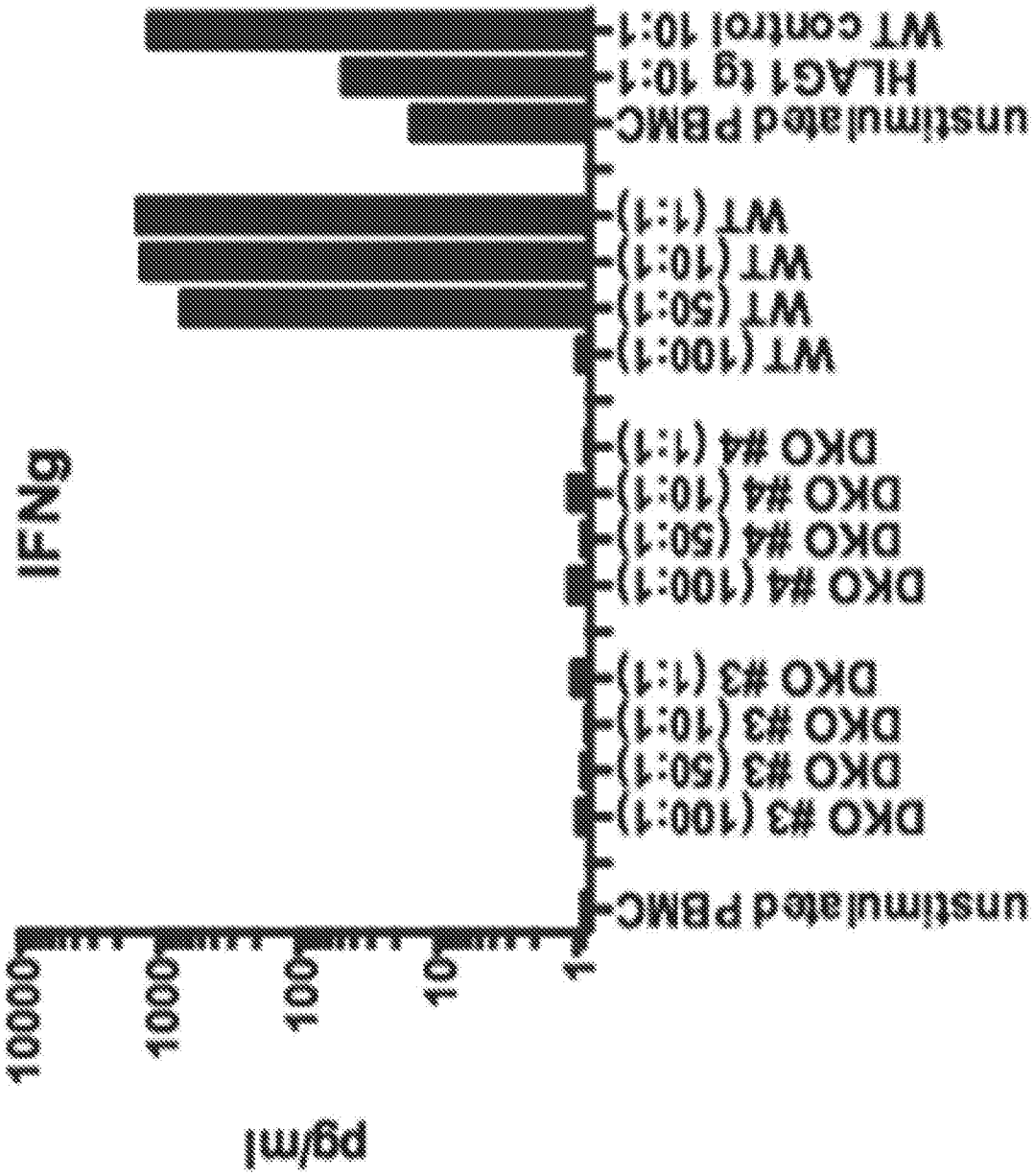

IFNg
pg/ml
10000
1000
100
10
1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1)
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1

FIG. 66

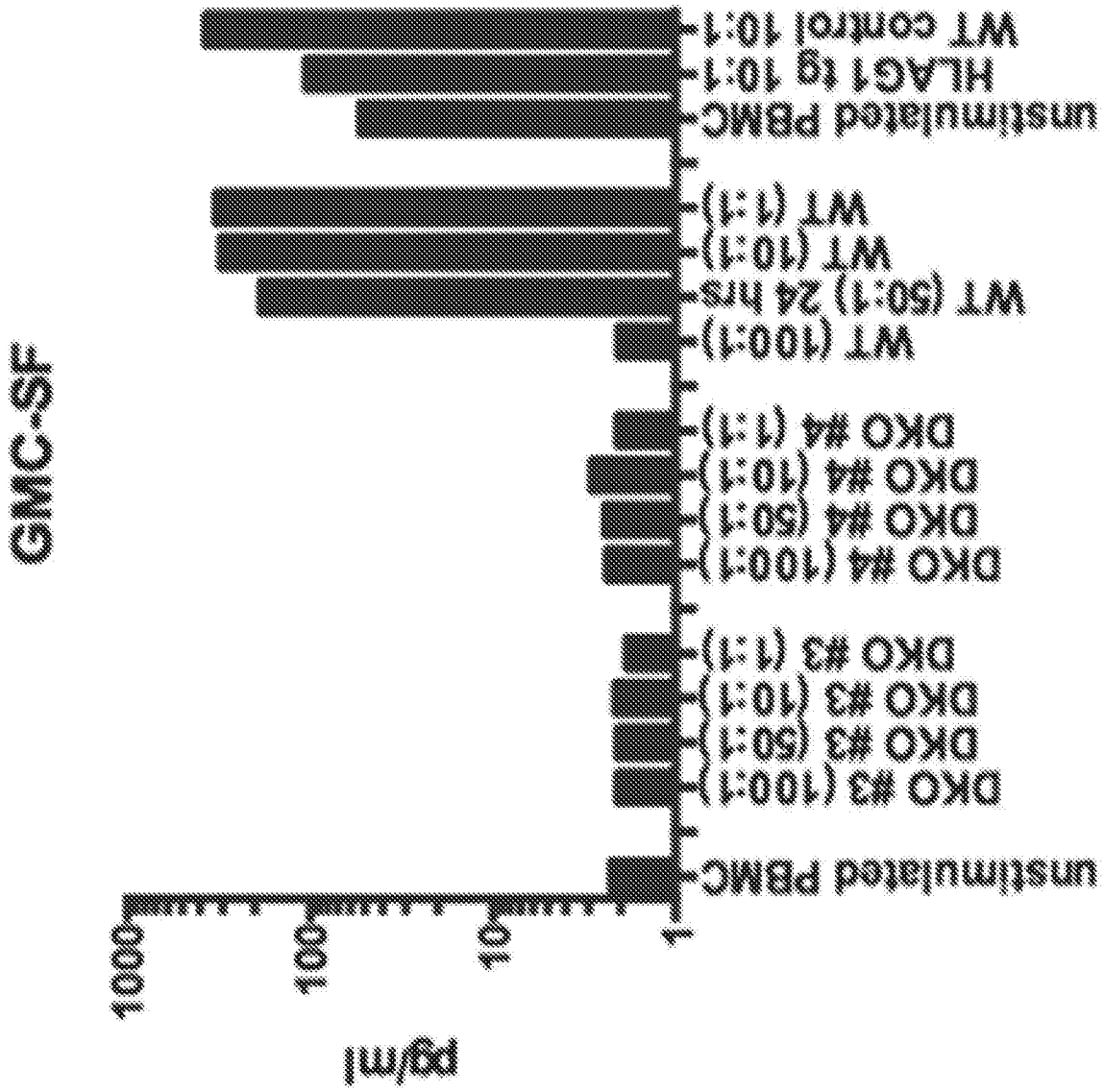

GMC-SF
pg/ml
1000
100
10
1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1

FIG. 67

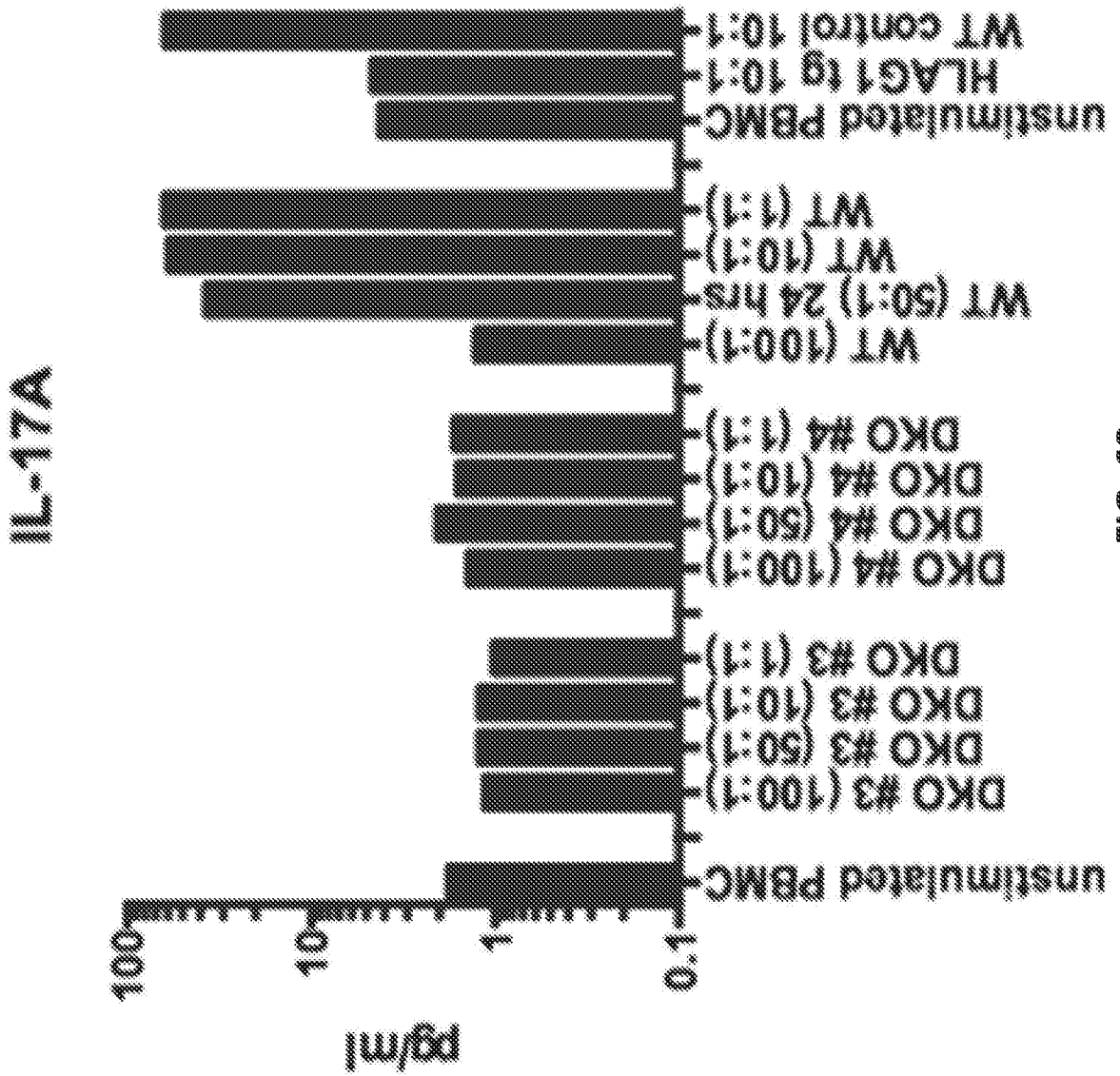

IL-17A
pg/ml
100
10
1
0.1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1

FIG. 68

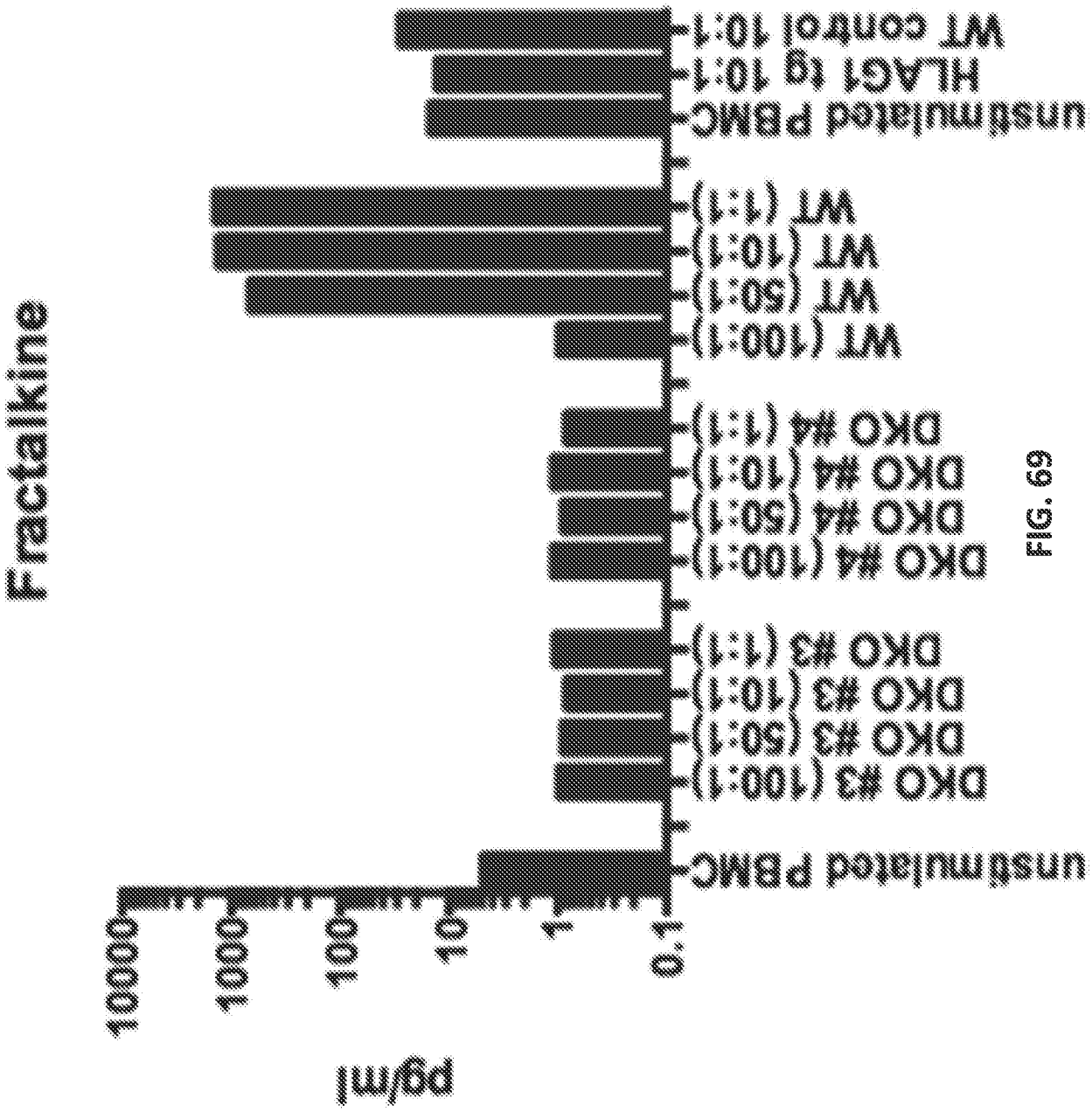

Fractalkine
pg/ml
10000
1000
100
10
1
0.1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1)
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1

FIG. 69

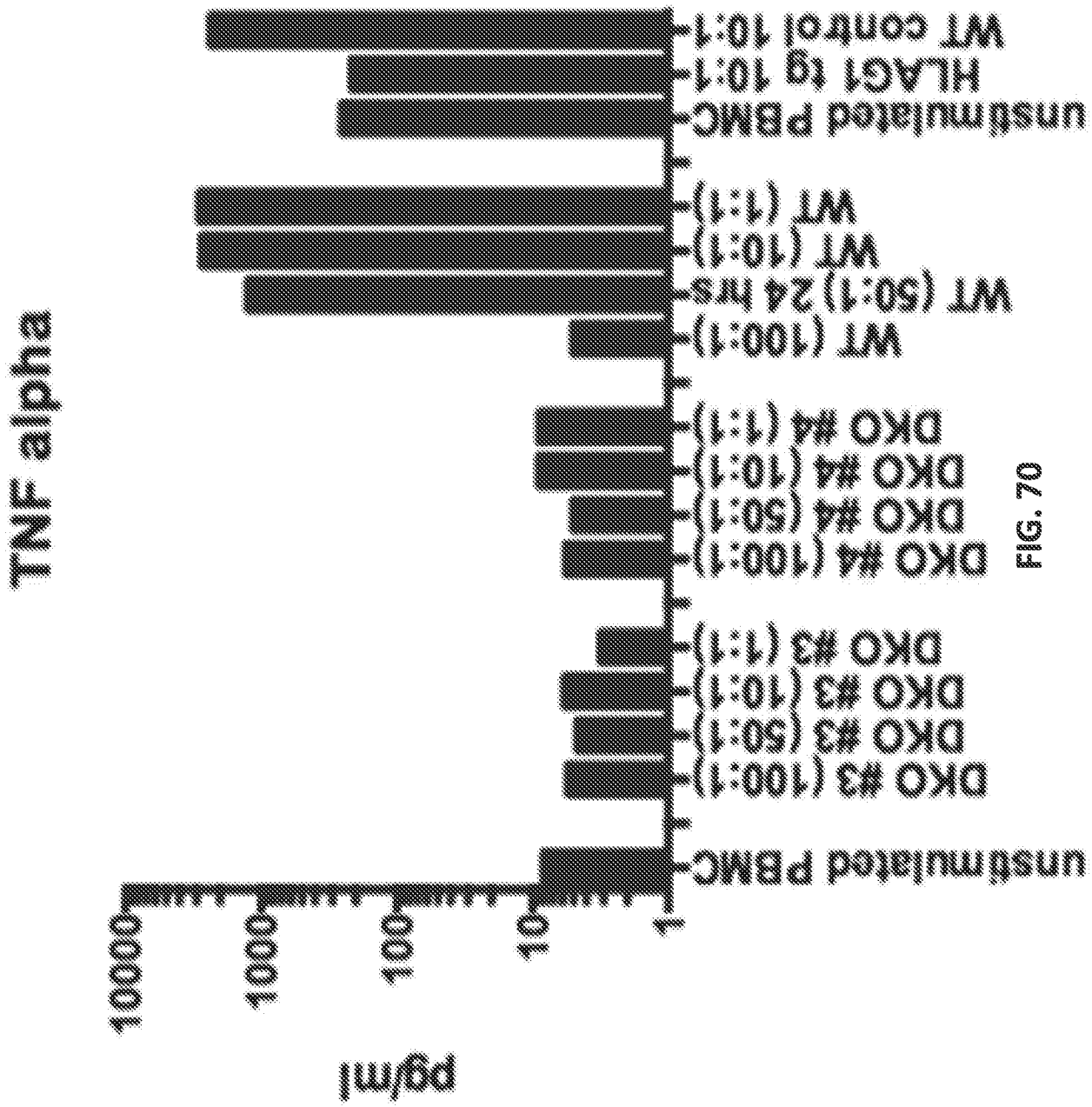

TNF alpha
pg/ml
10000
1000
100
10
1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1

FIG. 70

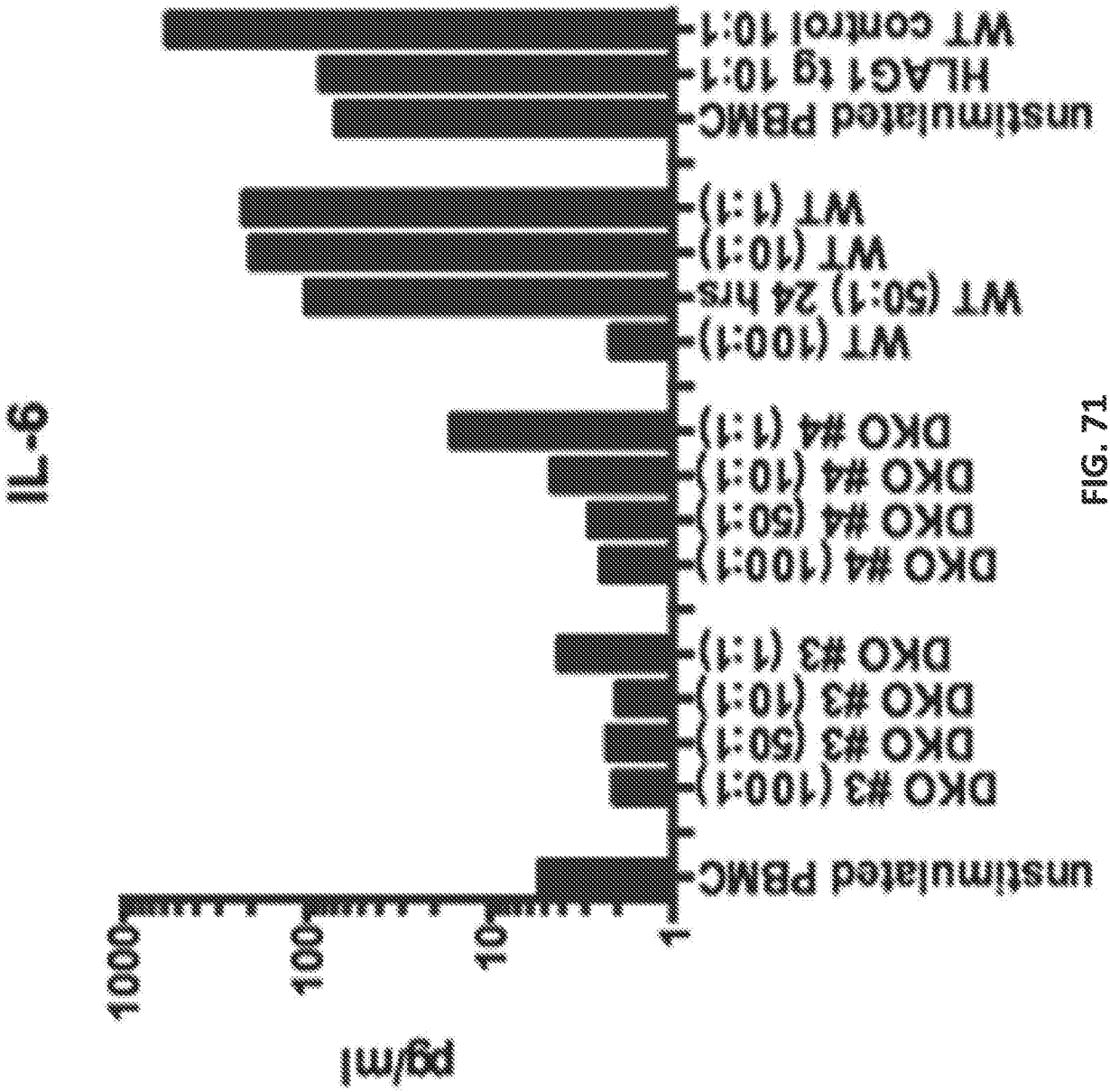

IL-6
pg/ml
1000
100
10
1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLAG1 tg 10:1
WT control 10:1

FIG. 71

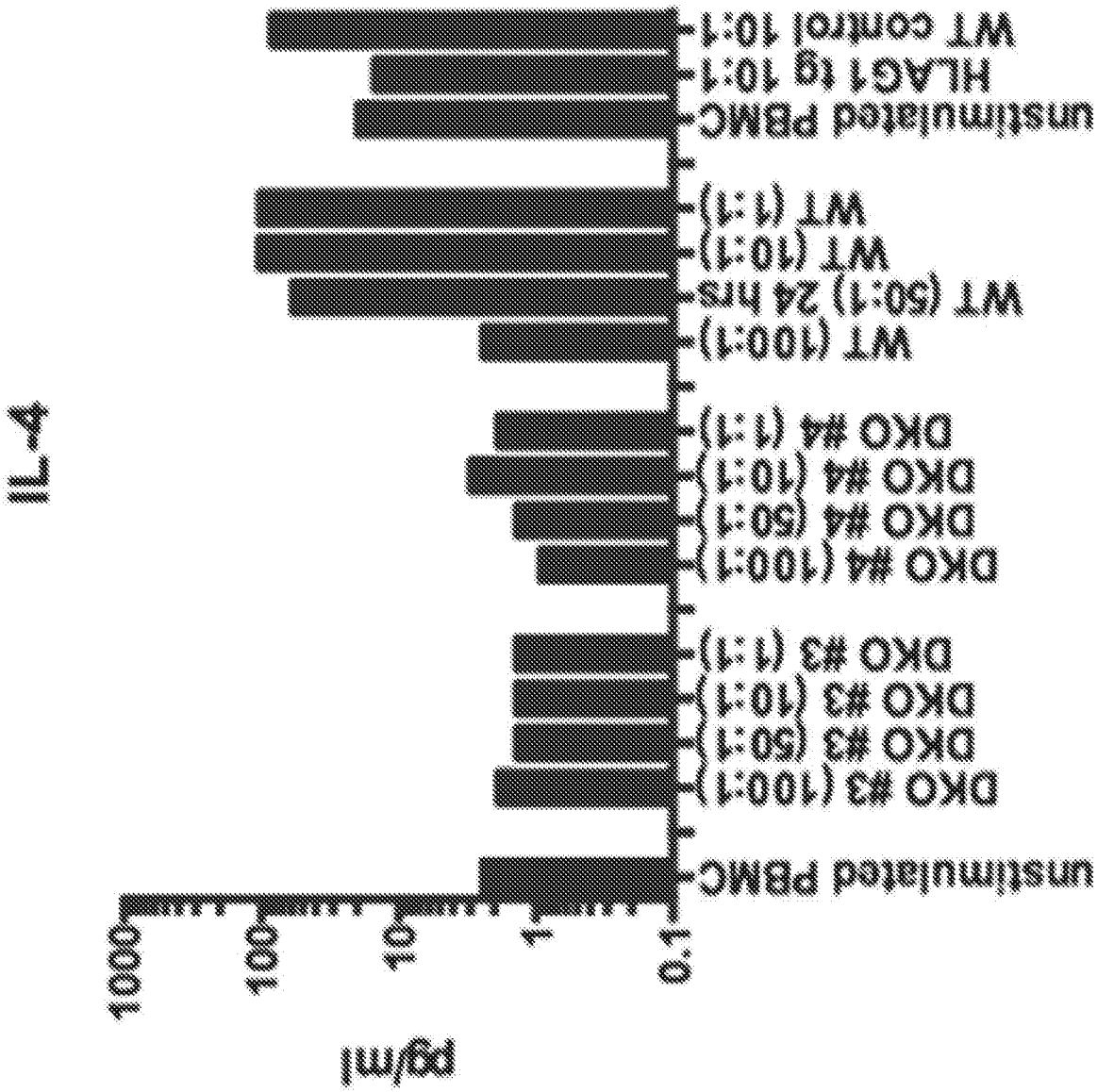

IL-4
pg/ml
1000
100
10
1
0.1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLAG1 tg 10:1
WT control 10:1

FIG. 72

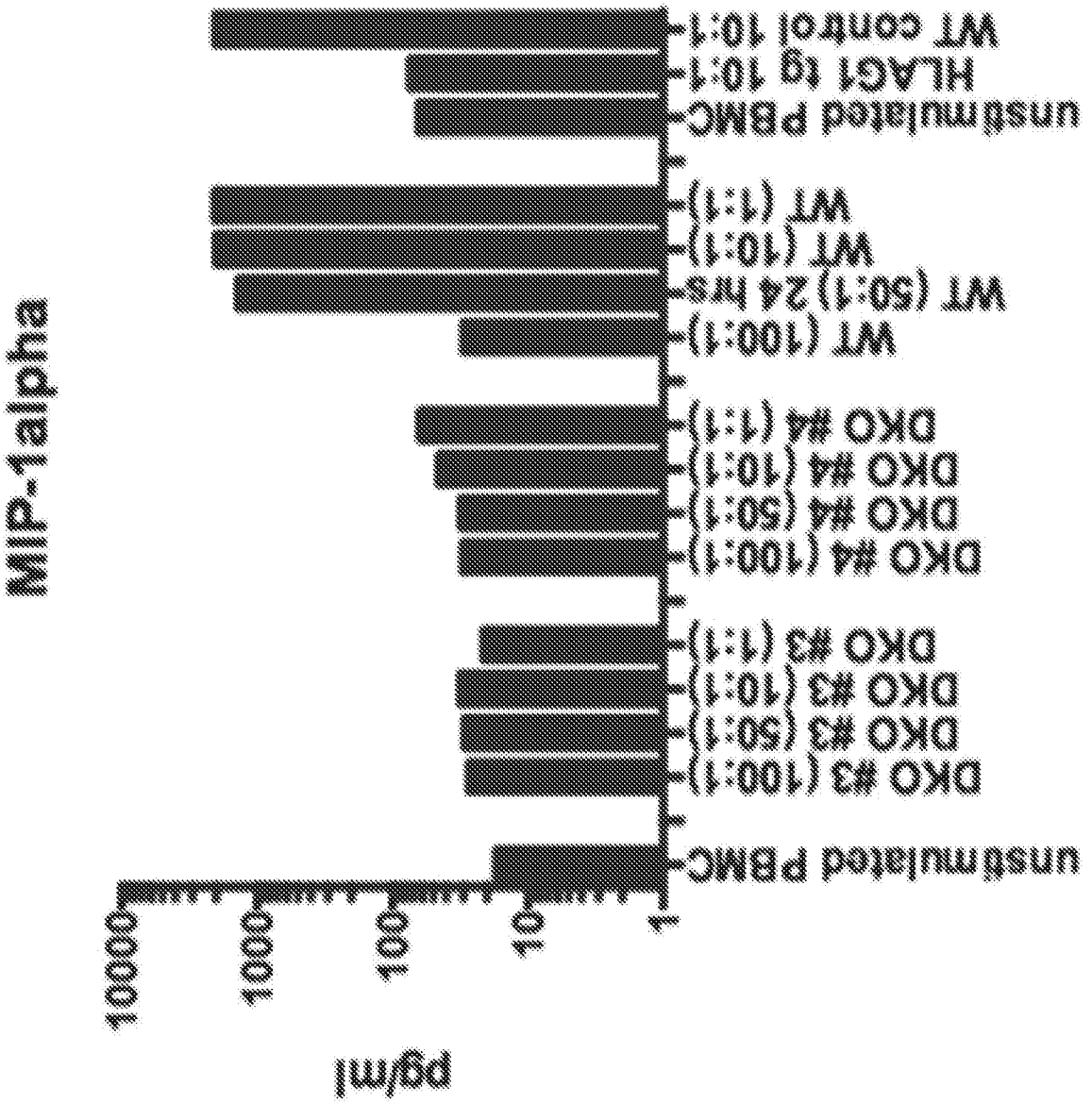

MIP-1alpha
pg/ml
10000
1000
100
10
1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1

FIG. 73

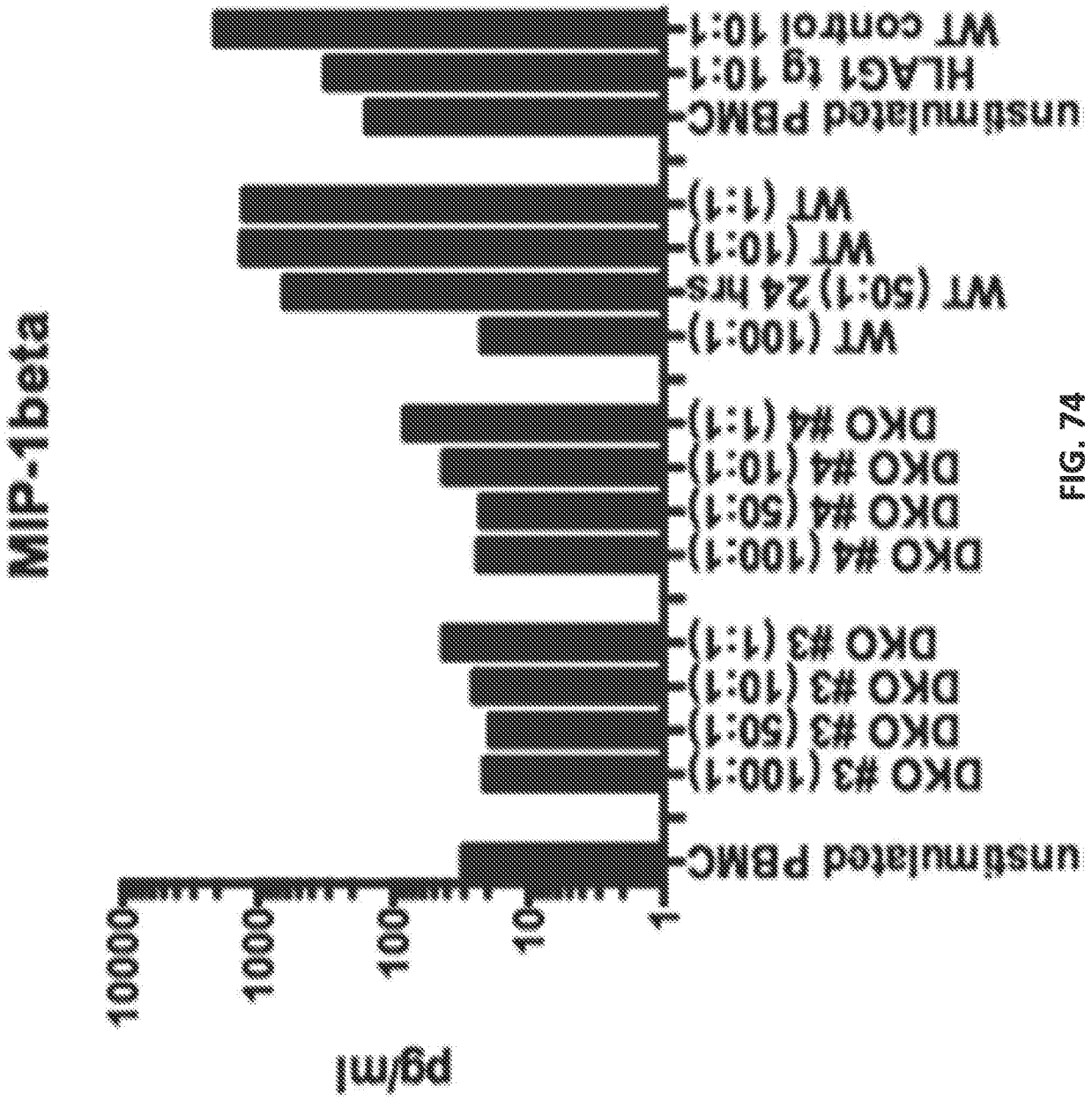

MIP-1beta
pg/ml
10000
1000
100
10
1
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLAG1 tg 10:1
WT control 10:1

FIG. 74

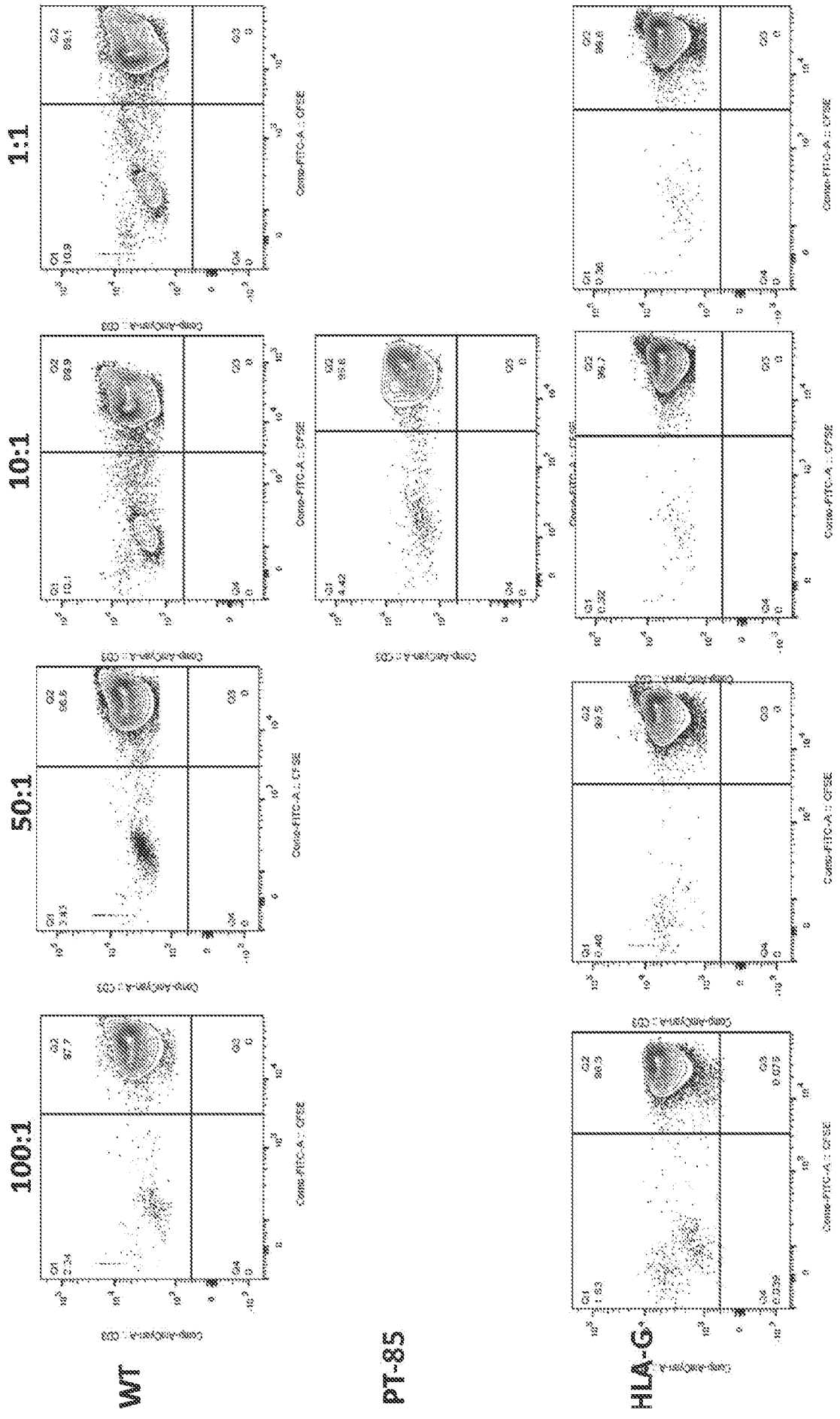


FIG. 75

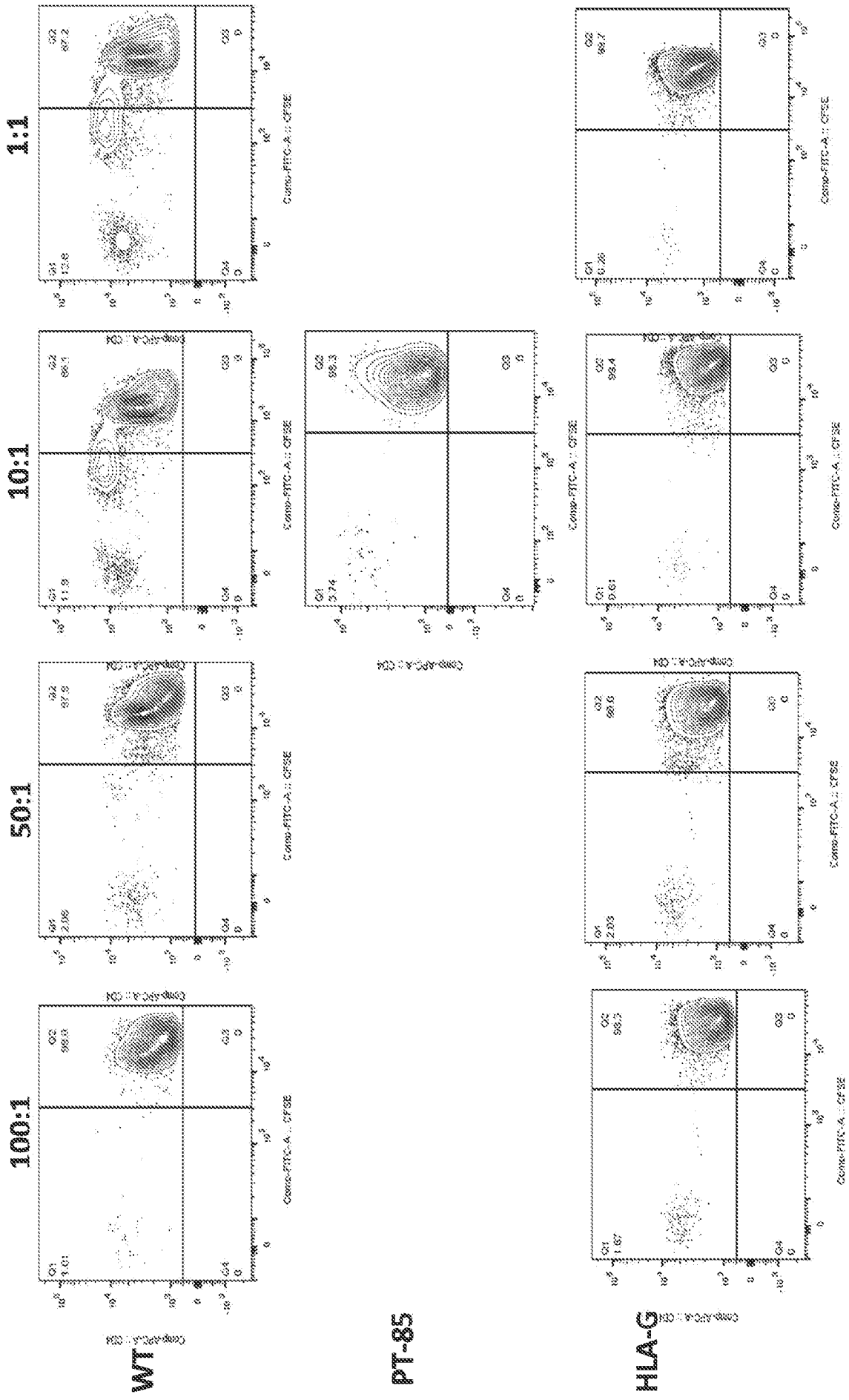


FIG. 76

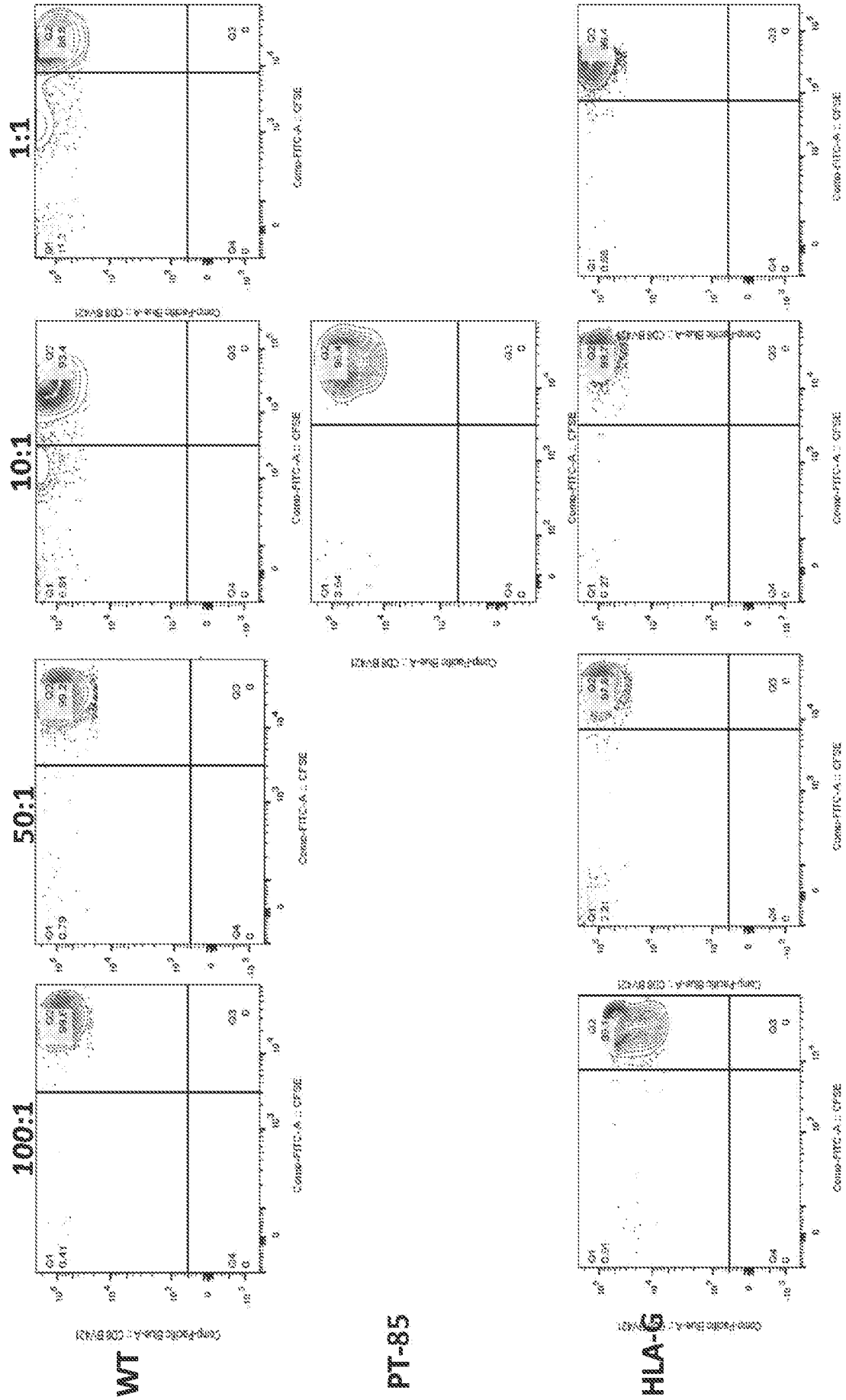


FIG. 77

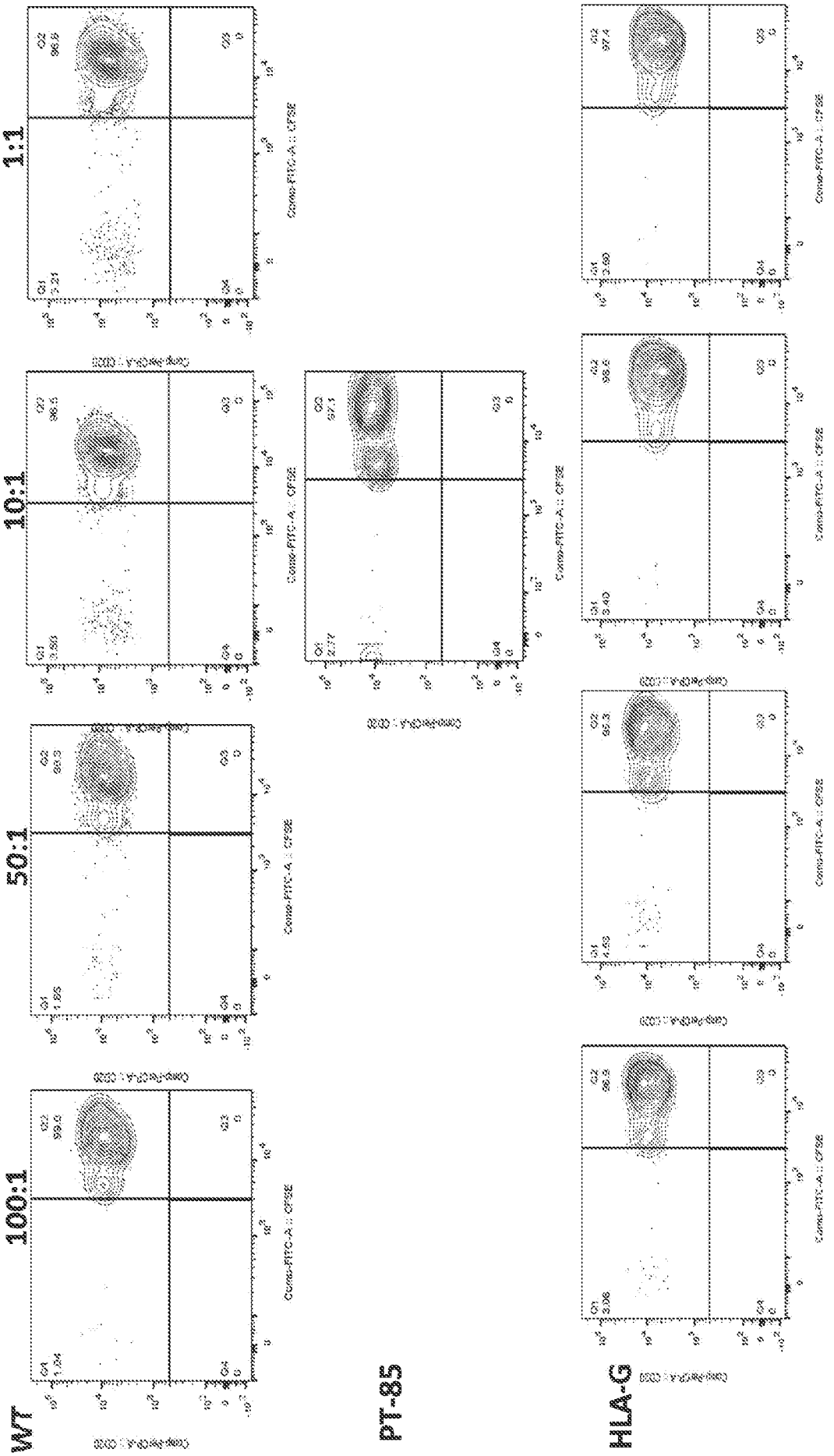
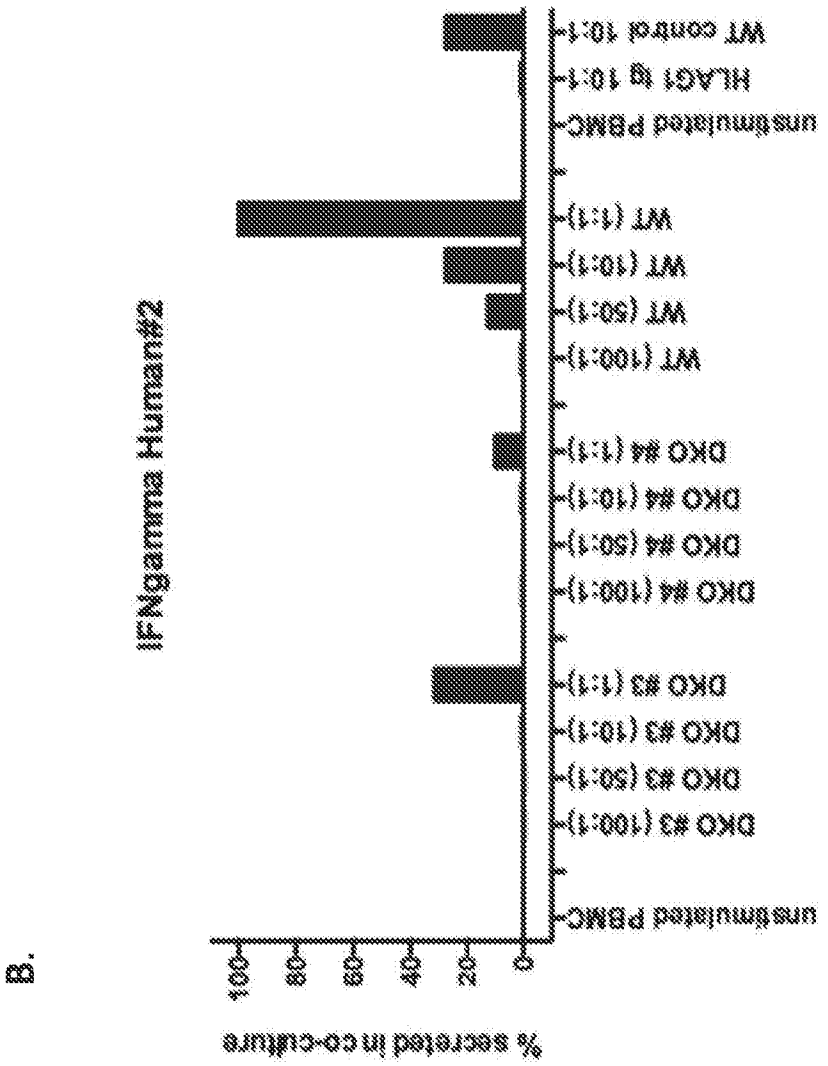


FIG. 78


B.
IFNgamma Human#2
% secreted in co-culture
0
20
40
60
80
100
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1)
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA01 tg 10:1
WT control 10:1

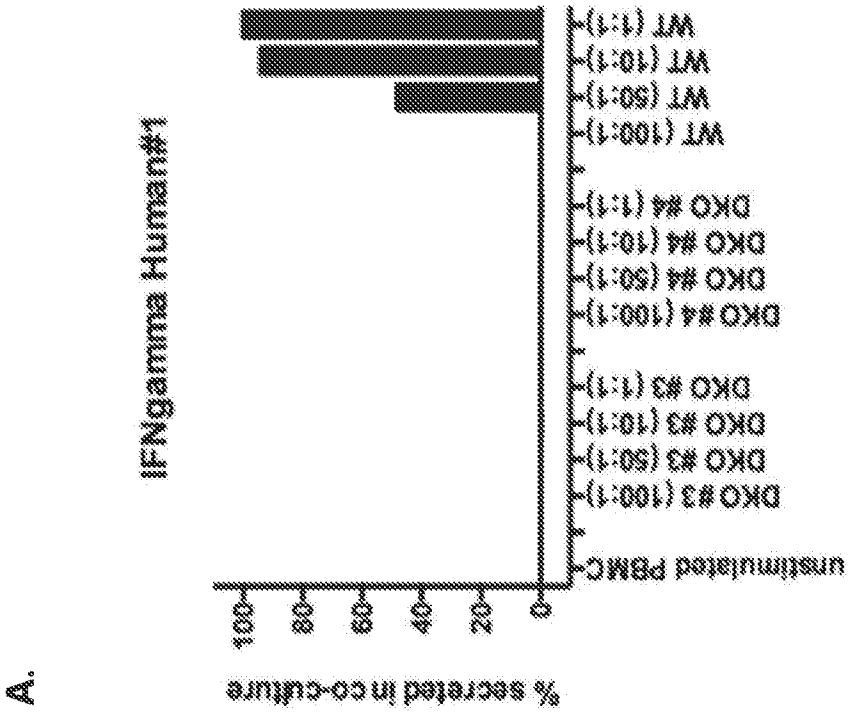

A.
IFNgamma Human#1
% secreted in co-culture
0
20
40
60
80
100
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1)
WT (10:1)
WT (1:1)

FIG. 79

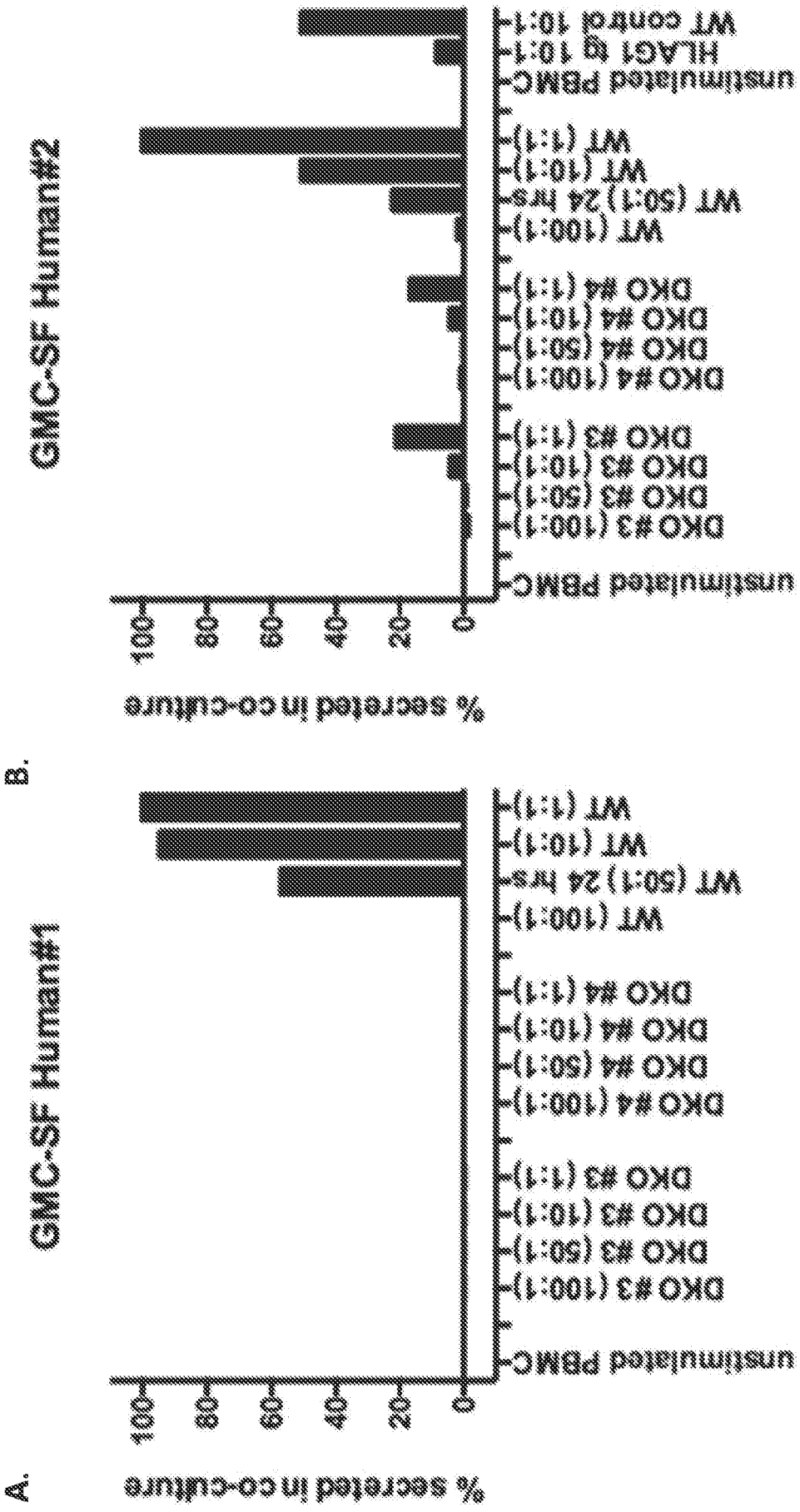

A.
GMC-SF Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
B.
GMC-SF Human#2
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLAG1 tg 10:1
WT control 10:1

FIG. 80

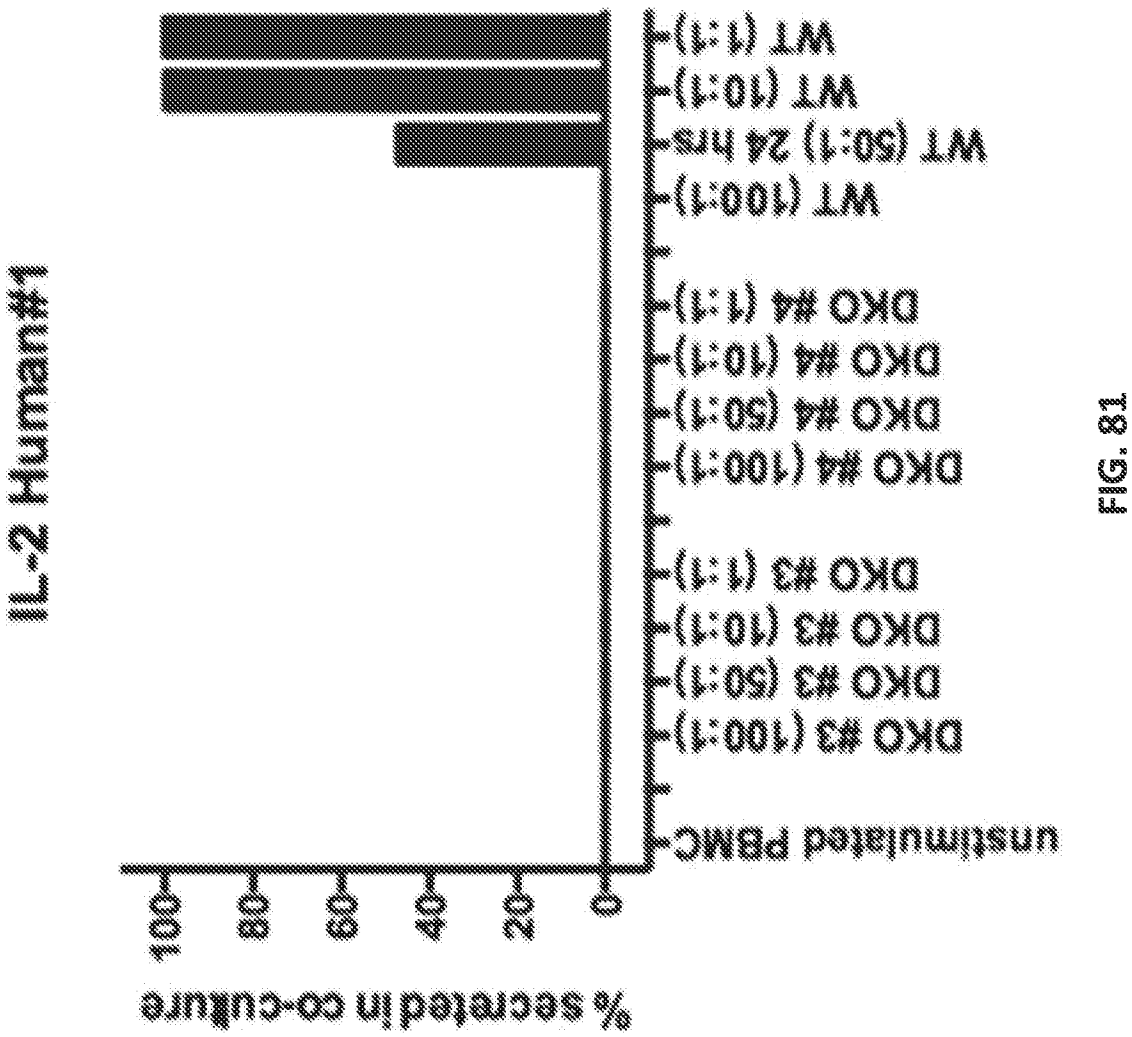

IL-2 Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)

FIG. 81

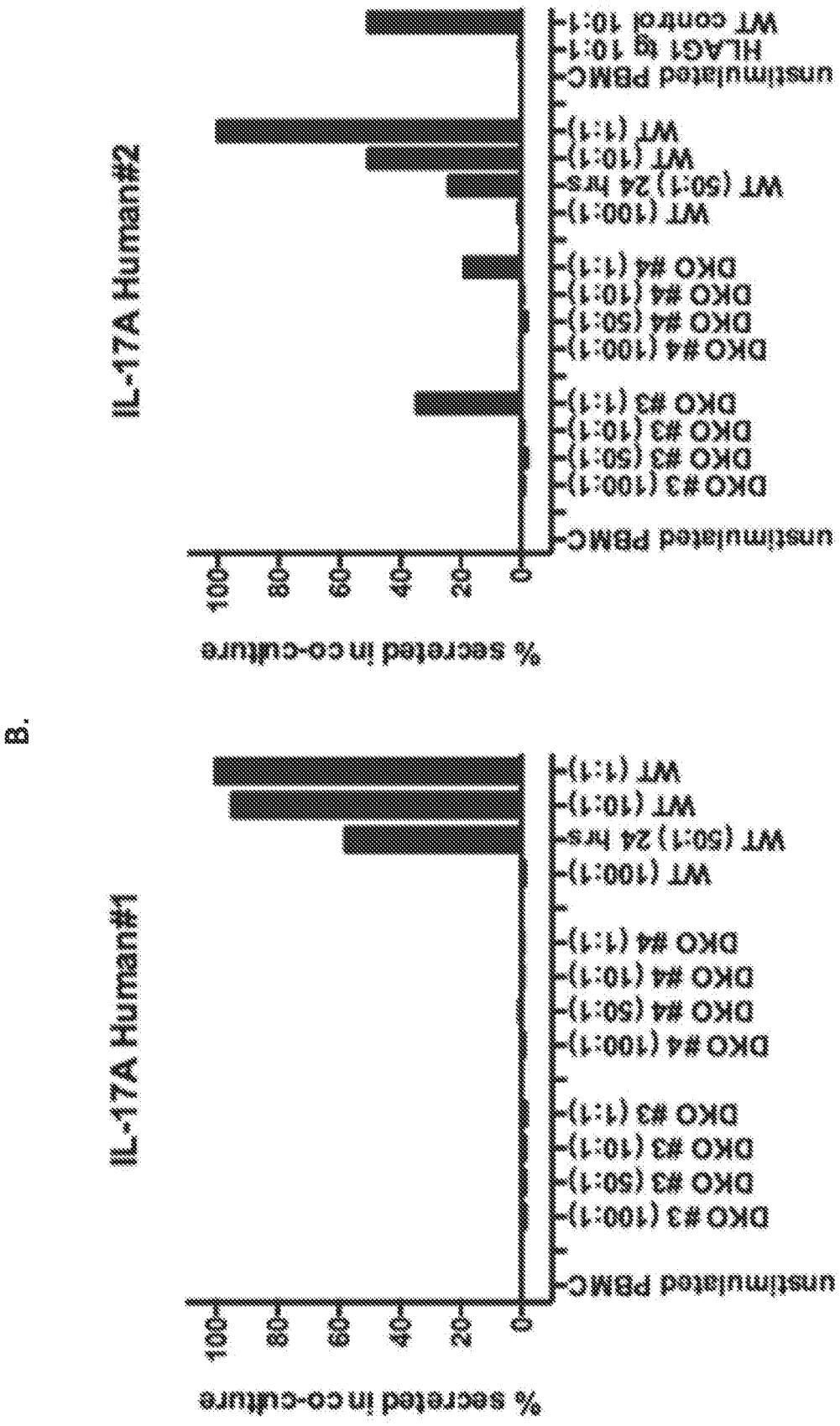

B.
IL-17A Human#2
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1
A.
IL-17A Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)

FIG. 82

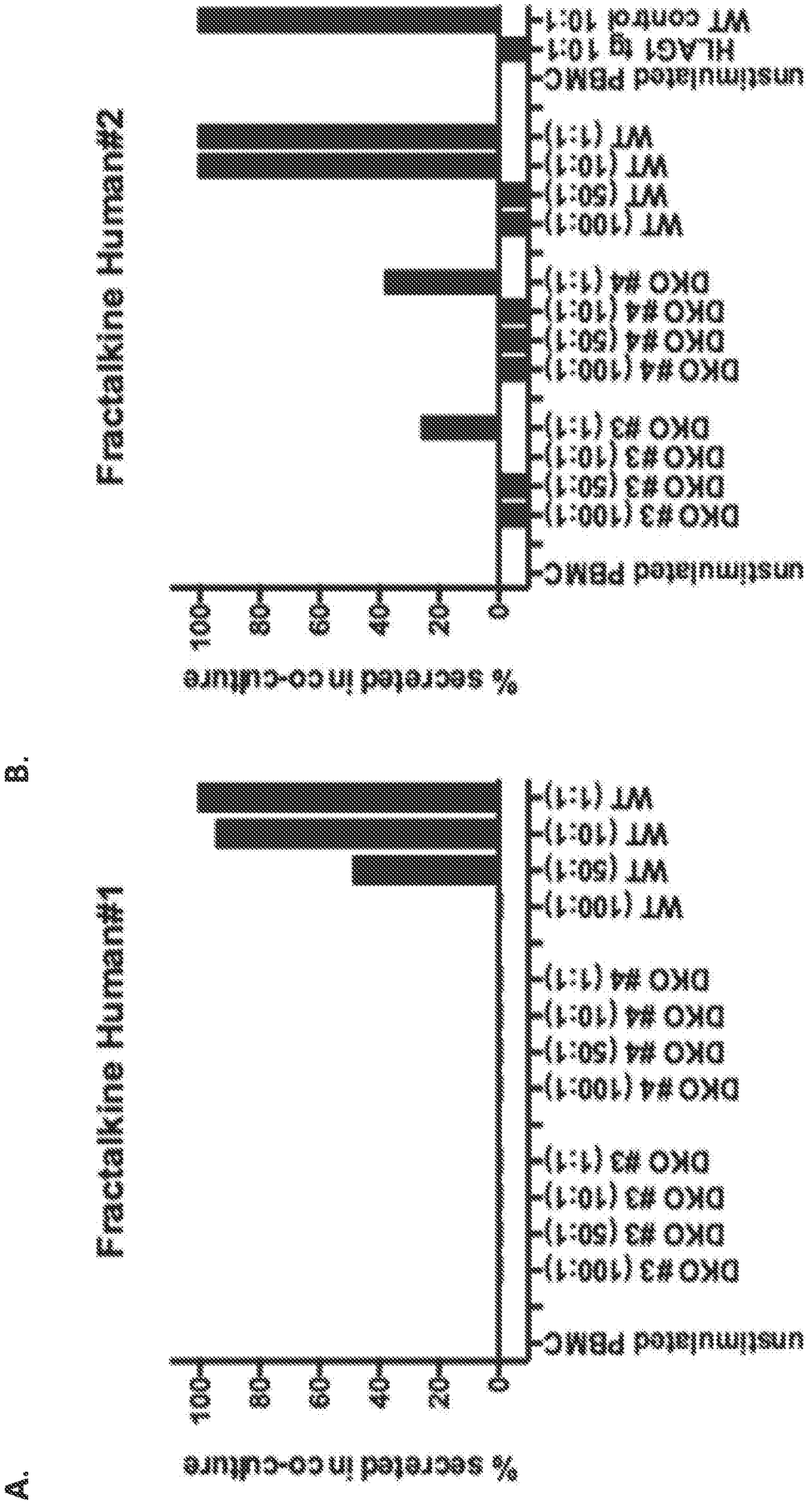

B.
Fractalkine Human#2
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1)
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 10:1
WT control 10:1
A.
Fractalkine Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1)
WT (10:1)
WT (1:1)

FIG. 83

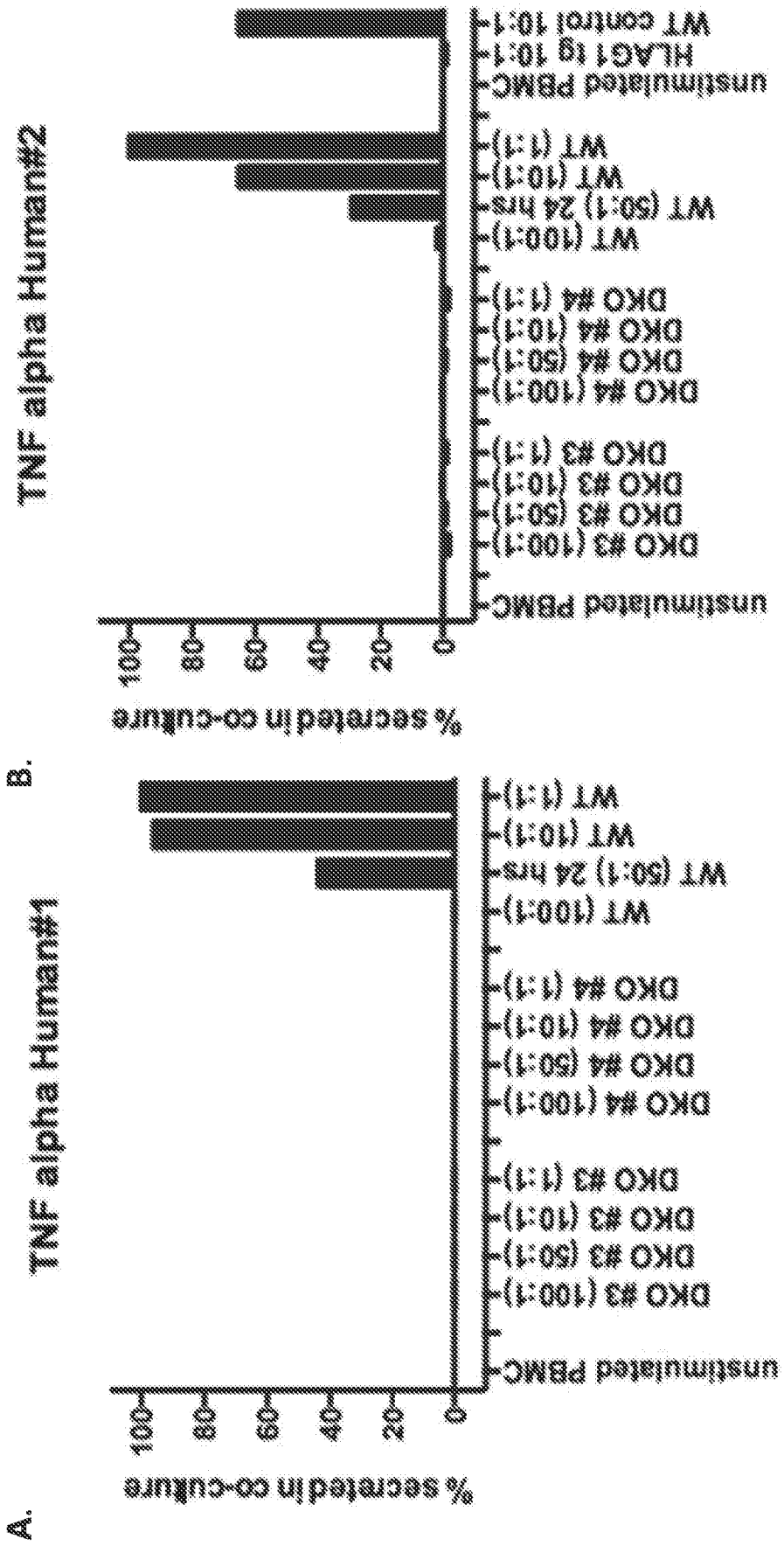

A.
TNF alpha Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
B.
TNF alpha Human#2
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA01 tg 10:1
WT control 10:1

FIG. 84

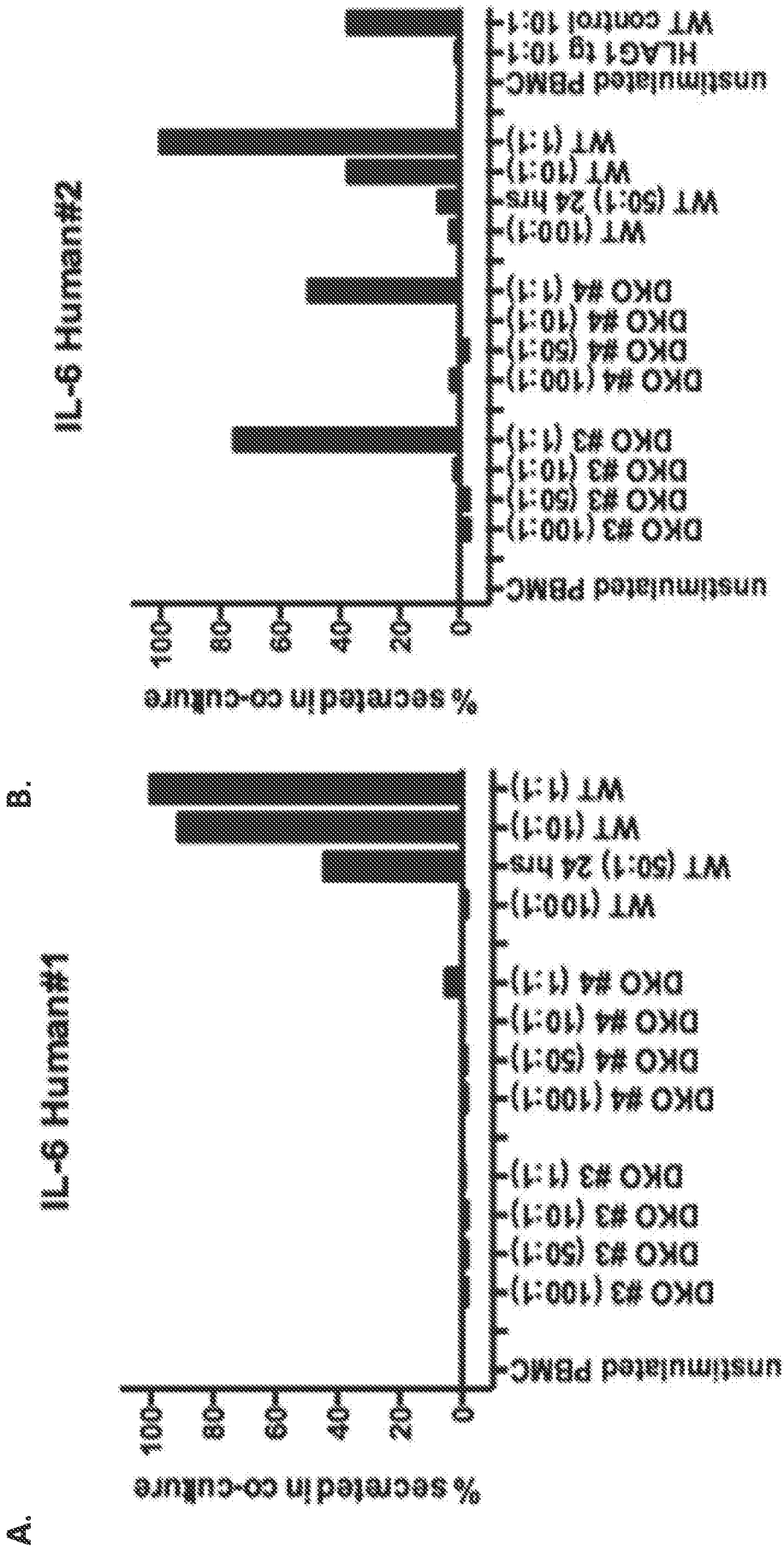

A.
IL-6 Human#1
% secreted in co-culture
0
20
40
60
80
100
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
B.
IL-6 Human#2
% secreted in co-culture
0
20
40
60
80
100
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
HLAG1 tg 10:1
WT control 10:1

FIG. 85

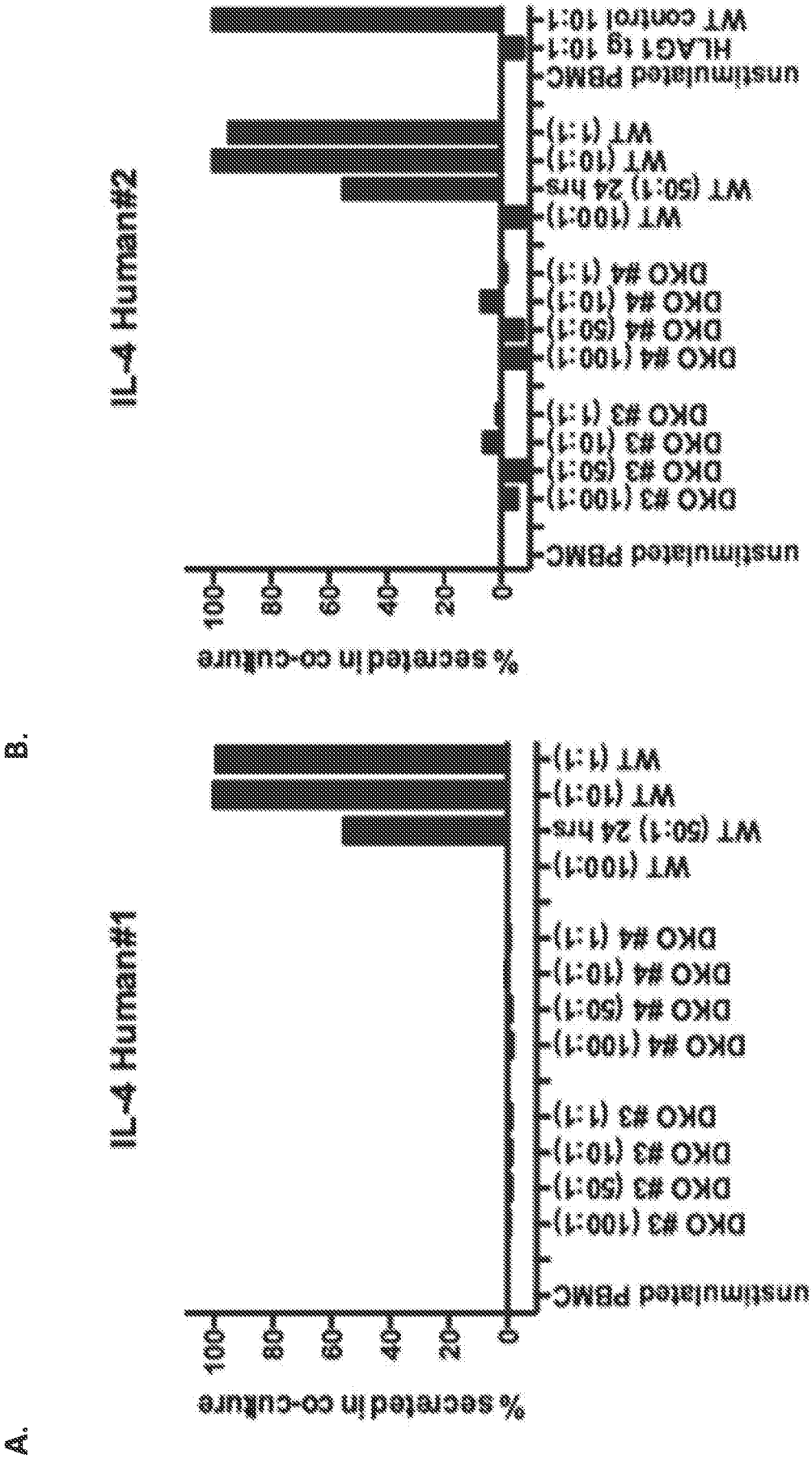

A.
IL-4 Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
B.
IL-4 Human#2
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1

FIG. 86

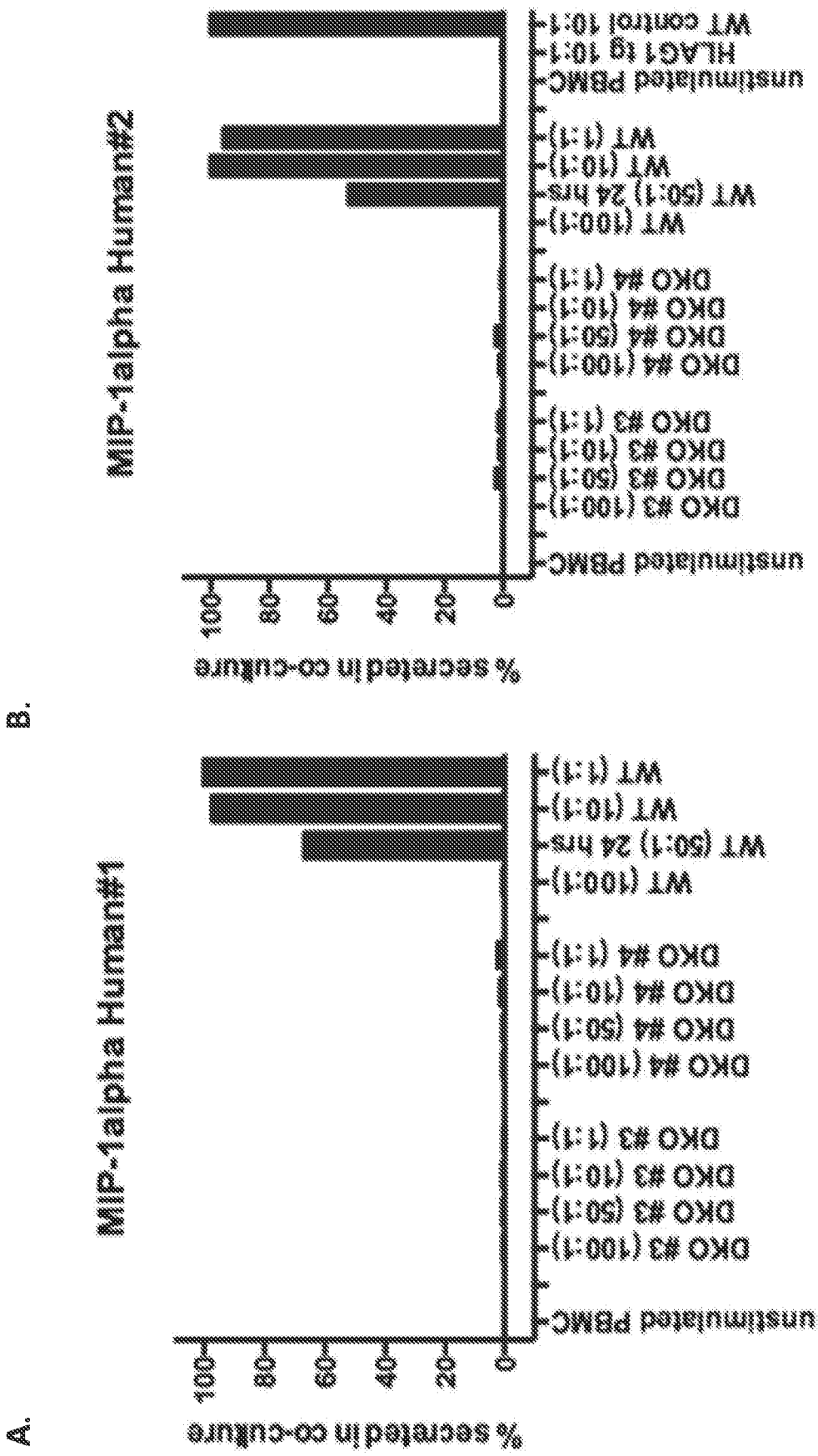
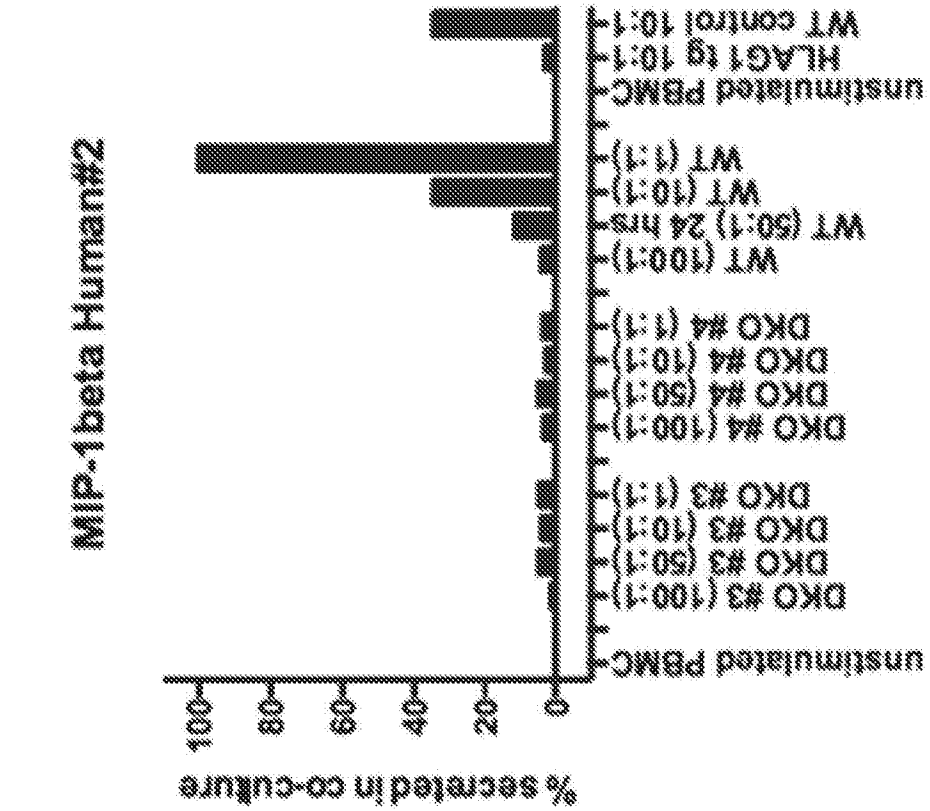

B.
MIP-1alpha Human#2
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
HLA-G1 tg 10:1
WT control 10:1
A.
MIP-1alpha Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)

FIG. 87


B.
MIP-1beta Human#2
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)
unstimulated PBMC
WT control 10:1
HLA-G1 tg 10:1

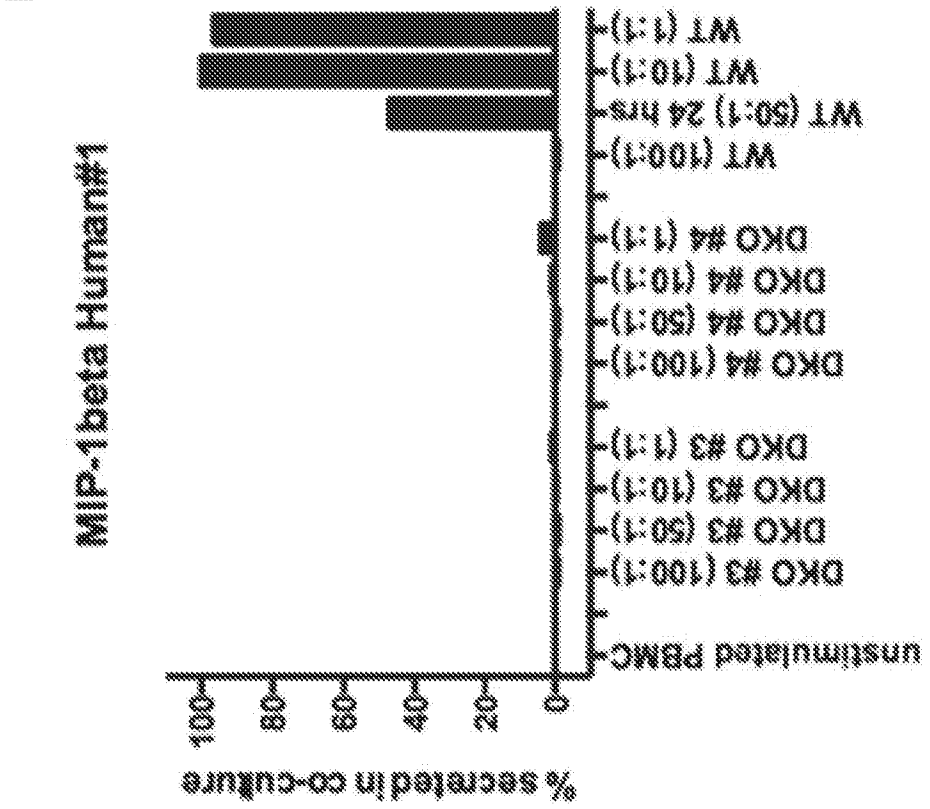

A.
MIP-1beta Human#1
% secreted in co-culture
100
80
60
40
20
0
unstimulated PBMC
DKO #3 (100:1)
DKO #3 (50:1)
DKO #3 (10:1)
DKO #3 (1:1)
DKO #4 (100:1)
DKO #4 (50:1)
DKO #4 (10:1)
DKO #4 (1:1)
WT (100:1)
WT (50:1) 24 hrs
WT (10:1)
WT (1:1)

FIG. 88

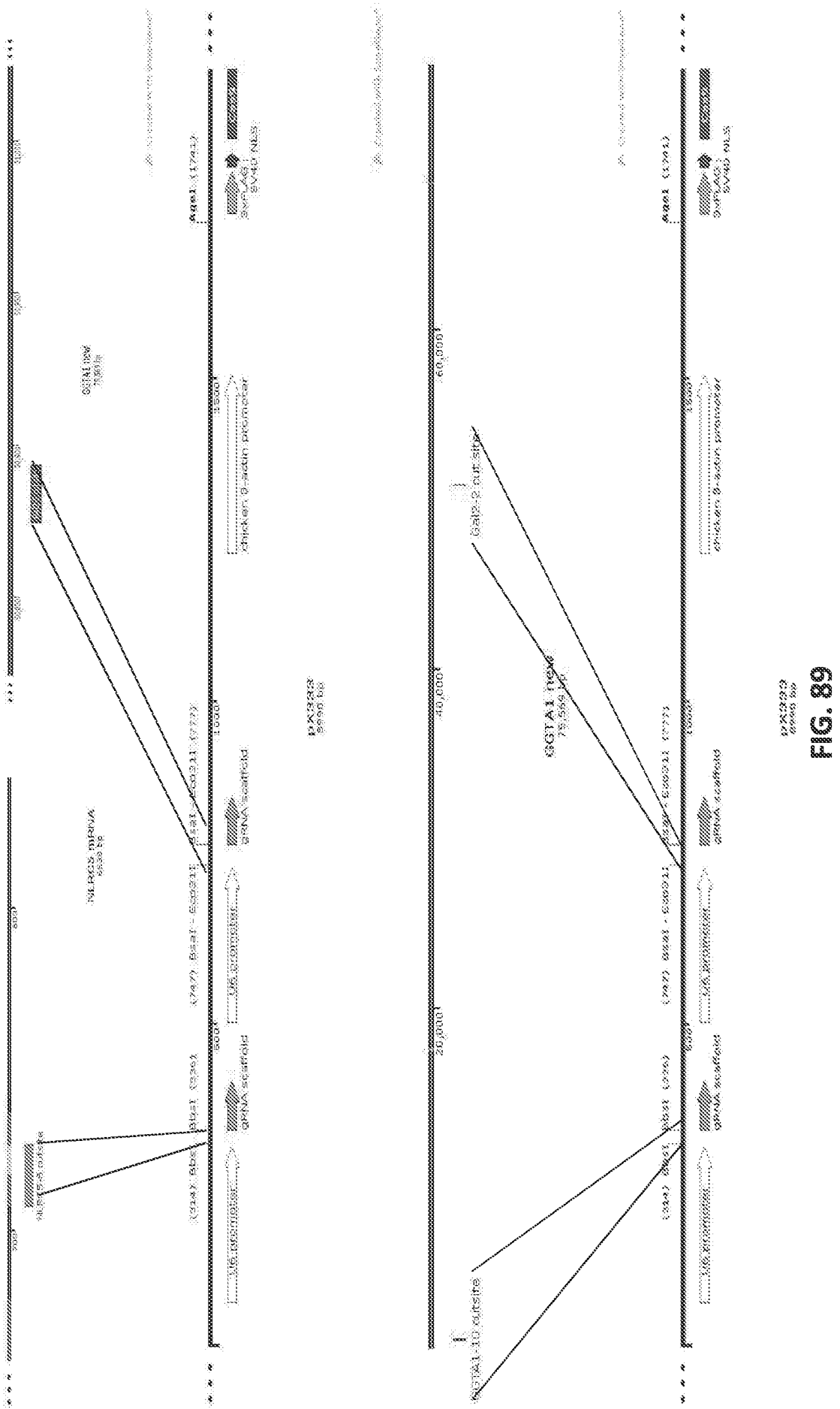


FIG. 89

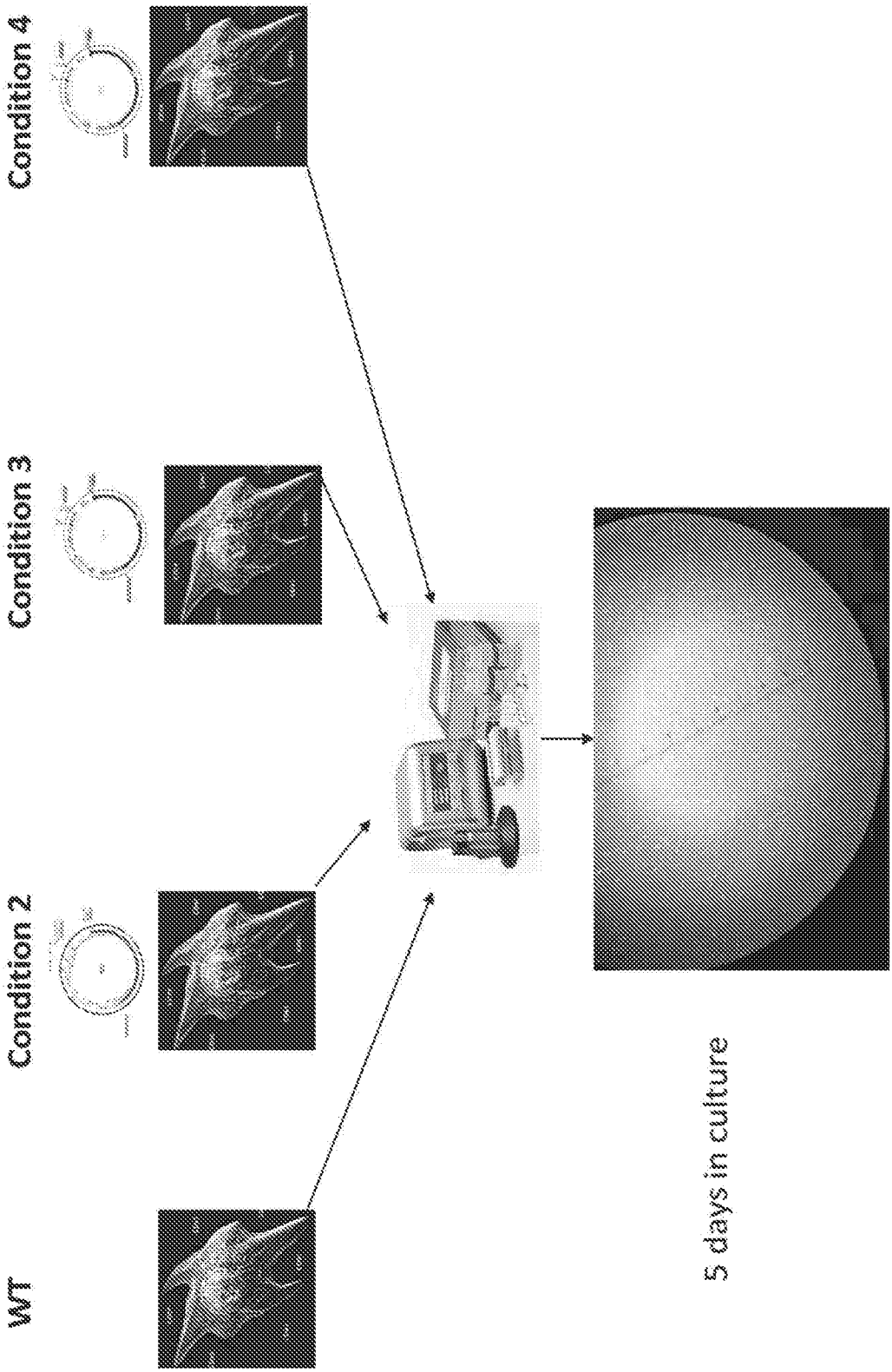
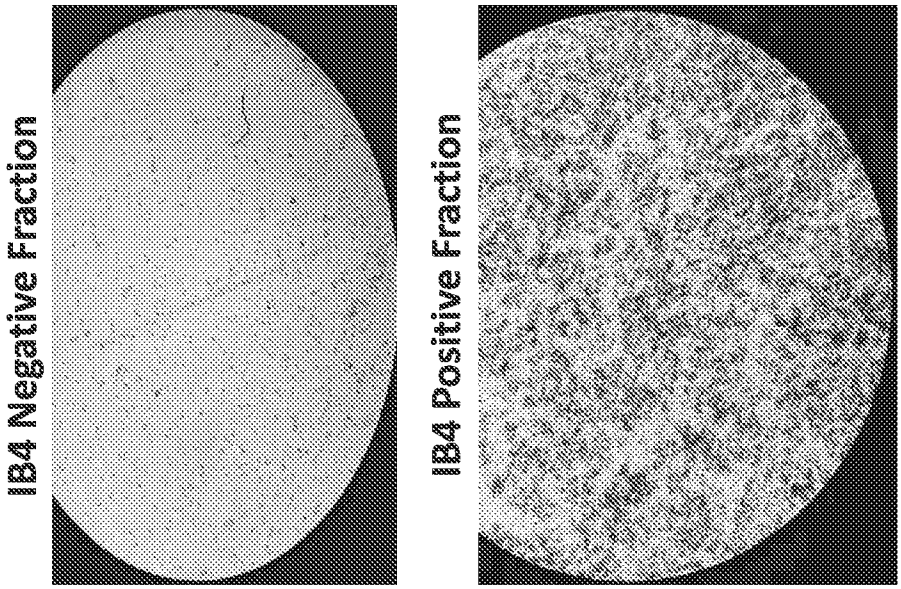


FIG. 90



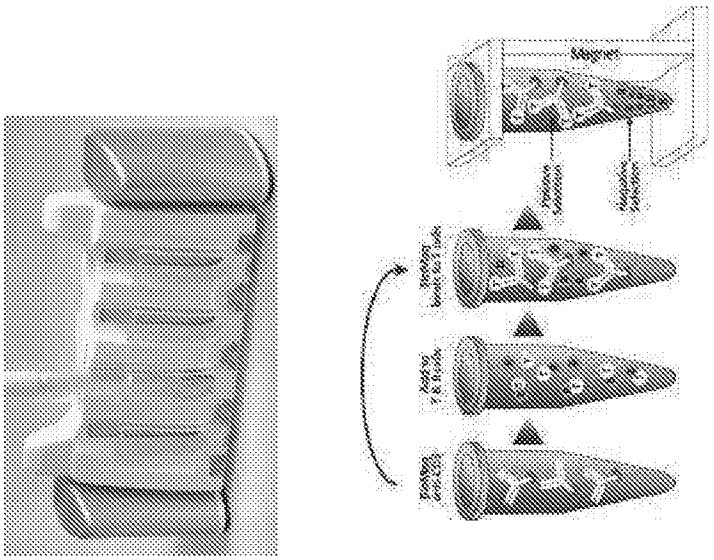


FIG. 91

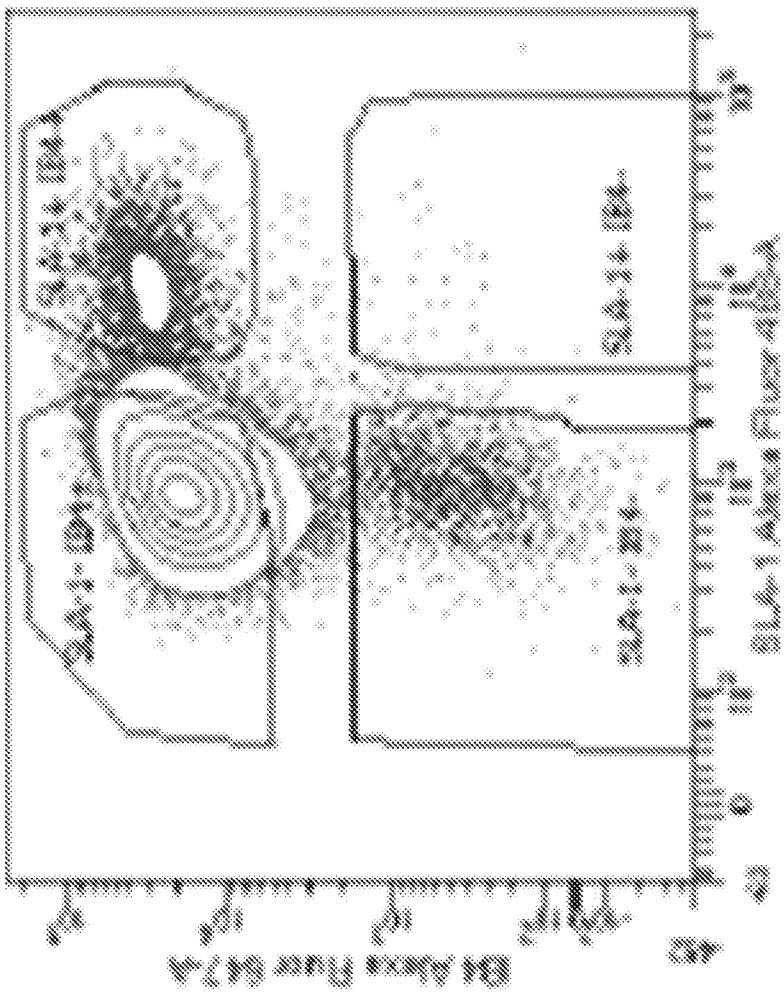

SLA-1 Alpha Fluor (Log)
SLA-1 Beta Fluor (Log)
SLA-1: 01
SLA-1: 02
SLA-1: 03
SLA-1: 04

FIG. 92

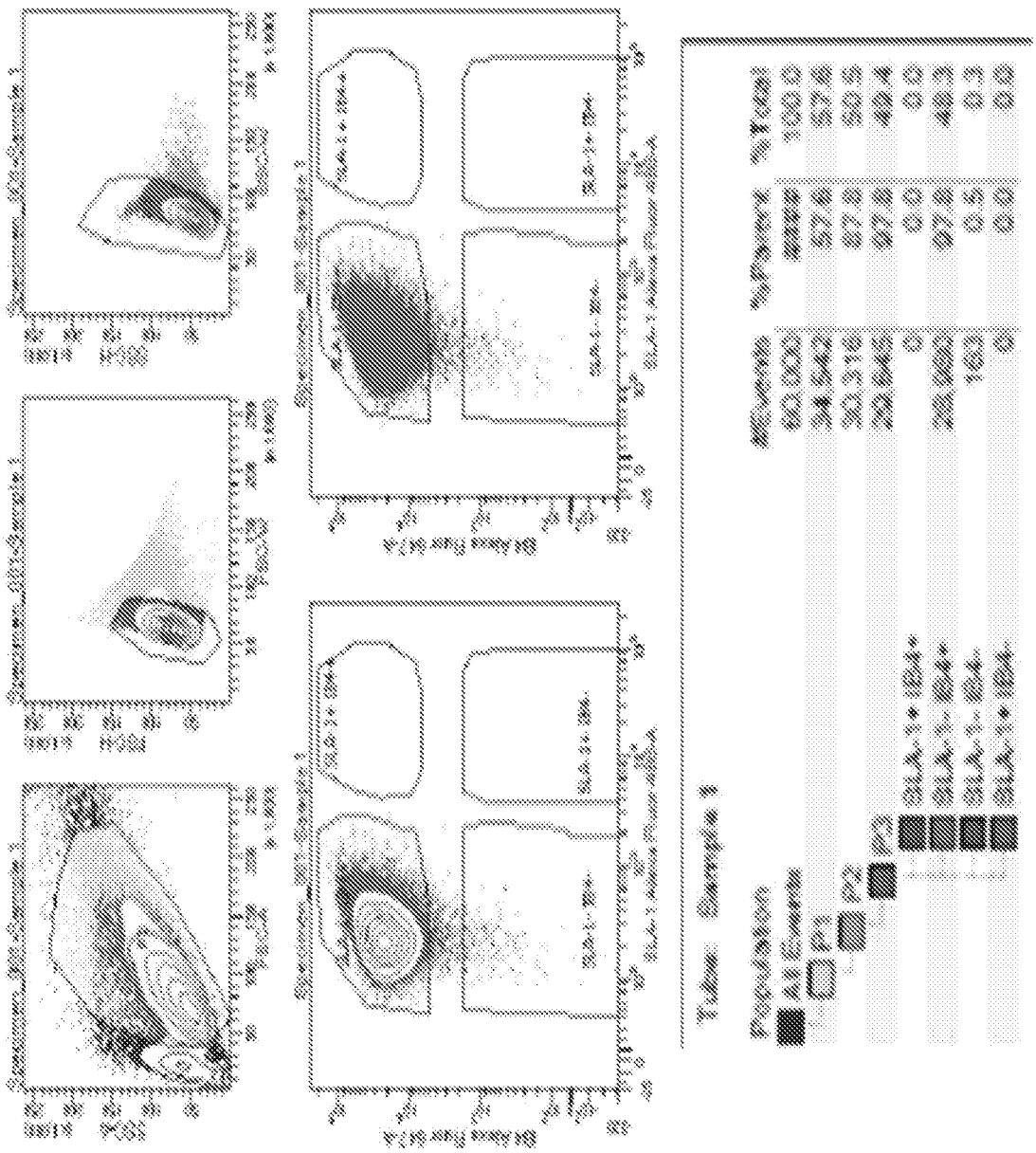


FIG. 93

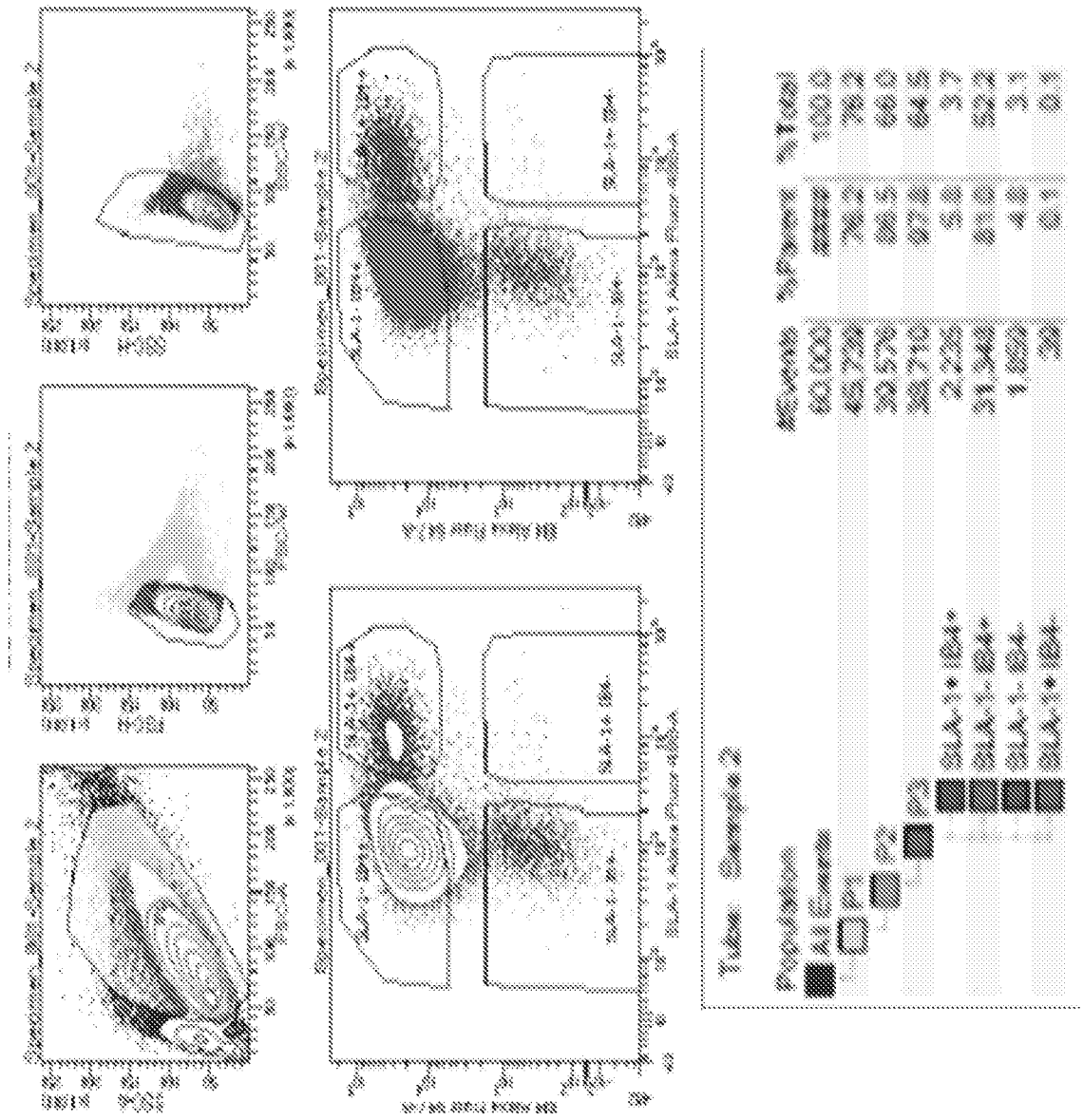


FIG. 94

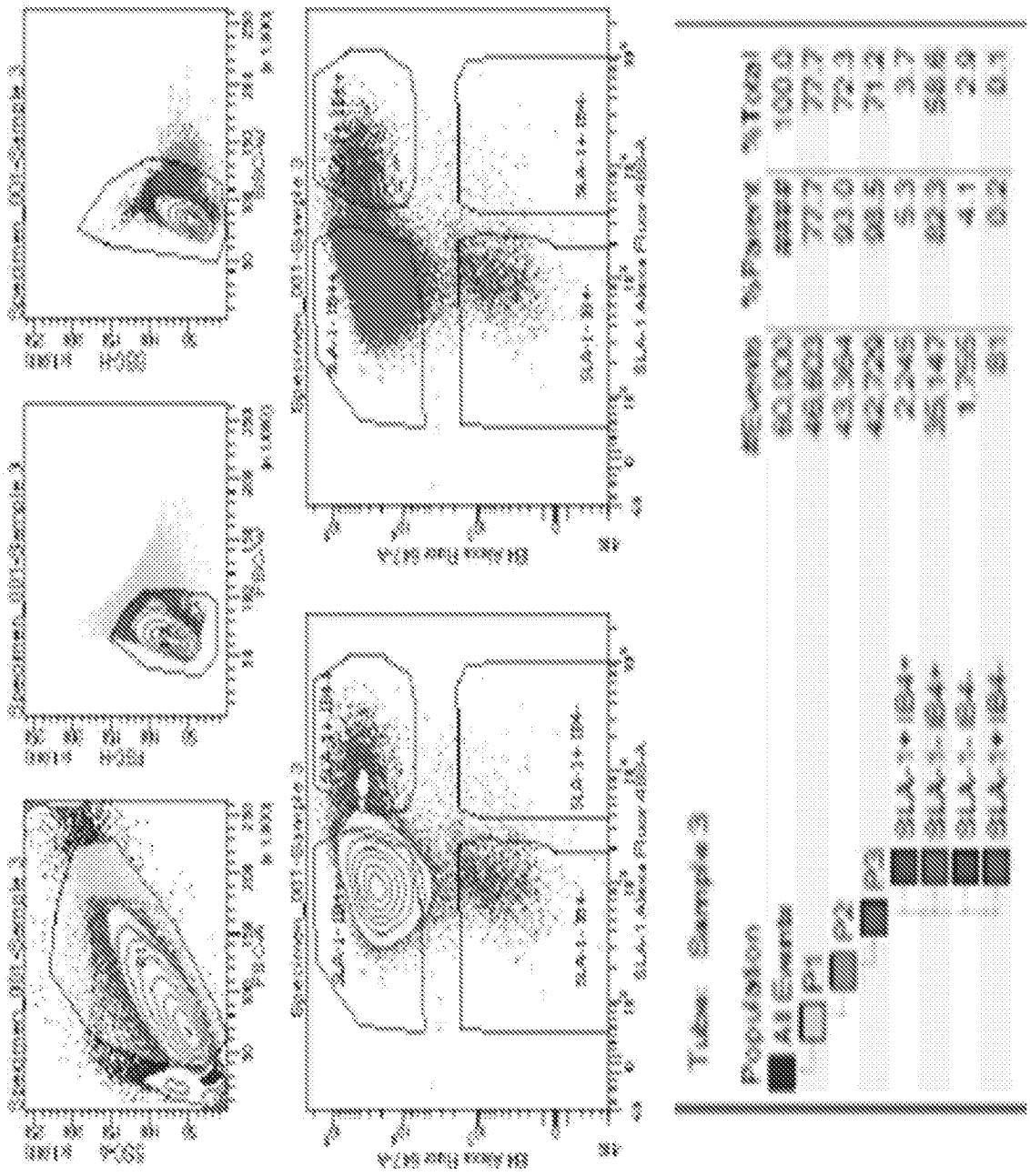


FIG. 95

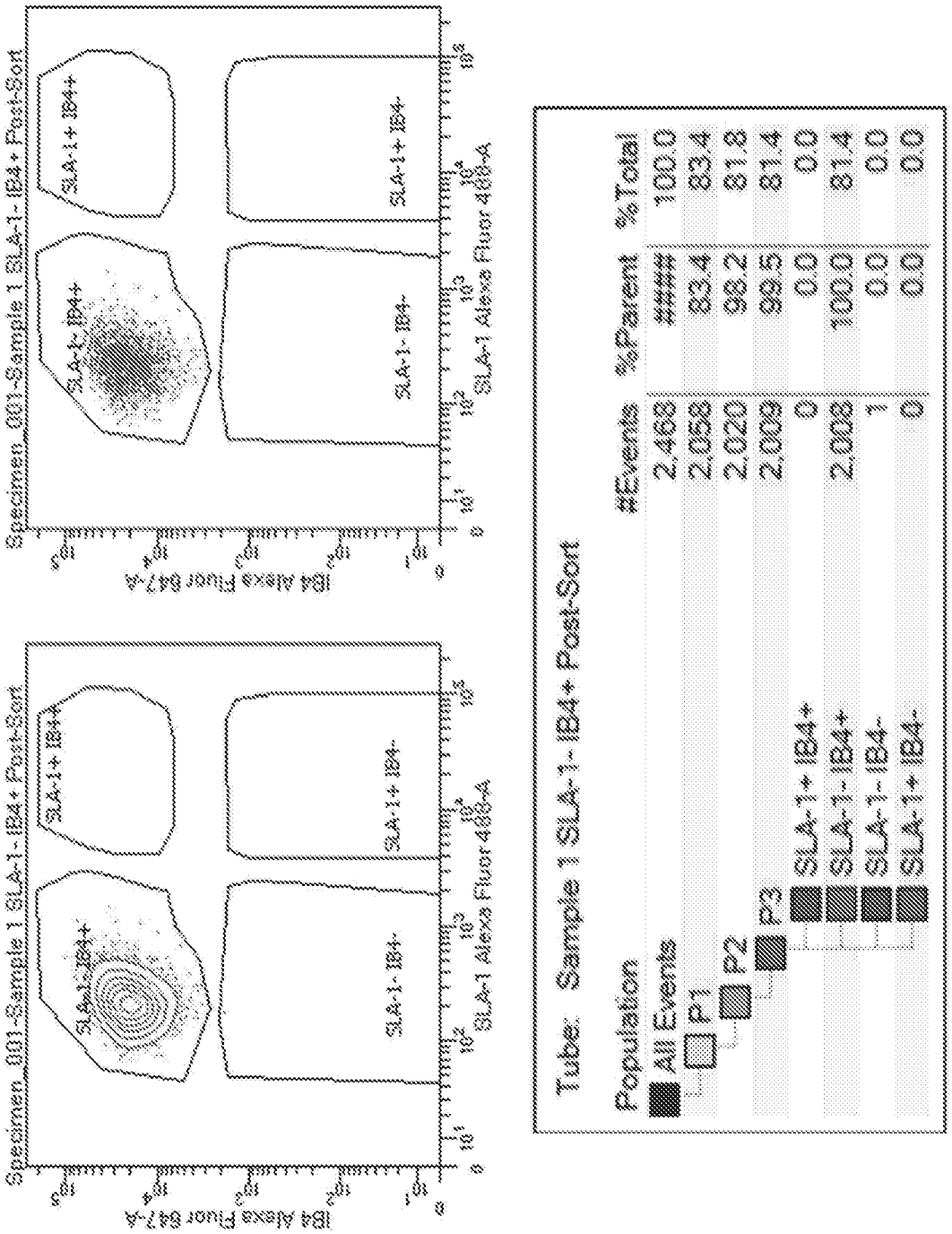

Specimen_001-Sample 1 SLA-1- IB4+ Post-Sort
SLA-1+ IB4+
SLA-1- IB4-
SLA-1+ IB4-
IB4 Alexa Fluor 647-A
SLA-1 Alexa Fluor 488-A
Tube: Sample 1 SLA-1- IB4+ Post-Sort
Population
#Events
%Parent
%Total
All Events 2,468 #### 100.0
P1 2,058 83.4 83.4
P2 2,020 98.2 81.8
P3 2,009 99.5 81.4
SLA-1+ IB4+ 0 0.0 0.0
SLA-1- IB4+ 2,008 100.0 81.4
SLA-1- IB4- 1 0.0 0.0
SLA-1+ IB4- 0 0.0 0.0

FIG. 96

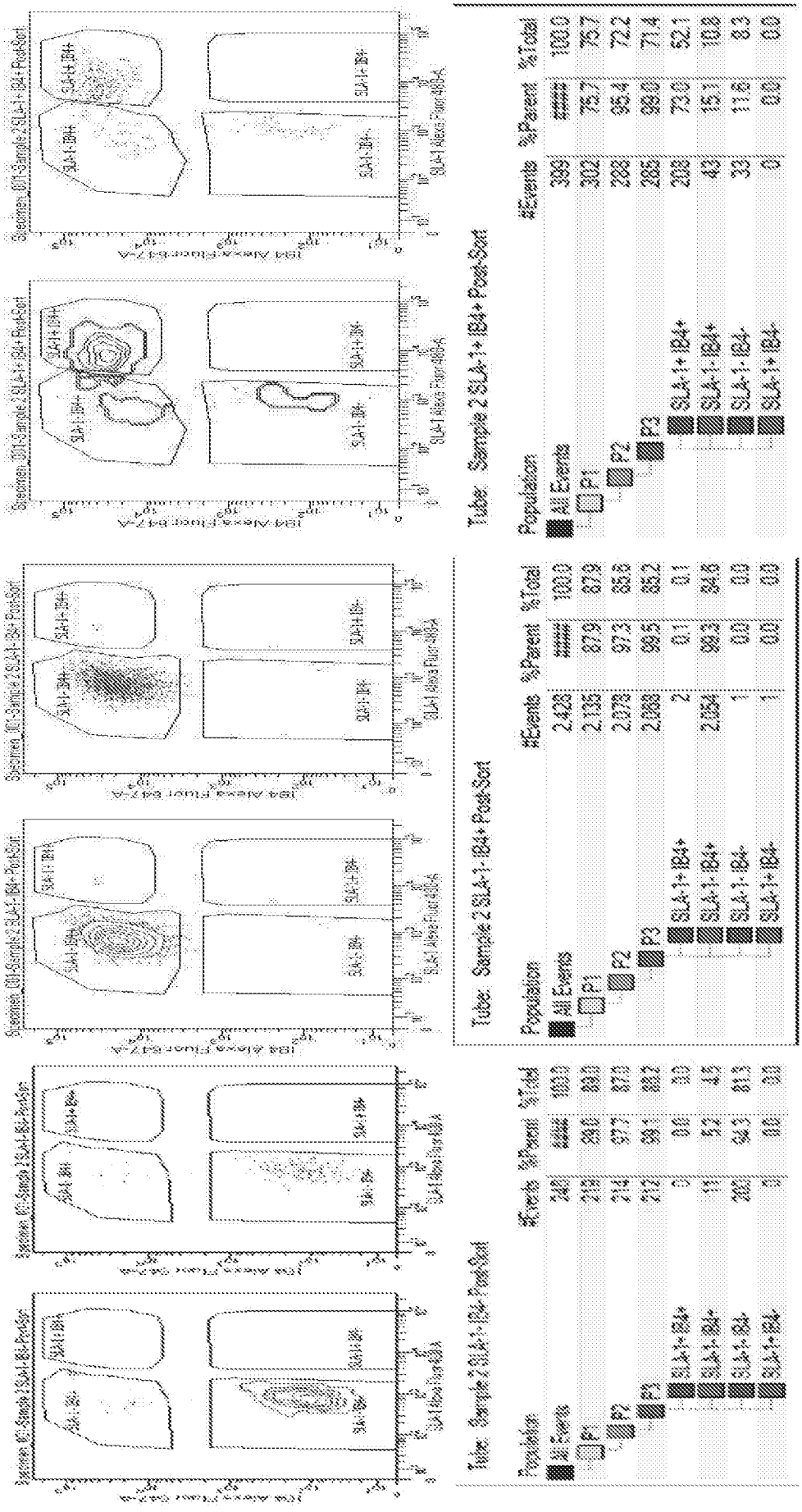

SLA- / IB4-
SLA- / IB4+
SLA+ / IB4+
Specimen_001-Sample 1 SLA-1- IB4- Post-Sort
Specimen_001-Sample 2 SLA-1- IB4+ Post-Sort
Specimen_001-Sample 2 SLA-1+ IB4+ Post-Sort
SLA-1- IB4-
SLA-1- IB4+
SLA-1+ IB4+
IB4 Alexa Fluor 647-A
SLA-1 Alexa Fluor 488-A
Tube: Sample 1 SLA-1- IB4- Post-Sort
Tube: Sample 2 SLA-1- IB4+ Post-Sort
Tube: Sample 2 SLA-1+ IB4+ Post-Sort
Population #Events %Parent %Total
All Events 240 ##### 100.0
P1 219 91.3 91.3
P2 214 97.7 87.5
P3 212 99.1 88.2
SLA-1+ IB4+ 0 0.0 0.0
SLA-1- IB4+ 11 5.2 4.6
SLA-1- IB4- 202 94.3 81.5
SLA-1+ IB4- 0 0.0 0.0
All Events 2,428 ##### 100.0
P1 2,135 87.9 87.9
P2 2,073 97.3 85.6
P3 2,068 99.5 85.2
SLA-1+ IB4+ 2 0.1 0.1
SLA-1- IB4+ 2,054 99.3 84.6
SLA-1- IB4- 1 0.0 0.0
SLA-1+ IB4- 1 0.0 0.0
All Events 399 ##### 100.0
P1 302 75.7 75.7
P2 288 95.4 72.2
P3 285 99.0 71.4
SLA-1+ IB4+ 208 73.0 52.1
SLA-1- IB4+ 43 15.1 10.8
SLA-1- IB4- 33 11.6 8.3
SLA-1+ IB4- 0 0.0 0.0

FIG. 97

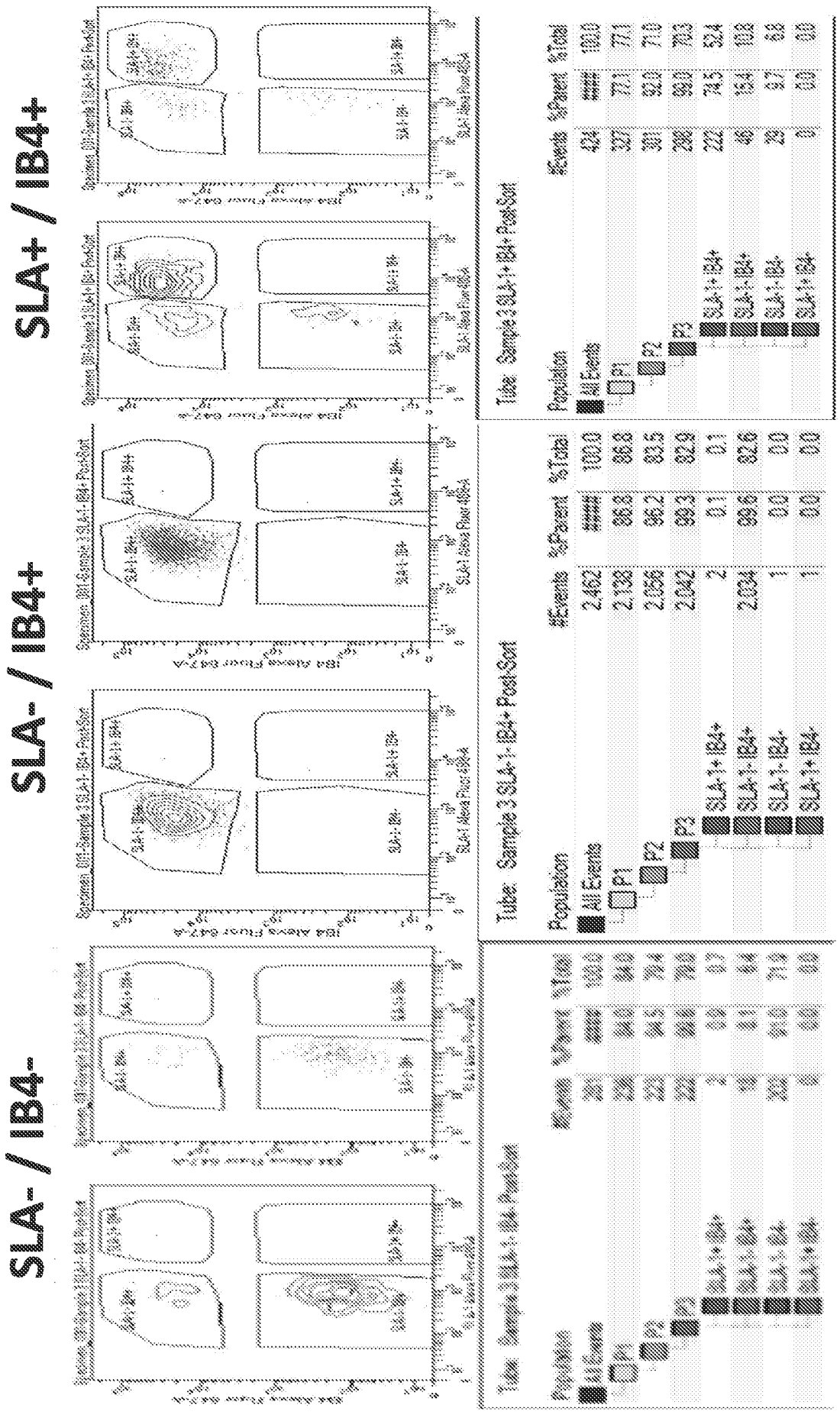

SLA- / IB4-
SLA- / IB4+
SLA+ / IB4+
Tube: Sample 3 SLA-1- IB4- PostSort
Tube: Sample 3 SLA-1- IB4+ PostSort
Tube: Sample 3 SLA-1+ IB4+ PostSort
Population
#Events
%Parent
%Total
All Events
P1
P2
P3
SLA-1+ IB4+
SLA-1- IB4+
SLA-1- IB4-
SLA-1+ IB4-

FIG. 98

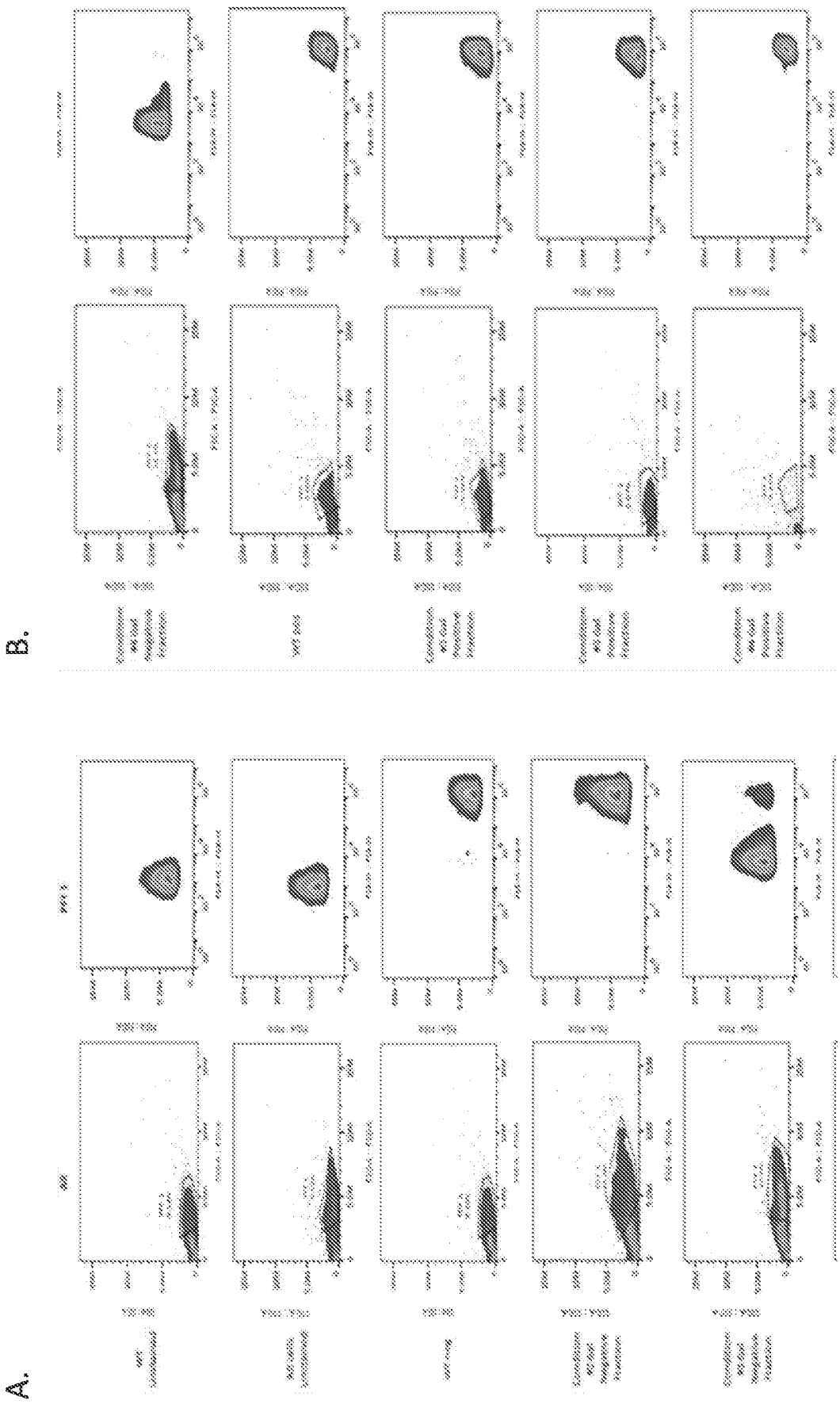


FIG. 99

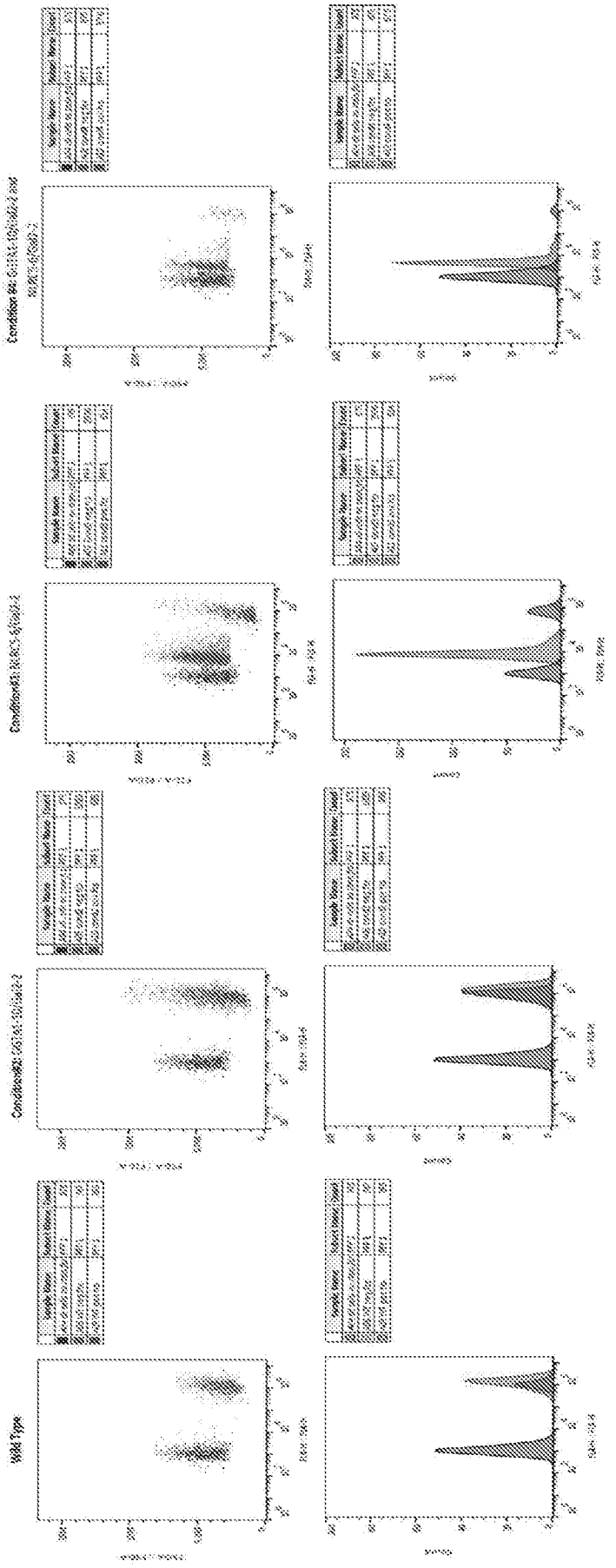


FIG. 100

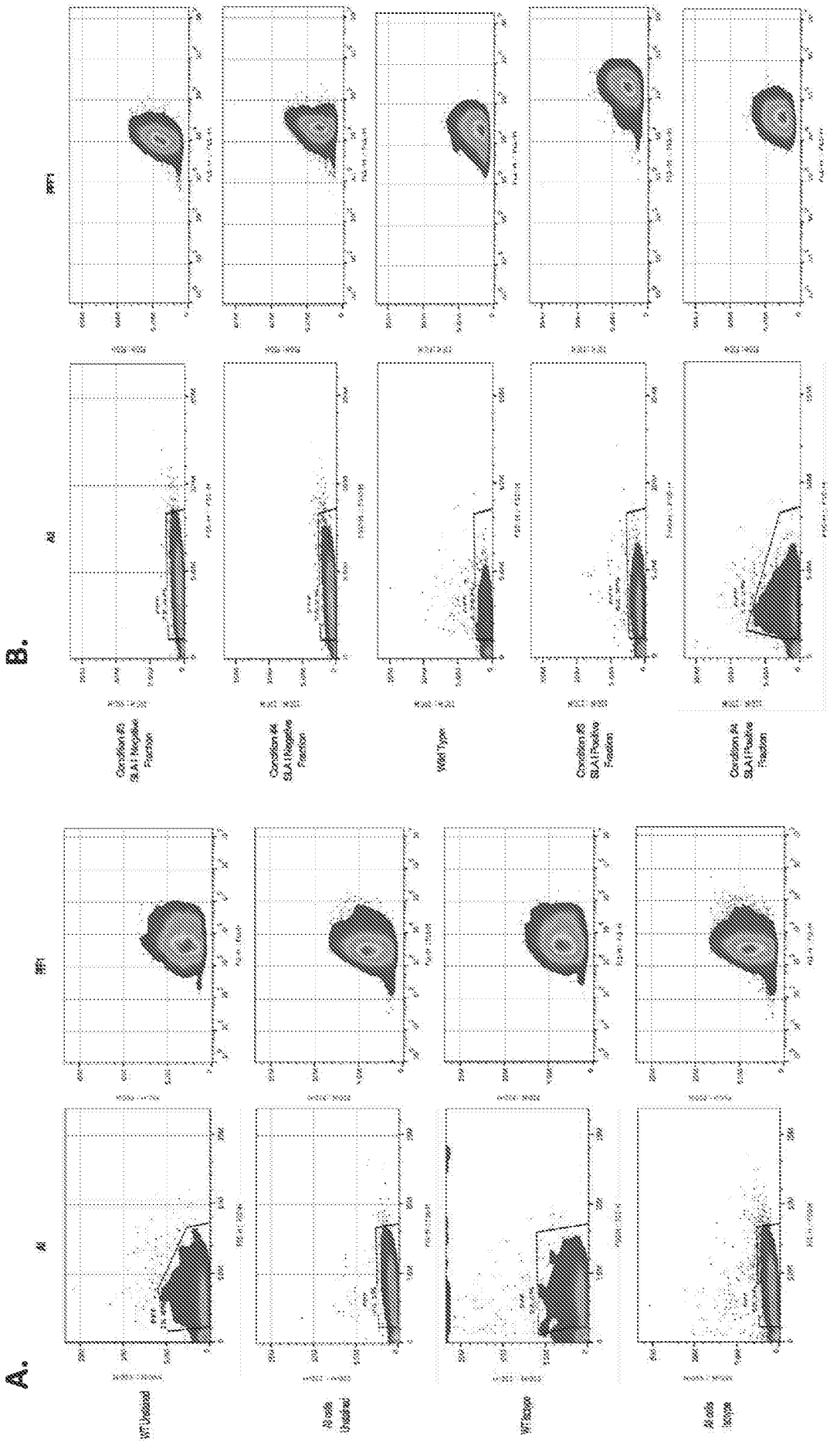

A.
B.
WT Unstained
Ab only Unstained
WT Isotype
Ab only Isotype
Condition #3 SLA1 Negative Fraction
Condition #4 SLA1 Negative Fraction
Wild Type
Condition #5 SLA1 Positive Fraction
Condition #6 SLA1 Positive Fraction

FIG. 101

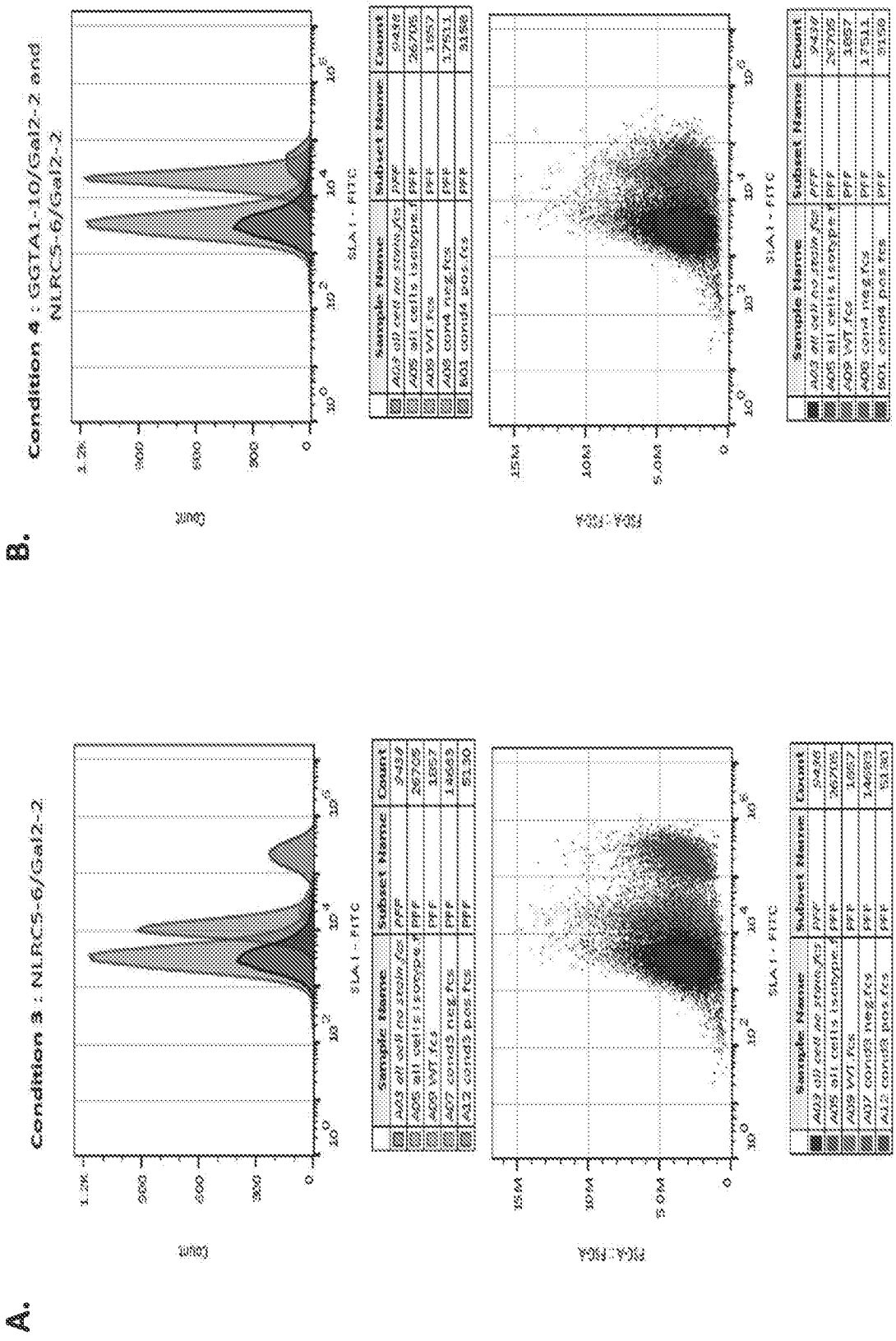

A.
Condition 3 : NLRC5-6/Gal2-2
Count
SLA1 - FITC
FSC-A : FSC-A
Sample Name | Subset Name | Count
A03 all cell no stain.fcs | PPP | 9436
A05 all cells isotype.fcs | PPP | 26706
A09 VVT.fcs | PPP | 3857
A07 cond3 neg.fcs | PPP | 14669
A12 cond3 pos.fcs | PPP | 53.30
B.
Condition 4 : GGTA1-10/Gal2-2 and NLRC5-6/Gal2-2
Count
SLA1 - FITC
FSC-A : FSC-A
Sample Name | Subset Name | Count
A02 all cell no stain.fcs | PPP | 9436
A05 all cells isotype.fcs | PPP | 26706
A09 VVT.fcs | PPP | 3857
A08 cond neg.fcs | PPP | 17511
B03 cond4 pos.fcs | PPP | 31.50

FIG. 102

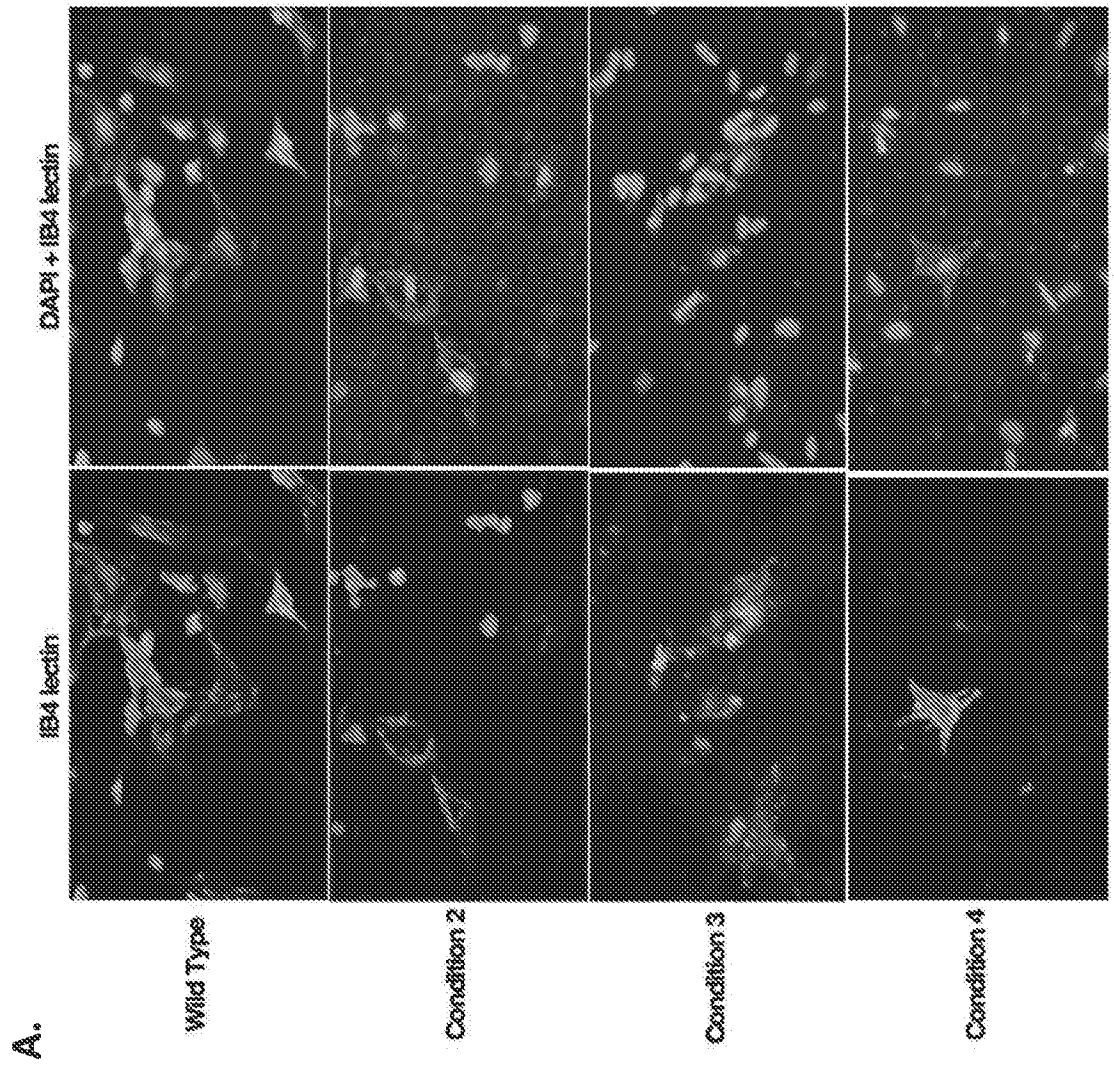

A.
IB4 lectin
DAPI + IB4 lectin
Wild Type
Condition 2
Condition 3
Condition 4
B.

FIG. 103

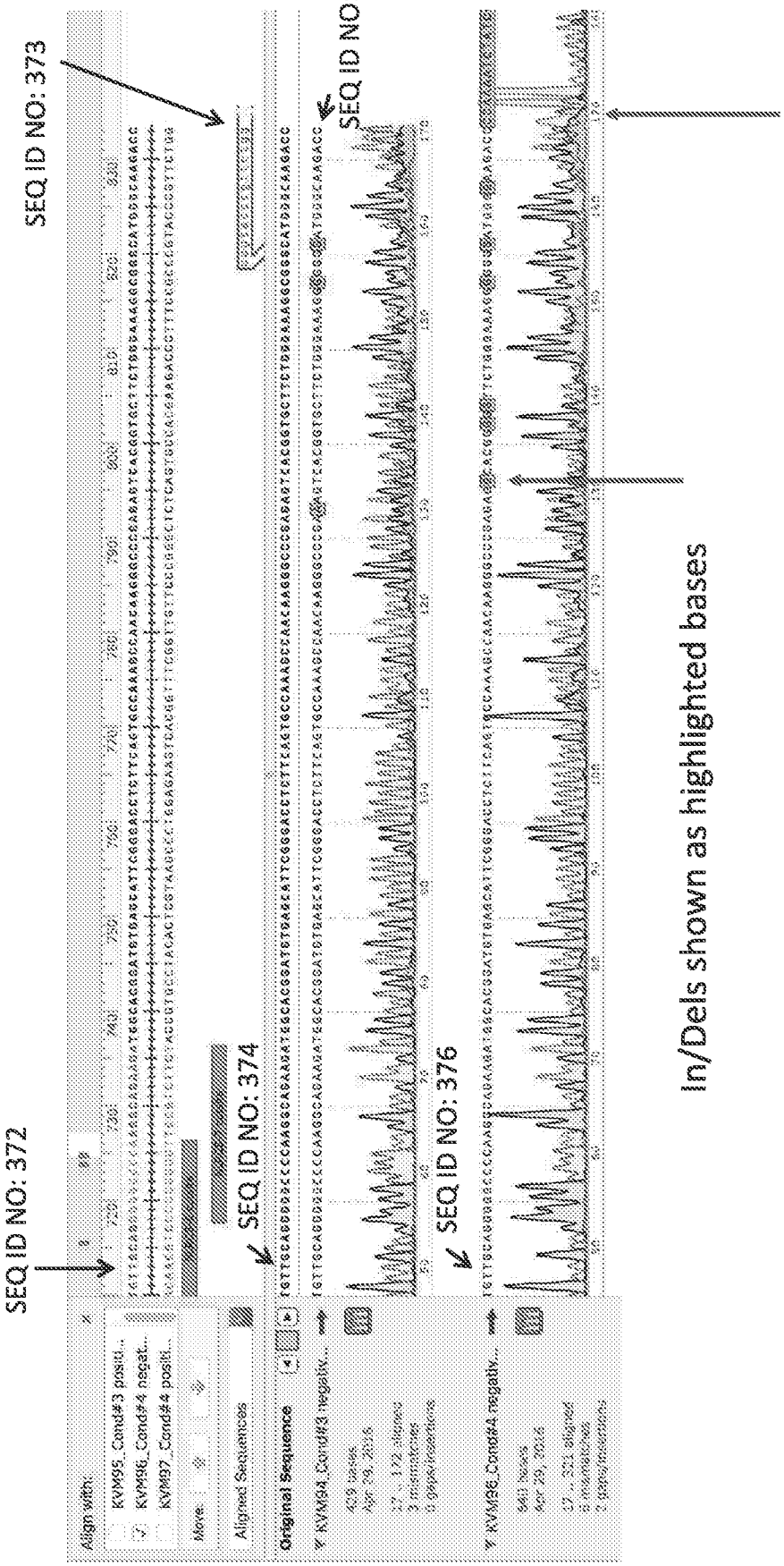

SEQ ID NO: 373
SEQ ID NO: 372
SEQ ID NO: 374
SEQ ID NO: 375
SEQ ID NO: 376
In/Dels shown as highlighted bases
condition 4: 146bp insertion followed by 2453bp deletion.

FIG. 104

Oligo	SEQ ID NOs: 377-404 Sequence	Forward screening primer	SEQ ID NOs: 405-413 Sequence	Reverse screening primer	SEQ ID NOs: 414-422 Sequence
G631_First_Forward	GAGAAAAAAAATGAAATGTTCAA				
G631_First_Reverse	TTTGACATTTCATTTATTTTTTC				
Gal2-1_Forward	ACACCCC

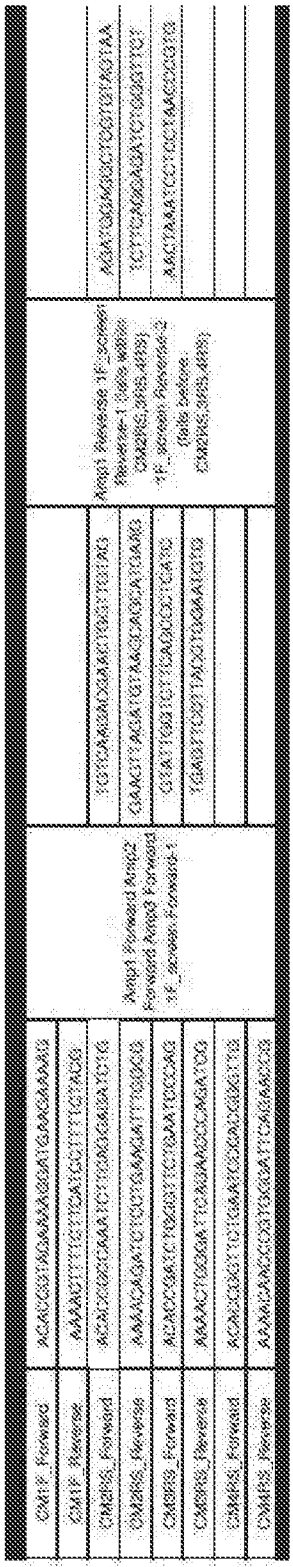

SEQ ID NOs: 423-430
SEQ ID NOs: 431-434
SEQ ID NOs: 435-437
CM1F_Forward
CM1F_Reverse
CM2RS_Forward
CM2RS_Reverse
CM8RS_Forward
CM8RS_Reverse
CM4RS_Forward
CM4RS_Reverse
Amp1 Forward Amp2 Forward Amp3 Forward 1F_screen_Forward-1
Amp1 Reverse 1F_screen Reverse-1 (falls within CM2RS_SNS_4RS) 1F_screen_Reverse-2 (falls before CM2RS_SNS_4RS)

FIG. 106

A.

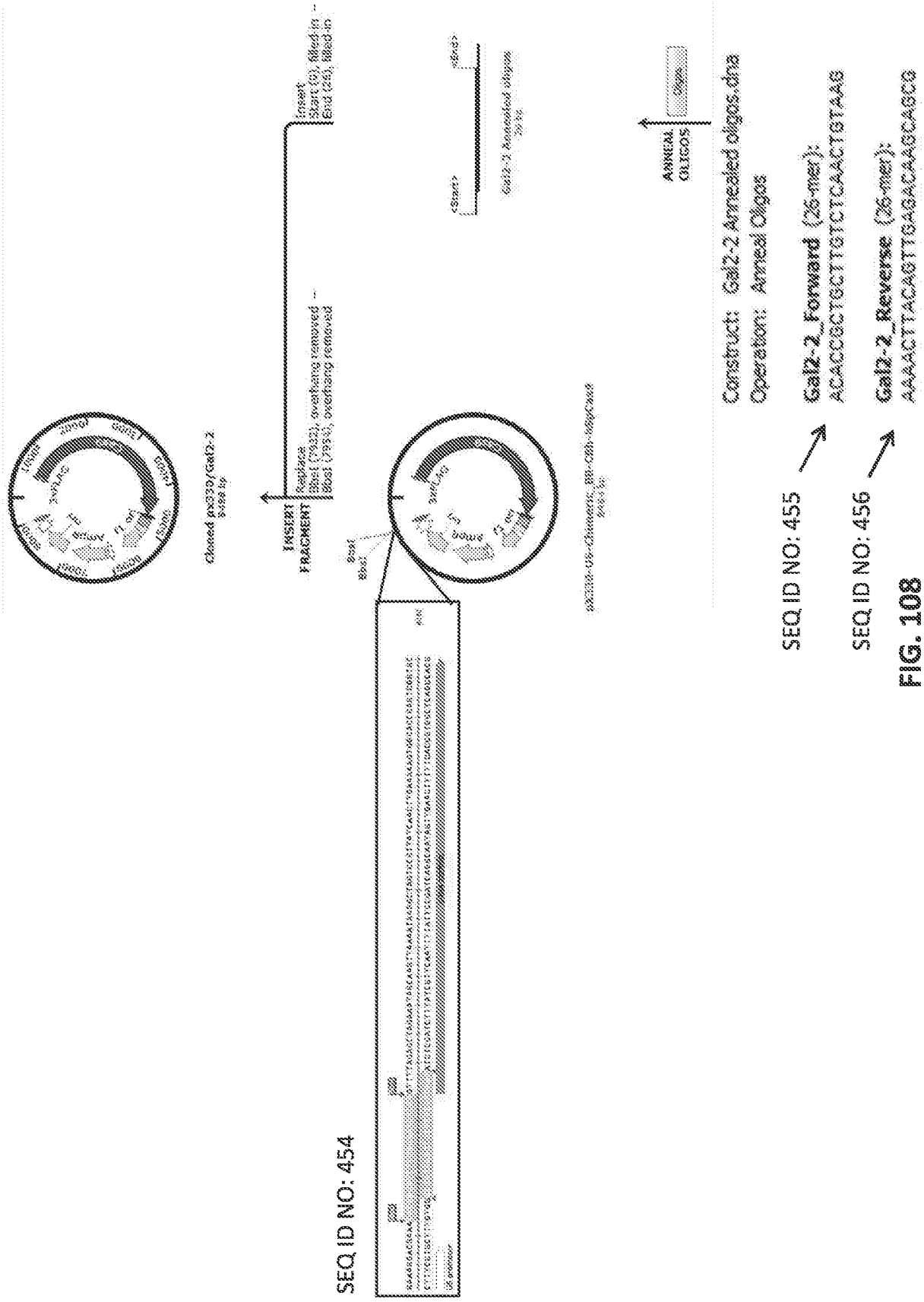
SEQ ID NOs: 438-447

B41_First_Forward	ACACCGGTCGAATGCTCAAGATATTGAG
B41_First_Reverse	AAAACTCAATATCTTGAGCGATCCGACG
B41_Second_Forward	ACACCGGTGCTTTGGATCCTCAGCGTG
B41_Second_Reverse	AAAACACGCTCAGGATCCAAAGCCAACG
C9-9_1	ACACCGGCCGCTCTTTGGGAACGTCCG
C9-9_2	AAAACGGACGTTCCCAAAGGGCGGTG
C9-5_1	ACACCGCCAAGGGGATATTCCGCTTTG
C9-5_2	AAACAAAGCGGAATATCCCCTTGCG
C9-15RS_1	ACACCGACGACAATGGTCTTGCCCGAG
C9-15RS_2	AAAACTCGGGCCAGACGATTGTCGTCG

B.

Deletion Screening Primers	SEQ ID NOs: 448-453 Sequence
Gal amp 1 forward	CAGCAGAAGCTCAACTAGAAACTTG
Gal amp 1 reverse	AACAACAAAGCCTCAGACTAAAC
Gal amp 2 forward	ATAAATAAAATTATTAATAATA
Gal amp 2 reverse	TGGTAACTTGTGAGTGCCATTG
Gal amp 3 forward	AGAGTGGTTCTGTCAATGCTG
Gal amp 3 reverse	GCCTATAGCGTCTTCTTCTTCG

FIG. 107


Construct: Gal2-2 Annealed oligos.dna
Operation: Anneal Oligos
Gal2-2_Forward (26-mer):
ACACCGCTGCTTGTCTCAACTGTAAG
Gal2-2_Reverse (26-mer):
AAAACTTACAGTTGAGACAAGCAGCG
SEQ ID NO: 455
SEQ ID NO: 456
SEQ ID NO: 454
FIG. 108

SEQ ID NO: 457
SEQ ID NO: 458
SEQ ID NO: 459
SEQ ID NO: 460
zas258 sequencing result of constructed plasmid (bottom)
shown against the expected clone (top)
SEQ ID NO: 462
SEQ ID NO: 461

FIG. 109

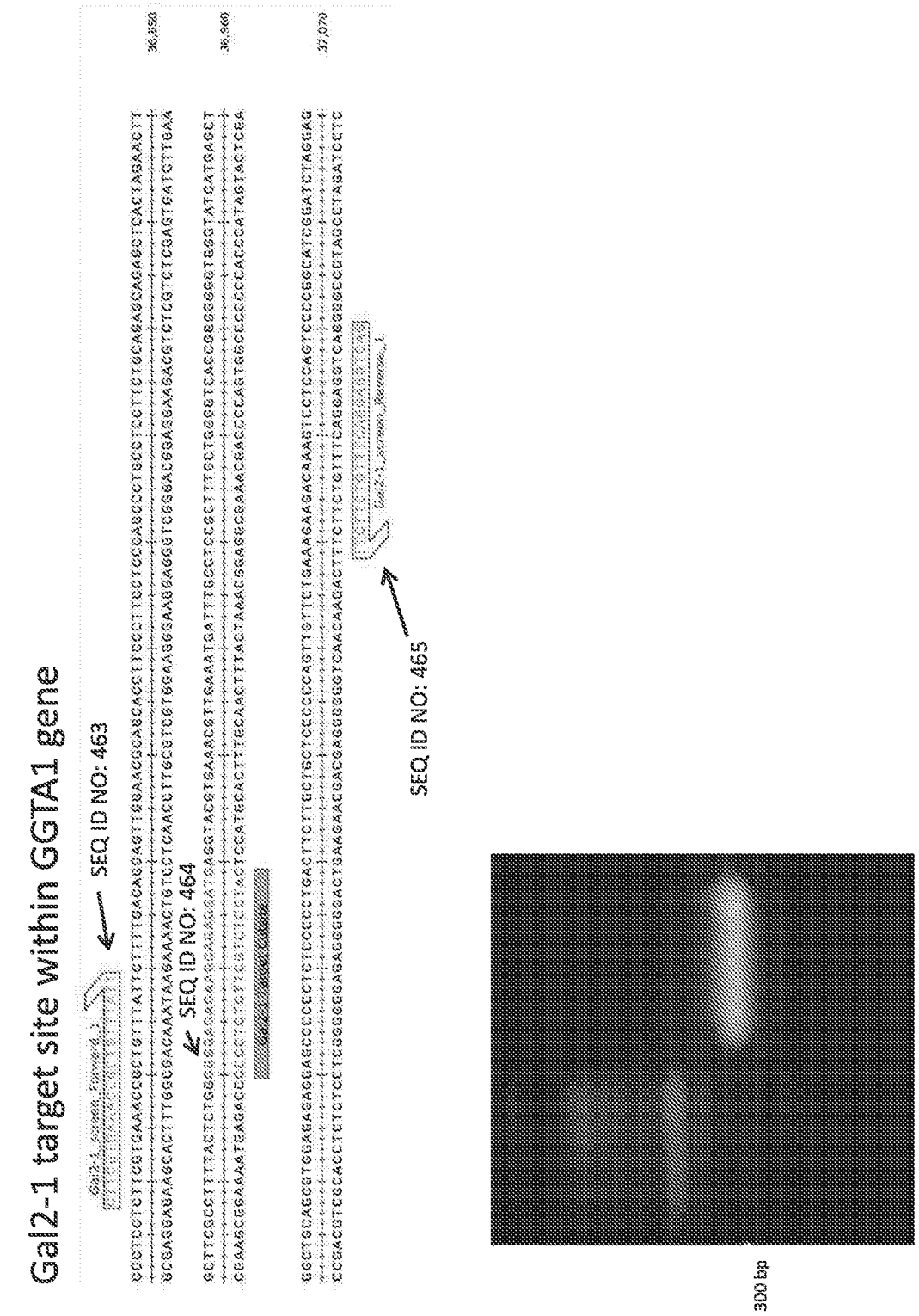

A.
Gal2-1 target site within GGTA1 gene
SEQ ID NO: 463
SEQ ID NO: 464
SEQ ID NO: 465
B.
300 bp

FIG. 110

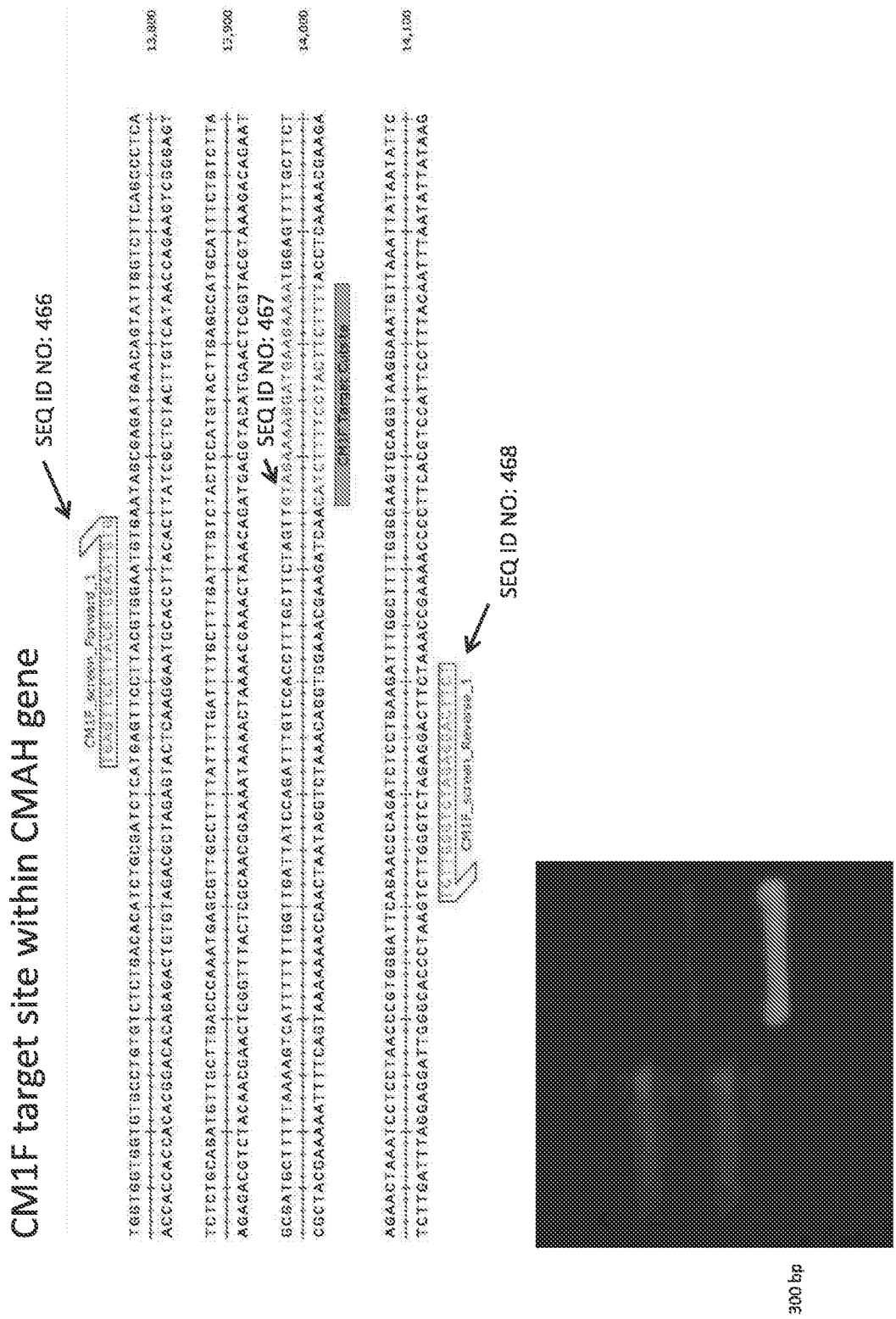

A.
CM1F target site within CMAH gene
SEQ ID NO: 466
SEQ ID NO: 467
SEQ ID NO: 468
B.
300 bp

FIG. 111

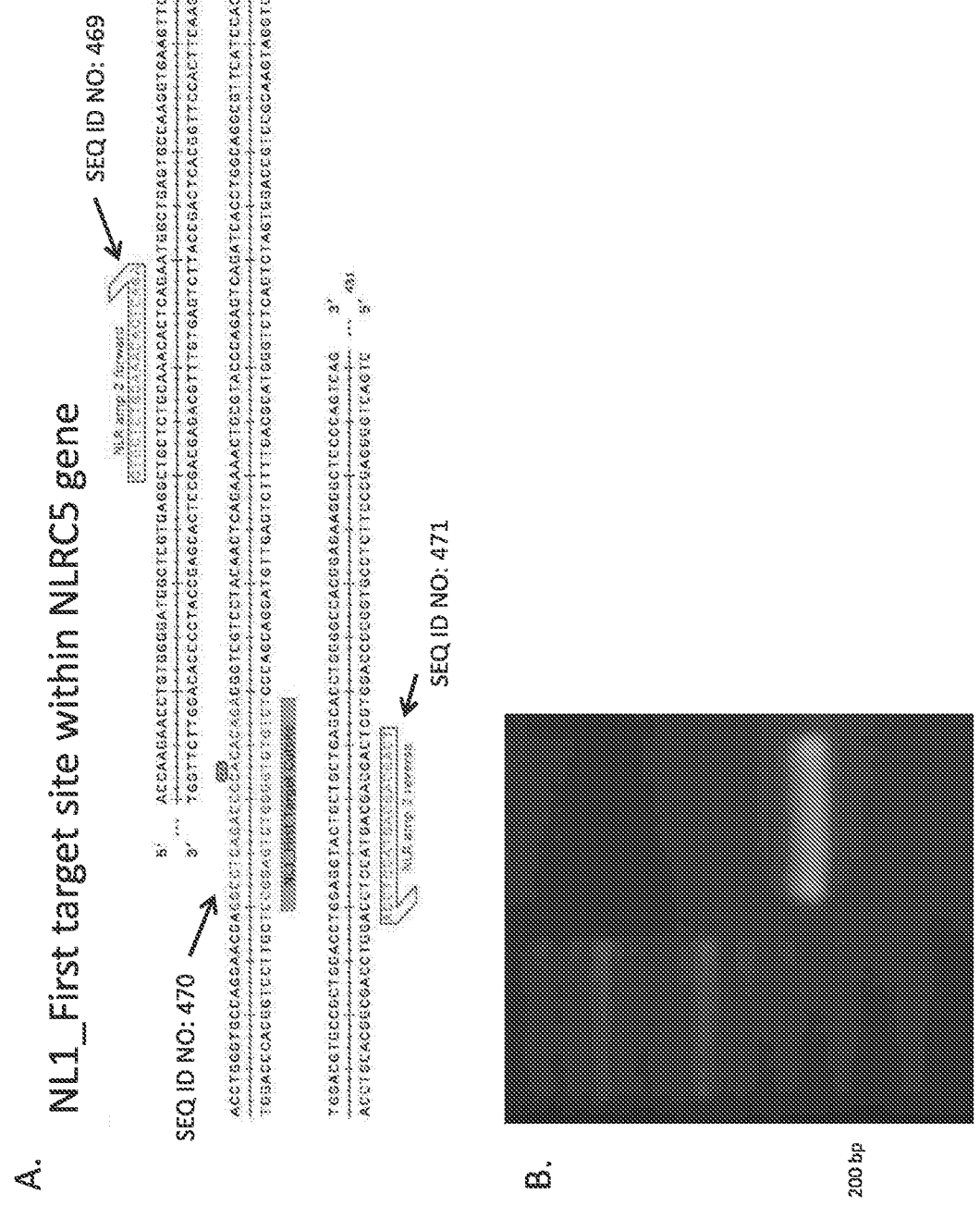

A.
NL1_First target site within NLRC5 gene
SEQ ID NO: 469
SEQ ID NO: 470
SEQ ID NO: 471
B.
200 bp

FIG. 112

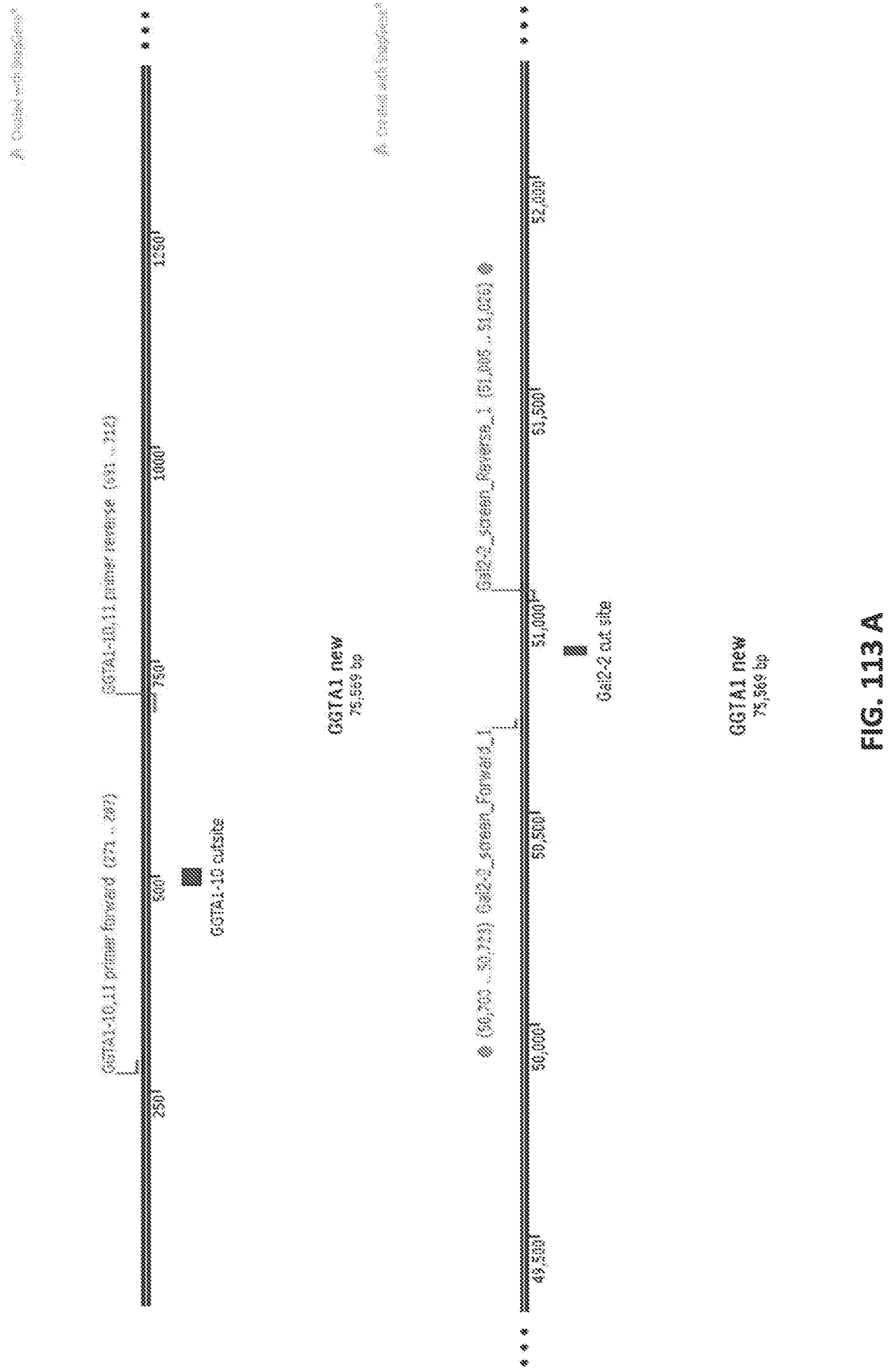

GGTA1-10,11 primer forward (271 .. 291)
GGTA1-10,11 primer reverse (991 .. 1011)
GGTA1-10 cutsite
GGTA1 new
75,569 bp
Gal2-2_screen_forward_1
(50,703 .. 50,723) Gal2-2_screen_forward_1
Gal2-2_screen_Reverse_1 (51,005 .. 51,025)
Gal2-2 cut site
GGTA1 new
75,569 bp

FIG. 113A

Expected Product Size: 324bp

1.2% gel with SYBR safe

1. Hi-Low molecular ladder (BN2050) Bionexus
2. PicoPure Wild Type
3. PicoPure Condition 3 Gal Negative
4. PicoPure Condition 3 Gal Positive
5. PicoPure Condition 4 Gal Negative
6. PicoPure Condition 4 Gal Positive
7. Qiagen Wild Type
8. Qiagen Condition 3 Gal Negative
9. Qiagen Condition 3 Gal Positive
10. Qiagen Condition 4 Gal Negative
11. Qiagen Condition 4 Gal Positive
12. No template control (water)

FIG. 113 B

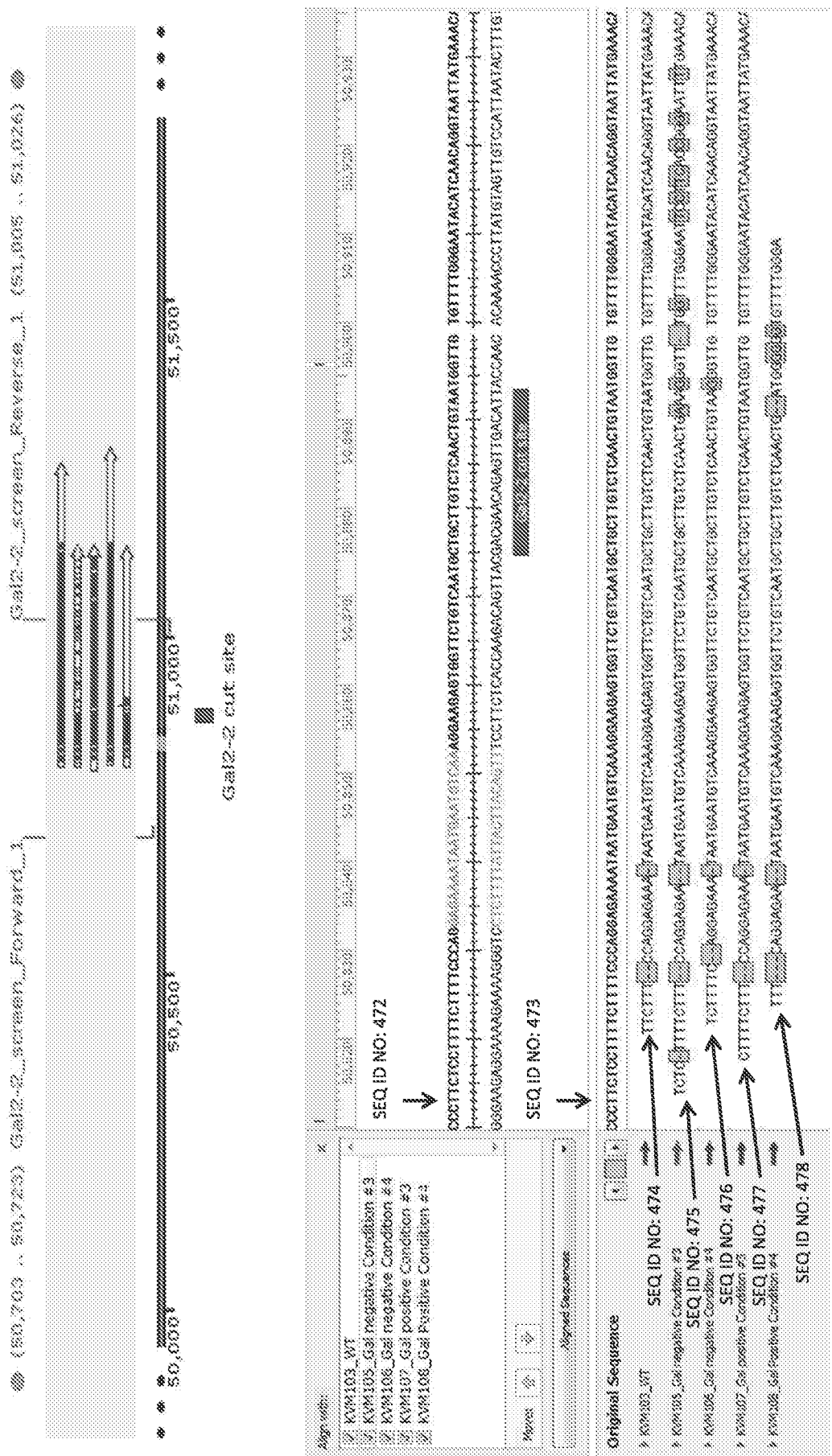

(80,703 .. 80,723) Gal2-2_screen_Forward_1
(Gal2-2_screen_Reverse_1 (81,005 .. 81,026)
80,000
80,500
81,000
81,500
Gal2-2 cut site
Align with:
KVM103_WT
KVM105_Gal negative Condition #3
KVM106_Gal negative Condition #4
KVM107_Gal positive Condition #3
KVM108_Gal Positive Condition #4
Name
Aligned Sequence
SEQ ID NO: 472
SEQ ID NO: 473
Original Sequence
KVM103_WT
KVM105_Gal negative Condition #3
KVM106_Gal negative Condition #4
KVM107_Gal positive Condition #3
KVM108_Gal Positive Condition #4
SEQ ID NO: 474
SEQ ID NO: 475
SEQ ID NO: 476
SEQ ID NO: 477
SEQ ID NO: 478

FIG. 113 C

Expected Product Size: 442bp
1.2% gel with SYBR safe
1. Hi-Low molecular ladder (BN2050) Bionexus
2. PicoPure Wild Type
3. PicoPure Condition 3 Gal Negative
4. PicoPure Condition 3 Gal Positive
5. PicoPure Condition 4 Gal Negative
6. PicoPure Condition 4 Gal Positive
7. Qiagen Wild Type
8. Qiagen Condition 3 Gal Negative
9. Qiagen Condition 3 Gal Positive
10. Qiagen Condition 4 Gal Negative
11. Qiagen Condition 4 Gal Positive
12. No template control (water)

FIG. 113 D

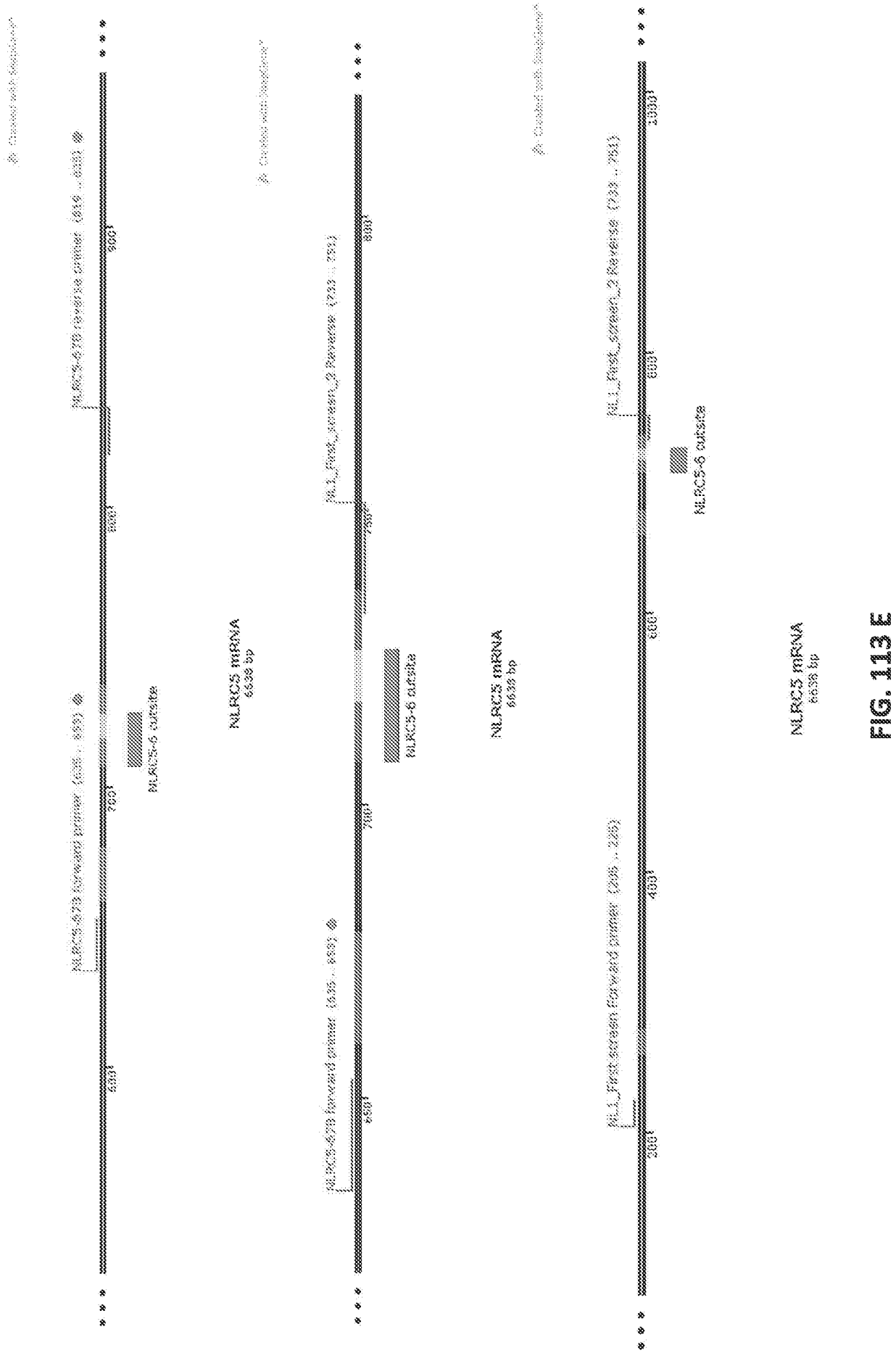

NLRC5 mRNA
6638 bp
NLRC5-6 outside
NLRC5 mRNA
6638 bp
NLRC5-6 outside
NLRC5 mRNA
6638 bp
NLRC5-6 outside

FIG. 113E

Expected Product Size: 201bp
2% gel with SYBR safe
1. Hi-Low molecular ladder (BN2050) Bionexus
2. PicoPure Wild Type
3. PicoPure Condition 3 Gal Negative
4. PicoPure Condition 3 Gal Positive
5. PicoPure Condition 4 Gal Negative
6. PicoPure Condition 4 Gal Positive
7. Qiagen Wild Type
8. Qiagen Condition 3 Gal Negative
9. Qiagen Condition 3 Gal Positive
10. Qiagen Condition 4 Gal Negative
11. Qiagen Condition 4 Gal Positive
12. No template control (water)

FIG. 113 F

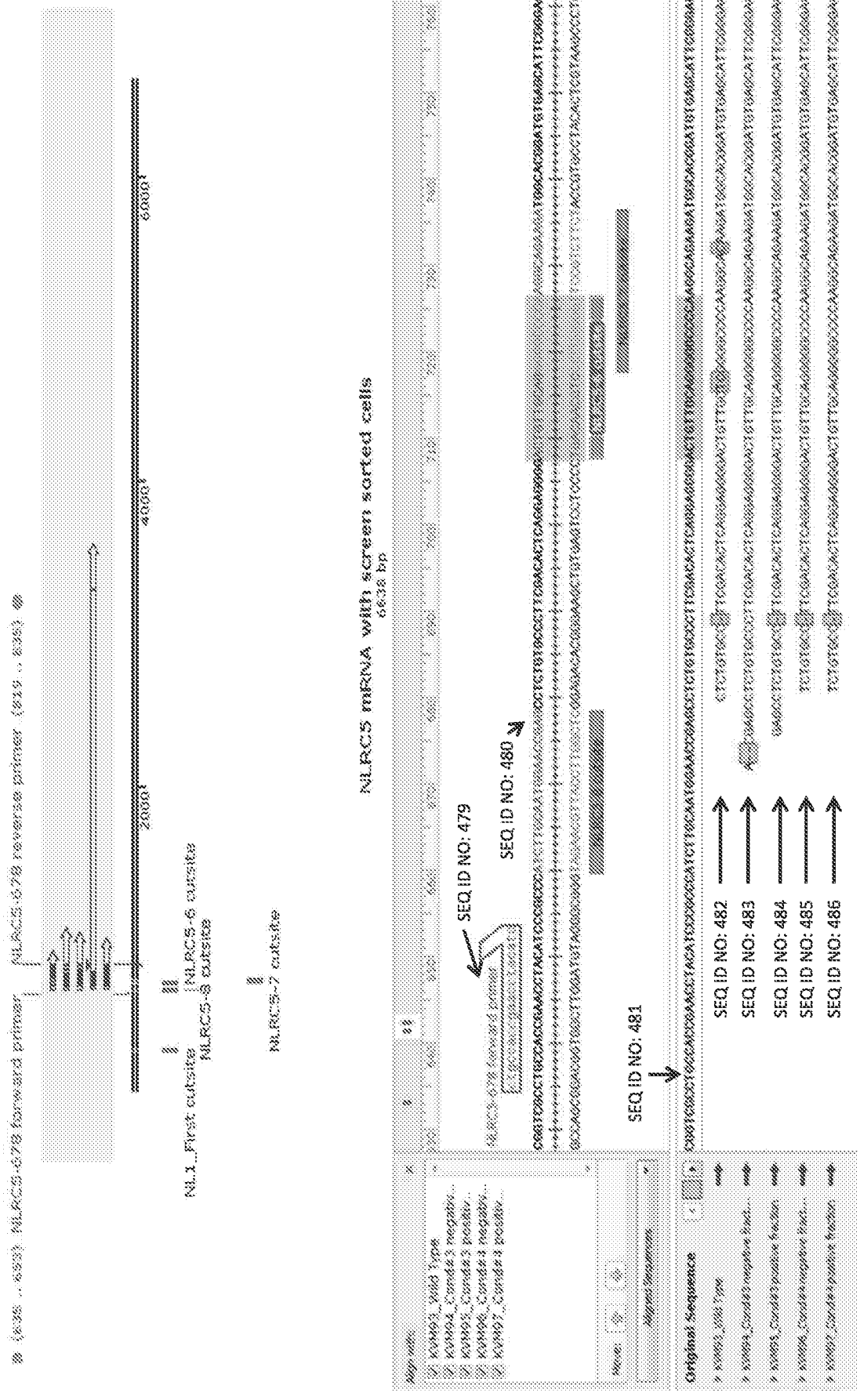

NLRC5 mRNA with screen sorted cells
6638 bp
SEQ ID NO: 479
SEQ ID NO: 480
SEQ ID NO: 481
SEQ ID NO: 482
SEQ ID NO: 483
SEQ ID NO: 484
SEQ ID NO: 485
SEQ ID NO: 486
NLRC5-678 forward primer
NLRC5-678 reverse primer
NLRC5-6 cutsite
NLRC5-8 cutsite
NLRC5-7 cutsite
NLR_First cutsite

FIG. 113 G

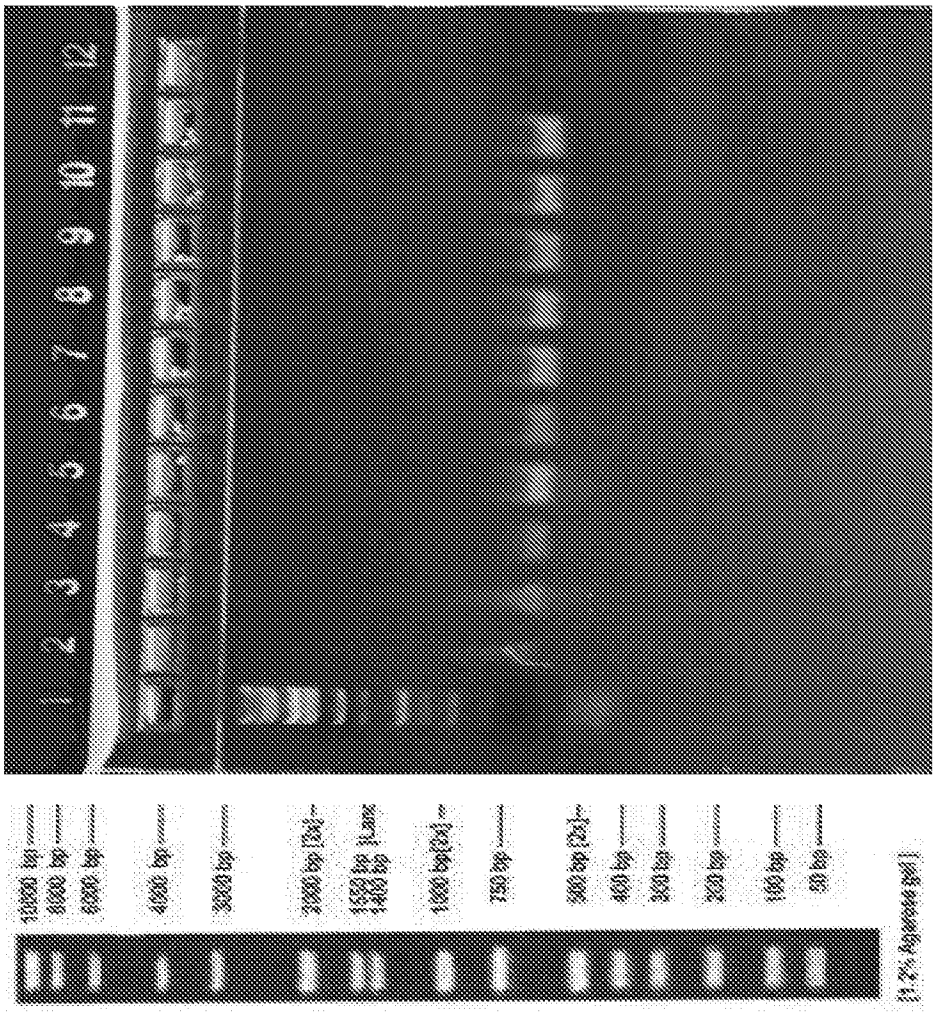

Expected Product Size: 117bp
2% gel with SYBR safe
1. Hi-Low molecular ladder (BN2050) Bionexus
2. PicoPure Wild Type
3. PicoPure Condition 3 Gal Negative
4. PicoPure Condition 3 Gal Positive
5. PicoPure Condition 4 Gal Negative
6. PicoPure Condition 4 Gal Positive
7. Qiagen Wild Type
8. Qiagen Condition 3 Gal Negative
9. Qiagen Condition 3 Gal Positive
10. Qiagen Condition 4 Gal Negative
11. Qiagen Condition 4 Gal Positive
12. No template control (water)
1 2 3 4 5 6 7 8 9 10 11 12
10000 bp
6000 bp
4000 bp
3000 bp
2500 bp (2x)
1650 bp
1400 bp
1000 bp (2x)
750 bp
500 bp (2x)
400 bp
300 bp
200 bp
100 bp
50 bp
(1.2% Agarose gel)

FIG. 113 H

Expected Product Size: 547bp
1.2% gel with SYBR safe
1. Hi-Low molecular ladder (BN2050) Bionexus
2. PicoPure Wild Type
3. PicoPure Condition 3 Gal Negative
4. PicoPure Condition 3 Gal Positive
5. PicoPure Condition 4 Gal Negative
6. PicoPure Condition 4 Gal Positive
7. Qiagen Wild Type
8. Qiagen Condition 3 Gal Negative
9. Qiagen Condition 3 Gal Positive
10. Qiagen Condition 4 Gal Negative
11. Qiagen Condition 4 Gal Positive
12. No template control (water)

FIG. 113 I

FIG. 114 B

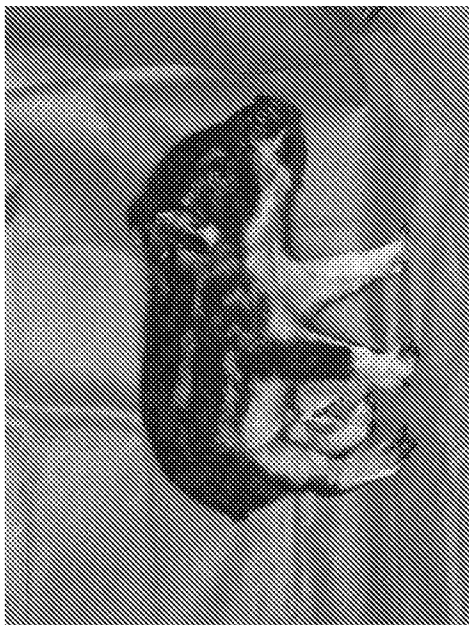


FIG. 114 A

FIG. 114 C

NextGen Sequencing to confirm piglet genotype

CAAGTAAAAGGTAAACGTGGAGTAGGCAGTTCCCAGGCTAGGGGTTGAATAGGCGTGGGGGGAGGGGAAGAGTCCTGACCCAGGGAAGACATTA
AAAAGGTAGTGGGGTCGACTAGATGAAGGAGAGCCTTTCTCTCTGGGCAAGAGCGGTGCAATGGTGTGTAAAGGTAGCTGAGAAGACGAAAAGG
GCAAGCATCTTCCTGCTACCAGGCTGGGAGAGGCCCAGGCCCACGACCCCGAGGAGAGGGAACGCAGGGAGACTGAGGTGACCCTTCTTTCCCCC
GGGGCCCGGTCGTGTGGTTCGGTGTCTCTTTTCTGTTGGACCCTTACCTTGACCCAGGCGCTGCCGGGGCCTGGGACCCAGGGCCAGCTCGCCG
CCAATCAGCAGTGTGGTACTTTGTCTTGAGGAGATGTCCTGGACTCACACGGAAACTTAGGGCTACGGAATGAAGTTCTCACTCCCATTAGGTG
ACAGGTTTTTTAGAGAAGCCAATCAGCGTCGCCGCGGTCCTGGTTCTAAAGTCCTCGCTCACCCACCCGGACTCATTCTCCCCAGACGCCAAGGA
TGGTGGTCATGGCGCCCCGAACCCTCTTCCTGCTCTCTCGGGGGCCCTGACCCTGAGCCGACACGTGGACGACGTTCGTGCGGTTCGACAGCGAC
CAGCGCCGCCGTGTCCCGGCCCGCGCCGCTTCATCGCCATGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGCGAC
TCGGCGTGTCCGAGGATGGAGCCCGCGGCGCCGTGGTGGAGCAGGAGGGCCGGAGTATTGGGAAGAGGAGACACGGAACACCAAGGCCCACG
CACAGACTGACAGAATGAACCTGCAGACCCTGCGCGGCTACTACAACCAGAGCGAGGCCAGTTCTCACACCCTCCAGTGGATGATTGGCTGCGA
CCTGGGGGTCCGACGGACGCCTCCTCCGCGGGTATGAACAGTATGCCTACGATGGCAAGGATTACCTCGCCCTGAACGAGGACCTGCGCTCCTGG
ACCGCAGCGGACACTGCGGCTCAGATCTCCAAGCGCAAGTGTGAGGCGGCCCAATGTGGCTGAACAAAGGAGAGCCTACCTGGAGGGCACGTGCG
TGGAGTGGCTCCACACAGATACCTGGAGAAGGAGATGCTGCAGCGCGCGGACCCCCCCAAGACACACGTGACCCACCACCCTGTCTTTGA
CTATGAGGCCACCCCTGAGGTGCTGGGCCCTTCTACCCTCGCGGAGATCATACTGACCTGGCAGCGGGATGGGGAGGACCCAGACCCAGGAC
GTGGAGCTCGTGGAGACCAGGCCTGCAGGGATGGAACCTTCCAGAAGTGGGCAGCTGTGGTGGTGCCTTCTGGAGAGGAGCAGATACACGT
GCCATGTGCAGCATGAGGGGCTGCCGGAGCCCCTCATGCTGAGATGGAAGCAGTCTTCCCTGCCCACCATCCCCATCATGGGTATCGTTGCTGG
CCTGGTTGTCCTTGCAGCTGTAGTCACTGGAGCTGCGGTCGCTGCTGTGCTGTGGAGAAAGAAGAGCTCAGATTGAAAGGAGGGAGGCTACTCT
CAGGCTGCAGAGACCAGCCCACCCTGTGCCACCATGACCCCTCTTCCTCATGCTGAACTGCATTCCTTCCCCAATCACCTTTCCTGTTCCAGAAA
AGGGGCTGGGATGTCTCCCGTCTCTCTGTCTCAAATTTGTGGTCACTTGAGCTATAACTTACTTCTGTATTTAAAATTGAATCTGAGTATAAATTTAC
TTTTTCAAATTATTTCCAAGAGAGATTGATGGGTTAATTAAGGAGAAGATTTCCTGAAAATTTGAGAAGACAAAATAAATGGAAGACATGAGAACT
TTCACCCTGCAGTTGGAAAGGGAACTATTTCGGCTTTGGGGCTCCTCCTCAGAGAGCCTCCGGCTAGGTAGGGGAGCGGGACTCTGGTTTGG
GGGAGGGCCGGCGGTTTGGCGGGGGATGGGTGCTTGAGGTGGTCTGACCGGTAGCGGGGGTCGCCTTCCCTAGCGGGAAGTCGGGAGCATATCG
TTTGTTACGCCTGGAAGGGGAAGAGGTGGTGAGAGGCAGGGCGGGACCCGCCCTGCGGCAACCGGAGGGGGAGGGAAGGGAGCGGAAA
AGCCTGGAATACGGGACGGAGCCATTGCTCCCGCAGAGGGAGGGAGCGCTTCCTTCTTCTTGTCACTGATTGGCCGCTTCTCCTCCC
GCCGTGTGTGAAAACACAAATGGCGTGTTTTGGTTCAGTTACAGCCTCGGGAGTGCGCAGCCTCCCAGGAACTCTCGC
ATTGCCCCCTGGGTGGGTAGGTGGGTGGAGAGAGCTGCACAGGGCGGGCGCTGTCGGCCTCCTGCGGGGGAGGGGTCAGTGAAAG
TGGCTCCCGCGCGGGCGTCCTGCCACCCTCCCCTCGGGGGAGTCGGTTTACCCGCCGCCTGCTCGGCTTTGGTATCTGATTGGCTGCTGAAGT
CCTGGGAACGGCCCCCTTGTTATTGGCTTGGGTCCCAAATGAG (SEQ ID NO:499)

FIG. 15

Sequence confirmation of correct construction of the homology directed recombination construct for inserting HA-G1 at Rosa26

aatgtctttggtgtgggaargaagccagccatctgagatagaggaaaacgagaggaaaaggcgtccaggaagatcttabggagggggagatcgvggcccccacgagcgacc
agattgtctgtcacaaggccgcgagaacggggtgggggtcgggggtcgtgctgtgtatttttgagmggagggcrgcgagaggcctvtcctcaadk
aaaagyaaacgtggagtaggcagttccaggaaaaggggtgaggggaagcgtcgcctgaccaggaaagacatgaaaaggtagtgggtcgactagat
taagaggggggcctctcctgggaaaagaggggtgttgcaaggbggcgaggaggggcagcatcctcctgctaagagcctgggaggcccag
gcccacgacccmgaggagcgagcgaggagtgaccctcccccgggccggtcgtgaggttcgtcctcgggcccctgaccttacctgtccca
ggcgctgccgggcctgggcgcacgcgcactccgggagcaacgaggaccaacgcggcgccaccgggttttcctgggccggaatggccgtacc
cgtgaggtgggggtgggggcagaaaaggcgggagcagcaggaaggaggggggccggcactactgtgttggccggactgggggactgggcgggac
tgggcctccgtgagtctctgagcgcagcgggcggcgccctcccccgcagcgccggccaggggcaccgggcagccccctccgcgccgcgcca
ttggcctctccgccacccgccccgccaccatcgccgcaatcagcgggggccgcctagagaagaggcctgtagtggtactttgtcttgaggagat
gtcctggactcacacggaaacttaggggctacgaatgaagtctctcactcccattaggtgacaggttttagagaagccaatcagcgtcgccgccgtttctaaagtcctc
gctcacccacccggactcatttcccagagcgcaaggatggtggtcatgggcgcccgaacctctcctgctgctcgggggcctgagcctgggagacctgggcggct
ccccactccatgaggtatttcaggcccgcgtgtcccgggcccgcgggggaagtgcgtcgctacgccatgggcttcgcggttcgacagcgact
cggcgtgtcccgaggatgggagccgcgggcccgtgggtgggagcagggggcccgggatattgggaagaggagacacggaacaccaaggccacgcacagactgacagaatgaacc
tgcagacctgcgcggctactacaacgagccgaggccagtctccacacccctccagtggatgattgggctgcgacctcctccgcgggtatgaacagt
atgcctacgatggcaaggattacctcgccctgaacgaggacctgcgctcctgggaccgcaagtgtgagggcggccaatgtggcctg
aacaaaggagagcgcctaccttgagtggcacgtgcgtgagtggcctccacagatacctgcgaccgcgcgaccccccaagacacacgtgacccacc
acctgtcttttgactatgagggccacccttgagggtctgtgggccctgggcttctacccttgcagcgcgcgggagtcatactactgaccttgggagc
tcgtgggagaccaggcctgcagggggatgggaacctccagaagtgggcagtgtggtgtgccttctggagaggagcagagatacacgtcgcagcatgagggggctgcggg
agccctcatgctgagatgggaagcagtcttccctgcccaccatcccccatcgttgcctggtgtgccaccatgaccctcctccatgctgaactgcattcctt
tgctgtggagaaagaagagctcagattgaaaaggagggagctactctcaggctgcagaggaccagcccacccctcctccatgctgaactgcattcctt
cccaatcacctttcctgttccagaaaaggggcctggatgtcctcgtctctgtctcactgagctataacttactttgtattaaaattagaatctgagtata
aatttactttttcaaattatttccaagagagattgatgggttaattaaaggagaagatttcctgaaatttgagagacaaaataaatggaagacatgagaacatttgcttttgggct
ccggctcctcagagagcctcgggctagggagggagcgggactcttggtgggagggagtgggtgcgtcctgcgaacccggagggggagg
gtygcctttccyagtgggacagtcgggaacatawygtttgttacgctggaaggggaagrgggcgggagtgcgggccccgcctgcgggcaaccggagggggagg
gagaagggagcggaaacbctcgaawccggagcgccattgctcbcgcgagggggcgcagcggagcgcttccggctvdcctctcttgtcgctgattggccgcttctcctcc
cgccgtccccgcgtgtgtgaaaacacaaatggcgtgtttttggttgtagtacagcctcgggagstgcgcagcctcccagggaactctcgccctg
ggtgggtaggtagggtgggggtggagagagctgcacagggcgggcgctgtgggcctcctgcgggggaggggaggggtcagtgaaagtgggctcccgggcgggcgtcctgccaccctcc
cctccgggggagtcggttaccgcgcctgctgcttgtgattctggctgtaagtcctgggaaccggccccttgttattgggcttgggtcccaaatgagcgaaaccac
tacgcgatccggcagggagagcgggtcttttgtacgggcctcccccgagccagcgccgcagtgtctggccctgccctgccctgcgcaggagagcgcgcgcagcgggg
gcgggctgccgggccgaggcttctgtgggtgactgcgggctccgccctgggcgctcctgaaggacgagactagctctctccaaaaaccccgcgcgag (SEQ ID NO:500).

FIG. 116

Sequence of left arm for construction of a homology directed recombination construct for inserting HLA-G1 at Rosa26

AATGTCTTTGGTGTGGGAAAGGAAGCAGCCATCTGAGATAGGAACCCTGAAAACGAGAGGAAAGGCGTCCAGGAAGATTC
TTGGGGAGGGGAGATCGAGGCCCCCACGAGCGACCAGATTGTCTGTCACAAGGCCGCGAGAACGGGGGTGGGGGGTGGGG
GTTCGGGGAGAGAAAAAAAAGTGTGCTGTGTATTTTGAGGGGAGGGCGGCGAGAGGCCTATCCTCAAGTAAAAGGTAAAC
GTGGAGTAGGCAGTTCCCAGGAAAAGGGGTGAAGAGGCGTGGGGGGAGGGGAAGCGTCCCTGACCCAGGAAAGACATGAA
AAGGGTAGTGGGGTCGACTAGATTAAGAGGGGGGCCTCTCTCCCTGGGAAAGAGGGGTGTTGCAATGGTGTGTCAAGGGG
GCGAGGGGGGGATGAGAAGGGGCAGCATCCTCCTGCTAAGAGCCTGGGGAGGGCCAGGCCCACGACCCCGAGGAGAGCGAG
CGCGGGAGACGGAGGAGGTGACCCTTCCCTCCCCCGGGGCCGGTCGTGAGGTTCGGTCTCTCTTTTCTGTCGGACCCTTA
CCTTGTCCCAGGCGCTGCCGGGCCTGGGCCCGGGCTGCGGCGCACGGCACTCCCGGGAGGCAGCAGGACTCGACTTAGGC
CCAACGCGGCGCCACGGCGTTTCCTGGCCGGAATGGCCCGTACCCGTGAGGTGGGGGTGGGGGGCAGAAAAGGCGGAGCG
AGCAAAGGCGGGGAGGGGGGGCAGGGCCAGGGAAGGAGGGGGGGGGCCGGCACTACTGTGTTGGCGGACTGGCGGGACTG
GGGCTGCGTGAGTCTCTGAGCGCAGGCGGGCGGCGGCCGCCCCTCCCCCGCAGCGGCGGCGGCCAGCGCCGGCGCCAGGG
GCACCCGGGACACGCCCCCTCCCGCCGCGCCATTGGCCTCTCCGCCCACCGCCCCGCACCCATTGGCCAGCTCGCCGCCA
ATCAGC (SEQ ID NO:501).

FIG. 117

Sequence of HLA-G1 for construction of a homology directed recombination construct for inserting HLA-G1 at Rosa26

AGTGTGGTACTTTGTCTTGAGGAGATGTCCTGGACTCACACGGAAACTTAgggctacggaatgaagttctcactcccatt
aggtgacaggttttagagaagccaatcagcgtcgccgcgggttcctggttctaaagtccctcgctcaccccacccggactcat
tctccccagacgccaaggatgggtcatggcgccccgaacccttcctcctgctgcttcgggggcccctgaccctgaccga
gacctgggcgggctcccactccatgaggtatttcagcgccgccgtgTCCAGACCTGGGAGAGGAGGAGccccgcttcatcg
ccatgggctacggtggacgacacgcagttccgtgcggttcgagactcgggcgtgtcccgagggatgggagccgcgggcgccg
tgggtgggagcaggagggggccggagtattgggaagagaggagacacgaaggcccacgcacagactgacagaatgaa
cctgcagaccctgcgccggctactacaaccagagccagttctcacacaccctccagtggatgattggctgcgacctgg
ggtcccgacggacgccctccctccgcgggtatgaacagtatgccctacgatggcaaggattacctcgccctgaacgaggaccctg
cgctcctggaccgcagcggacactgcggctcagatctccaagcgcaagtgtgagggcggccaatgtggctgaacaaaggag
agcctaccctggagggcacgtgcgtggagtggctccacagatacctggagaacgggaaggagatgctgcagcggcgcggacc
ccccaagacacacgtgaccaccaccctgtctttgactatgaggccacccctgaggtggctgggccctgggctttctaccct
gcggagatcatactgacctggcagcgggatgggggaggaccagacccaggacgtgggagctcgtgggagaccaggcctgcagg
ggatggaacctttccagaagtgggcagctgtggtggtgccttctggagaggagcagagatacacgtggccatgtgcagcatg
agggctgccggagccccctcatgctgagatgggaagcagtcttccctgcccaccatcccccatcatgggtatcgttgctggc
ctggttgtccttgcagctgtagtcactggagctgcggtcgctgtgctgtggagaaagaagctcagattgaaaagg
agggagctactctccaggctgccagagaccagccccacccctgtgccaccatgactgcatgctcatcctcctt
ccccaatcaccttttccctgttccagaaaaggggctgggatgtctccgtcttctgtctccaaatttgtggtcactgagctataa
cttacttcttgtattaaaattagaatctgagtataaaatttacttttttccaagagagattgatgggttaatt
aaagggagaagattccctgaaatttgagagacatgaggaagacatttCACCCTGCAGTTGGAAAGGGAAC
TA (SEQ ID NO:502).

FIG. 118

Sequence of right arm for construction of a homology directed recombination construct for inserting HLA-G1 at Rosa26

GCTTTGGGGCTCCGGCTCCTCAGAGAGCCTCGGCTAGGTAGGGGAGCGGGACTCTGGTGGGAGGGVGGGTGCGGTGCDTT
GGCGGGGGATGGGTGGCTGVGGBGGCCGTCTGDCCGVTHGCGGGGGGTYGCCTTTCCYAGTGGGACAGTCGGGAACATAWY
GTTTGTTACGCTGGAAGGGGAAGRGGRGGCGGGAGGCAGGCGGGAGTGCGGCCCGCCCTGCGGCAACCGGAGGGGGAGGG
AGAAGGGAGCGGGAAACBCTCGAAWCCGGACGGAGCCATTGCTCBCGCAGAGGGGGGCAGCGGAGGAGCGCTTCCGGCTVD
CCTCTCTTTGTCGCTGATTGGCCGCTTCTCCTCCCGCCGTCCCGCCGTGTGTGAAAACACAAATGGCGTGTTTTTGGTTGGA
GTAAAGCTCCTGTCAGTTACAGCCTCGGGAGTGCGCAGCCTCCCAGGAACTCTCGCATTGCCCCCTGGGTGGGTAGGTAG
GTGGGGGTGGAGAGAGCTGCACAGGCGGGCGCTGTCGGGCCTCCTGCGGGGGGGAGGGGTCAGTGAAAGTGGCTCCCGC
GCGGGCGTCCTGCCACCCTCCCCTCCGGGGGAGTCGGTTTACCCGCCGCCTGCTCGGCTTTGGTATCTGATTGGCTGCTG
AAGTCCTGGGAACGGCCCCCTTGTTATTGGCTTGGGTCCCAAATGAGCGAAACCACTACGCGAGTCGGCAGGGAGGCGGTC
TTTGGTACGGCCTCCCGAGGCCAGCGCCGCAGTGTCTGGCCCCTCGCCCCTGCAACGTGGCAGGAAGCGCGCGGCAG
GAGGCGGGGCGGCTGCCGGGCCGAGGCTTCTGGGTGGTGGTGACTGCGGCTCCGCCCTGGGCGTCCGCCGCCTGAAGG
ACGAGACTAGCTCTCTACCTGCTCTCGGACCCGTGGGGGGTGGAGGAAGGAGTGGGGGGGTCGGTCCTGCTGGCT
TGTGGGGTGGGAGGGCGCAT(SEQ ID NO:503).

FIG. 119

INTERNATIONAL SEARCH REPORT

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PCT/US2017/037566

A. CLASSIFICATION OF SUBJECT MATTER

A01K 67/027 (2006.01) C12N 15/12 (2006.01) C12N 15/85 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATENW & keywords: HLA-G, untranslated region, modified, CD47, pig, optimised and like terms; CPC: A01K2207/15, A01K2227/108, A01K2267/025, C12N15/8509, C07K14, C12N5, C12N15, A01K67; CAPLUS, BIOSIS, EMBASE, MEDLINE & keywords: HLA-G, untranslated region, modified, non-human, CD47, pig, optimised and like terms

GENOMEQUEST: SEQ ID NOs: 240, 359, 502

ESPACENET, PUBMED, AUSPAT, GOOGLE SCHOLAR, Internal Databases: Inventor names

GOOGLE SCHOLAR, GOOGLE PATENTS & keywords: CD40, ROSA26, ICP47, vaccine, apoptotic, C3, MICA, MICB, NLRC5, CXCL10, transplant, xenotransplantation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2017	24 August 2017
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Richard Filmer AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262832735

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2017/037566**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2014/022423 A2 (HANTASH, B. M et al.,) 06 February 2014 [0012], [0026], [0077]-[0080], [00103], [00104], [00129]-[00134]; Example 7; SEQ ID NO: 3 [0012], [0026], [0077]-[0080], [00103], [00104], [00129]-[00134]; Example 7; SEQ ID NO: 3	7-16, 31, 46-57, 65-72, 87, 102-114 24-29, 32-45, 80-85, 88-101, 115-147
Y	FISCHER, K., et al., "Multi-transgenic pigs for xenotransplantation", Xenotransplantation, 2013, vol. 20, pages 39-64 Abstract	32-35, 41, 43, 44, 88-91, 97, 99, 100
Y	US 2013/0177577 A1 (KOBAYASHI et al.) 11 July 2013 [0042]	33, 35-37, 89, 91-93
Y	WO 2001/019181 A1 (UNIVERSITY OF MASSACHUSETTS, A PUBLIC INSTITUTION OF HIGHER EDUCATION OF THE COMMONWEALTH OF MASSACHUSETS, as represented by ITS AMHERST CAMPUS) 22 March 2001 page 12, line 14 – page 14, line 3	33, 35, 36, 38, 43, 44, 89, 91, 92, 94, 99, 100
Y	FIANE, A., E., et al., "Compstatin, a peptide inhibitor of C3, prolongs survival of ex vivo perfused pig xenografts", Xenotransplantation, 1999, vol. 6, pages 52-65 Abstract	36, 39, 92, 95
Y	CN 102911270 A (ZHEJIANG UNIVERSITY) 06 February 2013 Abstract; Results (English translation obtained from Google Patents)	33, 35, 36, 40, 89, 91, 92, 96
Y	HANCOCK, W. W. et al., "Donor-derived IP-10 Initiates Development of Acute Allograft Rejection", Journal of Experimental Medicine, 2001, vol. 193, no. 8, pages 975-980 Abstract; Results and Discussion	33, 35, 36, 42-44, 89, 91, 92, 98-100
Y	US 6156306 A (BROWNLEE et al.) 05 December 2000 col. 5 line 31 – col. 6 line 20	45, 101
Y	US 2004/0038373 A1 (PLATZ et al.) 26 February 2004 [0005]	115-119, 124-147
Y	WO 1997/034633 A1 (BRISTOL-MYERS SQUIBB COMPANY) 25 September 1997 Abstract; page 11 lines 1-4	120-128, 133-140, 145-147
Y	TENA, A. et al., "Transgenic Expression of Human CD47 Markedly Increases Engraftment in a Murine Model of Pig-to-Human Hematopoietic Cell Transplantation", American Journal of Transplantation, 2014, vol. 14, no. 12, pages 2713-2722 Abstract, Results	24-29, 33-35, 41, 43, 44, 80-85, 89-91, 97, 99, 100

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/037566

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-16 and 58-72 (completely) and 24-57 and 80-147 (in part).

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT	International application No. PCT/US2017/037566

Supplemental Box

Continuation of: **Box III**
This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

• Invention 1 is defined by claims 1-16 and 58-72 (completely) and claims 24-57 and 80-147 (in part). The feature of a non-human animal or cell comprising an exogenous nucleic acid that is transcribed as a HLA-G mRNA with a modified 3'UTR is specific to this group of claims.

• Invention 2 is defined by claims 17-23 and 73-79 (completely) and claims 24-57 and 80-147 (in part). The feature of a non-human animal or cell comprising an exogenous nucleic acid that is at least 75% identical to SEQ ID NO: 240 (a human CD47 gene that is codon optimised for porcine expression) is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions is an animal or cell comprising an exogenous gene for the purposes of xenotransplantation. However it is considered that this feature is generic in this particular art.

Therefore this common feature cannot be a special technical feature. Hence there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2017/037566**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2017/037566**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2017/037566**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2017/037566**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2017/037566**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2017/037566**

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