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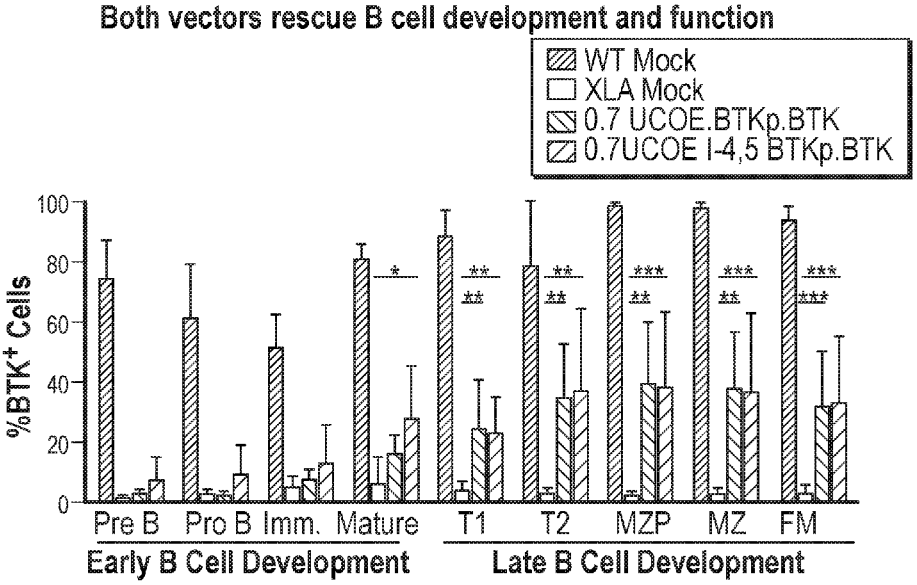

FIG. 5

(57) Abstract: Described herein are compositions and methods for treating, inhibiting or ameliorating X linked agammaglobulinemia (XLA) in subjects that have been identified or selected as being ones that would benefit from a therapy to treat, inhibit, or ameliorate XLA. Exemplary embodiments include constructs and methods for gene therapy, which restore or increase BTK expression.

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OPTIMIZED LENTIVIRAL VECTOR FOR XLA GENE THERAPY

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] The present application claims the benefit of priority to U.S. Provisional Patent Application No. 62/488,523, filed April 21, 2017. The entire disclosure of the aforementioned application is expressly incorporated by reference in its entirety.

REFERENCE TO FEDERAL FUNDING

[0002] This invention was made with support under grant number AI084457, awarded by the NIH National Institute of Allergy and Infectious Diseases.

REFERENCE TO SEQUENCE LISTING

[0003] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled Sequence Listing SCRI.148WO.txt, created April 17, 2018 which is 140 kb in size. The information is the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0004] Aspects of the present invention concern compositions and methods for treating, inhibiting or ameliorating X linked agammaglobulinemia (XLA) in subjects that have been identified or selected as being ones that would benefit from a therapy to treat, inhibit, or ameliorate XLA. Exemplary aspects include constructs and methods for gene therapy, which restore or increase Bruton's tyrosine kinase (BTK) expression.

BACKGROUND OF THE INVENTION

[0005] X linked agammaglobulinemia (XLA) is a rare X-linked genetic disorder resulting from mutations in the Bruton's tyrosine kinase (BTK) gene. These mutations contribute to the failure of afflicted individuals to generate mature B cells and the inability of these B cells to respond to B cell antigen receptor engagement, as well as, other cellular signals. Affected males are unable to generate protective antibody responses to pathogen

challenge and eventually succumb to viral or bacterial infection. Current therapy has not changed for over 5 decades and consists of immunoglobulin replacement and targeted anti-microbial agents. Despite this therapy, XLA subjects continue to suffer from chronic infections and are at an increased risk for a range of morbid or life-threatening complications. In rare settings, XLA subjects have been treated with stem cell transplantation without conditioning or using reduced intensity conditioning with variable outcomes. The need for more therapies to inhibit, treat, or ameliorate XLA is manifest.

SUMMARY OF THE INVENTION

[0006] Based upon iterative design and testing of candidate promoter, insulator, and enhancer elements and human codon-optimized BTK cDNA constructs, an identified novel lentiviral-based (LV) vector construct that mediates sustained BTK expression in B and myeloid cells derived from (murine or human) hematopoietic stem cells has been manufactured and is described in the alternatives herein. Following *ex vivo* transduction and transplantation into BTK deficient hosts, these alternatives have been shown to surprisingly sustain BTK expression and rescue B cell development. As shown in one of the exemplary alternatives herein, the constructs set forth herein utilize a truncated ubiquitous chromatin opening element (UCOE) element, a conserved enhancer element derived from intronic regions within the human BTK locus in association with the human BTK proximal promoter to drive expression of a human codon-optimized BTK cDNA.

[0007] LV vectors using this construct in mouse gene therapy experiments mediate sustained BTK expression in B and myeloid cells in primary and secondary transplant recipients and rescue B cell development and function without evidence of viral toxicity. Thus, this construct represents a unique LV vector for gene therapy treatment, inhibition, or amelioration of human XLA.

[0008] In a first aspect, a polynucleotide for sustained Bruton's tyrosine kinase (BTK) expression, the polynucleotide comprising: a first sequence encoding an ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter and a third sequence encoding BTK. In some alternatives, the UCOE is 2kb, 1.5kb, 1kb, 0.75kb, 0.5kb or 0.25 kb or any number of kilobases in between a range defined by any two afore mentioned values. In some alternatives, the first sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 1, and/or SEQ ID NO: 2. In some alternatives, the

promoter is a BTK promoter. In some alternatives, the BTK promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5. In some alternatives, the third sequence is codon optimized for expression in humans. In some alternatives, the third sequence comprises the sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7. In some alternatives, the promoter is a B cell specific promoter. In some alternatives, the B cell specific promoter comprises the B cell specific promoter B29. In some alternatives, the B29 promoter sequence comprises a sequence set forth in SEQ ID NO: 46. In some alternatives, the B cell specific promoter is an endogenous promoter. In some alternatives, the polypeptide further comprises one or more enhancer elements. In some alternatives, the one or more enhancer elements comprises at least one DNase Hypersensitive Site (DHS). In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5). In some alternatives, the DNase Hypersensitive Site comprises a sequence set forth in SEQ ID NO: 3. In some alternatives, the one or more enhancer elements comprise at least one intronic region. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter. In some alternatives, the at least one intronic region is intron 4, intron 5 and/or intron 13 of the human BTK locus that is in association with the human BTK proximal promoter. In some alternatives, the intronic region comprises the sequence set forth in SEQ ID NO: 9 (intron 4), SEQ ID NO: 10 (intron 5) and/or SEQ ID NO: 11 (intron 13). In some alternatives, the one or more enhancer elements comprise the sequence set forth in SEQ ID NO: 4, SEQ ID NO: 14 or SEQ ID NO: 15. In some alternatives, the UCOE is in a reverse orientation or forward orientation. In some alternatives, the UCOE is in a forward orientation. In some alternatives, the one or more enhancer elements comprises the sequences set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and/or SEQ ID NO: 20. In some alternatives, the polynucleotide further comprises a gene upstream of a BTK promoter. In some alternatives, the gene upstream of a BTK promoter is a BTK enhancer. In some alternatives, the BTK enhancer comprises the sequence set forth in SEQ ID NO: 21 or SEQ ID NO: 22. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0009] In a second aspect a vector for sustaining BTK expression in cells is provided, the vector comprising: a first sequence encoding an ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter, and a third sequence encoding BTK. In some alternatives, the first sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 1, and/or SEQ ID NO: 2. In some alternatives, the promoter is a BTK promoter. In some alternatives, the promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5. In some alternatives, the third sequence is codon optimized for expression in humans. In some alternatives, the third sequence comprises the sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7. In some alternatives, the vector further comprises a B cell specific promoter. In some alternatives, the B cell specific promoter comprises the B cell specific promoter B29. In some alternatives, the B29 promoter sequence comprises a sequence set forth in SEQ ID NO: 46. In some alternatives, the B cell specific promoter is an endogenous promoter. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the one or more enhancer elements comprise at least one intronic region. In some alternatives, the one or more enhancer elements comprises a DNase Hypersensitive Site (DHS). In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5). In some alternatives, the DNase Hypersensitive Site comprises a sequence set forth in SEQ ID NO: 3. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter. In some alternatives, the at least one intronic region is intron 4 intron 5 and/or intron 13 of the human BTK locus that is in association with the human BTK proximal promoter. In some alternatives, the intronic region comprises the sequence set forth in SEQ ID NO: 9 (intron 4), SEQ ID NO: 10 (intron 5) and/or SEQ ID NO: 11 (intron 13). In some alternatives, the one or more enhancer elements comprise the sequence set forth in SEQ ID NO: 4, SEQ ID NO: 14 or SEQ ID NO: 15. In some alternatives, the UCOE is in a reverse orientation or forward orientation. In some alternatives, the UCOE is in a forward orientation. In some alternatives, the vector is a lentiviral-based vector of a B lineage specific lentiviral vector. In some alternatives, the cells are B cells. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells.

In some alternatives, the one or more enhancer elements comprises the sequences set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and/or SEQ ID NO: 20. In some alternatives, the polynucleotide further comprises a gene upstream of a BTK promoter. In some alternatives, the gene upstream of a BTK promoter is a BTK enhancer. In some alternatives, the BTK enhancer comprises the sequence set forth in SEQ ID NO: 21 or SEQ ID NO: 22. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0010] In a third aspect, a cell for expression of BTK is provided, wherein the cell comprises a polynucleotide, which comprises a first sequence encoding a UCOE, a second sequence encoding a promoter and a third sequence encoding BTK. In some alternatives, the polynucleotide is in a vector. In some alternatives, the vector is a lentiviral vector. In some alternatives, the cell is a B cell. In some alternatives, the cells are a myeloid cell. In some alternatives, the cell is a hematopoietic stem cell. In some alternatives, the cell is a CD34+ hematopoietic stem cell. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0011] In a fourth aspect, methods of promoting or increasing B cell survival, proliferation and/or differentiation in a subject in need thereof are provided, wherein the method comprises administering the cells of any one of the alternatives herein to the subject or cells comprising the polynucleotide of any one of the alternatives herein or the vector of any one of the alternatives herein to the subject in need and, optionally identifying or selecting the subject as one that would benefit from receiving a therapy that would promote B cell survival, proliferation and/or differentiation in advance of administering the cells and/or, optionally, measuring B cell survival, proliferation and/or differentiation in said subject or in a biological sample obtained from said subject after receiving the administration of the cells. In some alternatives, the cells are from the subject and, wherein the cells are genetically modified by introducing the polynucleotide of any one of the alternatives herein or the vector of any one of the alternatives herein into the cells. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cells are B cells. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are

hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells. In some alternatives, the subject is male. In some alternatives, the subject is suffering from XLA. In some alternatives, the subject is selected to receive immunoglobulin replacement therapy. In some alternatives, the subject is selected to receive targeted anti-microbial agents. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0012] In a fifth aspect, methods of treating, inhibiting, or ameliorating X linked agammaglobulinemia (XLA) or disease symptoms associated with XLA in a subject in need thereof are provided, wherein the methods comprise administering the cell of any one of the alternatives herein to the subject or a cell comprising the polynucleotide of any one of the alternatives herein or the vector of any one of the alternatives herein to the subject in need and, optionally identifying or selecting the subject as one that would benefit from receiving a therapy for XLA or disease symptoms associated with XLA and/or, optionally, measuring an improvement in the progression of XLA or an improvement in a disease symptom associated with XLA in said subject. In some alternatives, the cell is from the subject, wherein the cell is genetically modified by introducing the polynucleotide of any one of the alternatives herein or the vector of any one of the alternatives herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a B cell. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells. In some alternatives, the subject is male. In some alternatives, the subject is selected to receive immunoglobulin replacement therapy. In some alternatives, the subject is selected to receive targeted anti-microbial agents. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0012a] In a sixth aspect there is provided a polynucleotide for sustained Bruton's tyrosine kinase (BTK) expression, the polynucleotide comprising:

(i) a first sequence encoding a ubiquitous chromatin opening element (UCOE), wherein the UCOE consists of a fragment from a human CBX3 gene, wherein the fragment comprises an exon 1 and an alternative exon 1 of the CBX3 gene, and a 3′ end of the alternative exon 1, and wherein the UCOE has a length in a range from 0.668 kb to 1 kb;

(ii) a second sequence encoding a BTK promoter; and

(iii) a third sequence encoding BTK.

[0012b] In a seventh aspect there is provided a vector comprising a polynucleotide of the sixth aspect. In an eighth aspect there is provided a cell comprising a polynucleotide of the sixth aspect or a vector of the seventh aspect. In a ninth aspect there is provided a pharmaceutical composition comprising a cell of the eighth aspect and a pharmaceutically acceptable carrier.

[0012c] In a tenth aspect there is provided a method of promoting B cell survival, proliferation and/or differentiation in a subject in need thereof, the method comprising administering the cell of the eighth aspect or the pharmaceutical composition of the ninth aspect to the subject.

[0012d] In an eleventh aspect there is provided a method of treating, inhibiting, or ameliorating X linked agammaglobulinemia (XLA) in a subject in need thereof, the method comprising administering the cell of the eighth aspect or the pharmaceutical composition of the ninth aspect to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **Figure 1** shows the optimized gene delivery platform for XLA.

[0014] **Figure 2** shows methods for optimizing lentiviral vectors for gene therapy for XLA.

[0015] **Figure 3** shows the methods for the preclinical models for the therapy plan.

[0016] **Figure 4** shows BTK expression in lymphocyte subsets: BTK expression in bone marrow (BM), spleen (SP) and peritoneal fluid (PF) B cells, monocytes and neutrophils from XLA mice transplanted with lentiviral vector 0.7UCOE or with 0.7UCOE-I4,5 expressing human BTK, as measured by flow cytometry and expressed as percent of the control BTK^+ population.

[0017] **Figure 5** shows rescue of B cell development and function. Analysis of BTK expression in B subsets from primary recipients. Splenic B cell subsets (right panel) are represented in order from least to more mature subsets: early B cell development (pre B cell, pro B cell, immature and mature B cell) to late B cell development (transitional1 (T1), transitional 2 (T2), marginal zone precursor (MZP), marginal zone (MZ) and follicular mature (FM).

[0018] **Figure 6** shows both vectors 0.7 UCOE.*BTK*p. BTK and 0.7UCOE I-4,5 BTKp. BTK rescue B cell development and function. (A) Absolute counts for splenic B cells (Right panel). (B) B cell proliferation in response to IgM stimulation. Naïve B cells were stimulated with soluble IgM. The percentage of BTK+ B cells proliferating at 72 hours is shown as normalized to WT Mock.

[0019] **Figure 7** shows responses to immunization with T-dependent antigens and autoantibody production. (A) Cumulative data for the levels of NP-specific IgG in serum from treated mice immunized with NP-CGG in Alum was detected by ELISA and measured relative to an IgG standard. ELISAs were used to detect levels of high-affinity NP-IgG before (-) and after primary (10) immunization, as well as following re-challenge or (20) secondary immunization.(B) Levels of anti-dsDNA IgG and IgG2c in serum from treated mice were measured by ELISA at the end point of the experiment depicted as absorbance readings (OD450). Serum from autoimmune WAS-/- chimeric mice are used as positive control (black triangles).

[0020] **Figure 8** shows viral integration number per cell. (A) Average viral integration number per cell in total BM and in splenic CD43- (B cell) vs. CD43+ (non B) cells in primary transplant mice as measured by qPCR. (B) Percent BTK+ B cells divided by average number of viral integrations in CD43- splenic B cell population in primary transplant

mice. Data represent mean ± SEM from 6 independent experiments, n = 9 (WT Mock), 10 (XLA Mock) 16 (0.7UCOE.BTKp),14 (0.7UCOE.INT4,5 BTKp).

[0021] **Figure 9** shows expression profiles of four LV constructs and rescue of B cell development and function in primary recipient mice. (**9A**) Schematic of the lentiviral constructs with RRL backbone used to express human BTK in murine cells with the BTK promoter (BTKp), a 1.5kb ubiquitous chromatin opening element (UCOE) or Eμ enhancer, and codon-optimized human BTK cDNA (co). (**9B**) BTK marking in bone marrow, spleen, peritoneal B and myeloid cells from gene therapy treated mice was determined by flow cytometry and is shown as percent of the population that is BTK+. (Data represent mean ± SEM from 10 independent experiments, n = 14 (WT Mock), 12 (KO Mock), 5 (BTKp), 24 (1.5kb.UCOE.BTKp), 18 (1.5kb.UCOE.BTKp.co), 21 (Eμ.BTKp). (**9C-9E**) B cells (B220+) in the bone marrow, spleen, and peritoneum were stained for surface markers indicative of B cell subsets and analyzed for counts or percentage of live lymphocytes: (**9C**) Early B cell development: Pro-B (CD43+, IgM-), Pre-B (CD43-, IgM-, IgD-), Immature (CD43-, IgM+ IgD-), and Mature (CD43-, IgM+, IgD+); (**9D**) late B cell development: transitional T1 (CD24hi, CD21-), transitional T2 (CD24hi, CD21int), marginal zone/precursor MZ/MZP (CD24hi, CD21hi), and follicular FM (CD24int, CD21int); (**9E**) peritoneum B cells: B2 (B220hi), B1b (B220lo, CD5-), and B1a (B220lo, CD5+). Data represent mean ± SEM from 10 independent experiments with n (BM,SP,PE) = 11,13,14 (WT Mock); 10,11,10 (KO Mock); 5,5,5 (BTKp); 20,21,22 (UCOE.BTKP); 14,14,17 (UCOE.BTKp.co); 18,19,20 (Eμ.BTKp) (**9F**) Total splenocytes from treated mice were stimulated with media alone, anti-murine IgM, LPS or PMA/Ionomycin and proliferation was measured by incorporation of 3H-thymidine, depicted as the counts per minute (cpm) averaged from 3 replicate wells. Data represent mean ± SEM from 5 independent experiments, n = 10 (WT Mock), 7 (KO Mock), 5 (BTKp), 13 (1.5kbUCOE.BTKp), 9 (1.5 kbUCOE.BTKp.co), 10 (Eμ.BTKp). (**9G-9H**) Total serum IgG (**9G**) and IgM (**9H**) in serum from treated mice was measured by ELISA. Data represent mean ± SEM from 4 independent experiments, n = 9 (WT Mock), 10 (KO Mock), 2 (BTKp), 19 (1.5kb.UCOE.BTKp), 14 (1.5kbUCOE.BTKp.co), 16 (Eμ.BTKp). (**9I**) Levels of NP-specific IgG in serum from treated mice immunized with NP-CGG in Alum, measured by ELISA and expressed relative to an IgG standard. ELISAs were used to detect levels of low-affinity (Supp) and high-affinity (i) NP-IgG before (-) and after (+) immunization, as well as

following later re-challenge (++). Data represent mean ± SEM from 5 independent experiments with n = 9 (WT Mock), 10 (KO Mock), 2 (BTKp), 19 (1.5.UCOE.BTKp), 14 (1.5kb.UCOE.BTKp.co), 16 (Eμ.BTKp). ***P < .001; **P = .001-.01; *P = .01-.05, between total B cells or B cell subsets from the indicated experimental group and KO Mock group.

[0022] **Figure 10** shows Eμ.BTKp gene therapy treated mice develop broad specificity IgG autoreactive antibodies. Levels of anti-dsDNA IgG (a) in serum from treated mice were measured by ELISA prior to any immunizations and are depicted as absorbance readings (OD450). Data represent mean ± SEM from 10 independent experiments, n = 18 (WT Mock), 16 (KO Mock), 6 (BTKp), 30 (1.5kb.UCOE.BTKp), 18 (1.5 kb.UCOE.BTKp.co), 29 (Eμ.BTKp), 2 (WASp control). (b) Anti-dsDNA IgG subclasses IgG2c and IgG3 were measured by ELISA from Eμ.BTKp mice (n=23). (c) Subclasses of anti-dsDNA IgG in sera from 9 Eμ.BTKp treated mice were measured by ELISA. ***P < .001; **P = .001-.01; *P = .01-.05, between the indicated experimental groups.

[0023] **Figure 11** shows 1.5kbUCOE.BTKp and 1.5kbUCOE.BTKp.co lead to sustained BTK expression with lower copy numbers in primary and secondary recipients. Splenic granulocytes (CD11b+, GR1hi) from secondary transplant mice were evaluated for %BTK+ cells by flow cytometry. (a) Graphical analysis of %BTK+ granulocytes in secondary transplant recipients. Data represent mean ± SEM from 3 independent experiments with n = 3 (WT Mock), 2 (KO Mock), 3 (BTKp), 8 (1.5.UCOE.BTKp), 7 (Eμ.BTKp). (b) Percent BTK+ granulocytes divided by average number of viral integrations in splenocytes from primary transplant mice. (c-d) Average viral integrations per cell in bone marrow (c) and splenocytes (d) from primary and secondary transplant mice measured by qPCR. Data represent mean ± SEM from 8 primary and 3 secondary transplant experiments with n (primary and secondary) = 5, 3 (BTKp); 18, 8 (UCOE.BTKp); 10, 1 (UCOE.BTKp.co); 18, 7 (Eμ.BTKp). ***P < .001; **P = .001-.01; *P = .01-.05, between the indicated experimental groups.

[0024] **Figure 12** shows restoration of BTK expression in affected hematopoietic lineages and B cell development in gene therapy mice treated with 0.7kb UCOE.BTKp.co LV. The proportion of BTK+ cells and numerical reconstitution of B cell subsets was assessed at 16-25 weeks post-transplant. (a) Schematic diagram of a lentiviral construct with RRL backbone expressing codon optimized human BTK with a 0.7 kb ubiquitous chromatin

opening element (UCOE). (b-c) Percent of BTK+ cells in bone marrow (b) and splenic (c) lymphocyte subsets (Neutrophils, Monocytes, B cells and T cells) from gene therapy treated groups, determined by flow cytometry. Data represent mean ± SD from 7 unique experiments, n = 13 (WT Mock), 12 (KO Mock), 36 (0.7kb.UCOE.BTKp.co). (d) Representative flow plots of BTK expression in splenic Neutrophils (CD11b+ GR1+), Monocytes (CD11b+), B cells (B220+) and T cells (CD4+CD8+), (e) BTK expression in Peritoneal B cells (CD19+) and B cell subsets B1a (CD5- CD43+), B1b (CD5+ CD43+) and B2 (CD5- CD43-). Representative data from 7 unique experiments with SD and n = 2 (WT Mock), 2 (KO Mock), 8 (0.7kb.UCOE.BTKp.co). (f) Rescue of B cell development by Btk expression in the subsets, as measured by flow cytometry. Early B cell development: Pro-B (CD43+, IgM-), Pre-B (CD43-, IgM-, IgD-), Immature (CD43-, IgM+ IgD-), and Mature (CD43-, IgM+, IgD+); and late B cell development: transitional T1 (CD24hi, CD21-), transitional T2 (CD24hi, CD21int), marginal zone/precursor MZ/MZP (CD24hi, CD21hi), and follicular FM (CD24int, CD21int). Cumulative data from 7 independent experiments, n = 13 (WT Mock), 12 (KO Mock), 36 (0.7kb.UCOE.BTKp.co). (g-h) Total cell counts of the B cell subsets from in BM (g) and Spleen (h). (i) B cell subsets as percent of total lymphocyte population in peritoneal fluid. Data represent mean ± SD from 2 independent experiments, n =4 (WT Mock), 4 (KO Mock), 11 (0.7 kbUCOE.BTK.co) The * represent significant difference between KO Mock and 0.7 kb.UCOE.BTK.co. P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0025] Figure 13 shows reconstitution of B cell function following 0.7.UCOE.Bkp.co LV gene therapy in primary recipients. Assays of B cell function after 16-25 weeks post bone marrow transplantation. Bars show the mean ± SD (a) The percentage of B cells (CD43- splenocyte) that underwent ≥ 1 cell division 72 hours after incubation with anti-mouse IgM antibodies, LPS or P/I (as measured by CFSE dilution and read out by flow cytometry). Representative data from one independent experiment; n = 4 (WT Mock), 3 (KO Mock), and 5 (0.7.UCOE.BTKp.BTK.co). (b) Flow cytometry analysis showing CFSE labeled B cells (CD43- splenocytes) 72 hours post-IgM stimulation, gated on live and B220+ populations (working on the flow plot). (c) Levels of high-affinity NP-specific IgG in serum from treated mice immunized with NP-CGG in Alum, measured by ELISA. The values are measured before (-) and post (+) immunization as well as following re-challenge (++). Data

represent 7 independent experiments with n = 11 (WT Mock), 10 (KO Mock), 13 (0.7 kb.UCOE.BTKp.co) in primary immunization (+) and n= 3 (WT Mock), 3 (KO Mock), 3 (0.7 kb.UCOE.BTKp.co) for re- challenge (++). (d) Total IgG and IgM and (e) anti-dsDNA antibody levels in the serum of immunized primary recipients as determined by ELISA 16-25 weeks post-transplant. Data are from 7 independent experiments; n = 10 (WT Mock), 8 (KO Mock) and 26 (0.7.UCOE.BTKp.BTK.co.). Serum from 2 autoimmune WAS chimera with high serum anti-DNA antibodies was run as a positive control (e). P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0026] **Figure 14** shows VCN and BTK expression are maintained after serial passage of gene therapy-treated bone marrow cells into secondary TBK-/- recipients. Percent of BTK+ expressing cells within affected lineages of the BM (a) and spleen (b) of secondary recipients 16 weeks post-transplantation with BM from primary recipients was measured by flow cytometry. Data represents two individual experiments; n = 4 (WT Mock), 4 (KO Mock), 19 (0.7 UCOE.BTKp.BTKco). (c) Viral copy number (VCN) determined by qPCR of gDNA extracted from total BM and splenic B (CD43-) and non-B (CD43+) cells of primary recipients. (d) VCN of total BM and splenic cells from secondary recipient mice; each dot represents a single animal. Data are from 7 unique experiments for primary (n=21 0.7.UCOE.BTKp.BTK.co) and secondary recipients (n = 11 0.7.UCOE.BTKp.BTK.co) (e) Splenic gDNA from primary and secondary recipients was assessed for methylation. n for primary recipients = 2(BTKp.BTK), 5 (1.5kb UCOE.BTKp.BTK), 6 (Eu.BTKp.BTK.), 6 (0.7kb.UCOE.BTKp.co). n for secondary recipients = 4 (1.5kb.UCOE.BTKp.BTK) and 6 (0.7 UCOE.BTKp.co). In all panels the mean ± SD value are shown; P values comparing the means of KO Mock to 0.7.UCOE.BTKp.BTK.co. P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0027] **Figure 15** shows 0.7UCOE.BTKp.co leads to sustained BTK expression and lower copy numbers in XLA CD34 cells. XLA and control CD34 cells were transduced with 0.7UCOE.BTKp.co at various multiplicities of infection (MOI) and cultured in vitro for 15 days. (a) Schematic diagram of the lentiviral transduction protocol of healthy and XLA CD34 cells. Cells were stimulated for 48hr in SCGM media supplemented with 100ng of human TPO, SCF and Flt3. Cells were transduced with 0.7UCOE.BTKp.co and grown in culture for 15 days. At day 15 cells were analyzed for BTK expression and VCN. (b)

Representative flow plots of BTK staining in CD34 cells from an XLA patient 15 days post-transduction at various MOIs. (c) Viability of transduced cells after 24 hr transduction, determined by flow cytometry. (d) Viral copy number (VCN) determined by qPCR of gDNA extracted from total cells collected after 15 days in culture. Data represent mean ± SD from 3 unique experiments done in duplicate wells. Each dot represents an individual donor, either healthy or XLA.

[0028] **Figure 16** shows the BTK promoter mimics BTK's endogenous expression pattern in mice.(a-b) Bone marrow, spleen, peritoneal wash, peripheral blood and thymus were collected from a wildtype mouse and cells were stained for B, myeloid, T and NK cell markers, intracellular BTK and read on a flow cytometer. Samples from the various tissues are designated by the shape of the symbol, as outlined in the legend. The percent of cells that are BTK+ is shown for each subset (a), as well as the median fluorescence intensity of BTK+ cells (b). (c) Schematic of lentiviral constructs with RRL backbone, Eμ enhancer and human BTK cDNA, under control of either the B29 promoter (top panel) or the endogenous BTK promoter BTKp (bottom panel). (d-e) Bone marrow, spleen and peritoneal cells were collected from Eμ.B29 or Eμ.BTKp gene therapy treated KO mice and stained with markers for B (CD11b-, B220+), myeloid (CD11b+) and T (CD11b-, CD3+) cells, intracellular BTK, and analyzed by flow cytometry. (d) The percent of cells that are BTK+. (e) The median fluorescence intensity of BTK staining in indicated cell populations. Data represent mean ± SEM from 2 independent experiments with n=4 (EμB29) and n=5 (EμBTKp). ***P < .001; **P = .001-.01; *P = .01-.05, between Eμ.B29 and Eμ.BTKp.

[0029] **Figure 17** shows (a) Schematic of lentiviral constructs under control of the BTK promoter with Eμ enhancer and human BTK cDNA, either wild type of codon-optimized, with a T2A-linked GFP. (b) Chicken BTK-/- DT40 cells were transduced with BTK-GFP or coBTK-GFP constructs; histograms show GFP and BTK expression. (c) BTK-GFP and coBTK-GFP transduced cells were stained with an Indo-1 Ester AM fluorescent dye and stimulated with anti-IgM; calcium mobilization was monitored via flow cytometry.

[0030] **Figure 18** shows (a) Representative plots of BTK expression by flow cytometry in peripheral blood B cells and myeloid cells from gene therapy-treated KO mice. (b) BTK marking in bone marrow, spleen, peritoneal B and myeloid cells from gene therapy treated mice was determined by flow cytometry and the median fluorescence intensity of the

BTK+ cells is shown. (Data represent mean ± SEM from 10 independent experiments, n = 14 (WT Mock), 12 (KO Mock), 5 (BTKp), 24 (1.5kb.UCOE.BTKp), 18 (1.5kb.UCOE.BTKp.co), 21 (Eμ.BTKp). (c) Representative flow cytometry plots from bone marrow of gene therapy treated mice, stained with markers for early B cell development. (d) Graphs depict the percentage of B cells following Hardy fractions of decreasing maturity: Fr I (IgMlo, IgDhi), Fr II (IgMhi, IgDhi), FrIII (IgMhi, IgDlo), each ring represents one mouse and the mean percent of B cells in each fraction is shown inside the graphic. Data represent mean ± SEM from 11 independent experiments, n = 18 (WT Mock), 14 (KO Mock), 7 (BTKp), 43 (1.5 kb.UCOE.BTKp), 18 (1.5kb.UCOE.BTKp.co), 23 (Eμ.BTKp). (e-f) Levels of NP-specific IgG in serum from treated mice before (-) and after (+) immunization with NP-CGG in Alum were measured by ELISA and expressed relative to an IgG standard. Low-affinity NP-specific antibodies are shown for all groups (e) and for individual mice (f). Data represent mean ± SEM from 5 independent experiments with n = 9 (WT Mock), 10 (KO Mock), 2 (BTKp), 19 (1.5.UCOE.BTKp), 14 (1.5kb.UCOE.BTKp.co), 16 (Eμ.BTKp). (g) Levels of TNP-specific IgM in serum from treated mice immunized with TNP-Ficol, measured by ELISA and expressed relative to an IgM standard. Data represent mean ± SEM from 3 independent experiments with n = 4 (WT), 6 (WT Mock), 4 (KO), 3 (KO Mock), 14 (UCOE.BTKp). ***P < .001; **P = .001-.01; *P = .01-.05, between the indicated experimental group and KO Mock group.

[0031] **Figure 19** shows (a) Survival curve of Eμ.BTKp primary transplant mice with high and low anti-dsDNA IgG titers, compared to controls. (b) Correlation of BTK MFI of BTK+ cells and Anti-dsDNA IgG titers as measured by flow cytometry and ELISA, respectively, in Eμ.BTKp primary transplant mice.

[0032] **Figure 20** shows sera from WT Mock (4), 1.5kb.UCOE.BTKp (4) and Eμ.BTKp (8) mice were analyzed by autoantigen array for levels of IgM and IgG reactive to 88 murine antigens. Data from each row was subject to z-transformation and Z-scores are displayed on a colorimetric scale from lowest reactivity (red) to highest (blue).

[0033] **Figure 21** shows the development of B cells and the pathway in which the enzyme BTK is involved.

[0034] **Figure 22** shows development of the optimal BTK LV gene therapy vector.

[0035] **Figure 23** shows LV vectors containing the BTK endogenous promoters. As shown, the 2 kb CBX3-HNRPA2B1 element- UCOE 1.5- eliminates the A2 promoter but retains the CBX3 in reverse orientation.

[0036] **Figure 24** shows the development of LV vectors containing the BTK endogenous promoter. As shown, Eμ associated with higher level Btk MFI in B cells.

[0037] **Figure 25** shows the results from a FACs assay of LV vectors containing the Btk endogenous promoter.

[0038] **Figure 26** shows the expression of BTK in myeloid cells that were obtained from splenocytes of treated mice.

[0039] **Figure 27** shows the results of BTK expression in B cells in which the LV expressing the BTK comprises a B cell specific promoter Eμ.B29.

[0040] **Figure 28** shows BTK expression in B cells and monocytes from the lentiviral vector comprising the promoter region BTKpro.BTK

[0041] **Figure 29** shows BTK expression in B cells and monocytes from the lentiviral vector comprising the promoter region BTKpro.BTK and the ubiquitous chromatin opening element (UCOE).

[0042] **Figure 30** shows BTK expression in B cells and monocytes from the lentiviral vector comprising the promoter region Eμ.BTKpro.BTK (BTK promoter) and huBTK.

[0043] **Figure 31** shows the expression profile of BTK of several BTK promoters in B cells and myeloid cells of the bone marrow, spleen and peritoneum.

[0044] **Figure 32** shows the expression profile of BTK of several BTK promoters in B cells and myeloid cells of the bone marrow, spleen and peritoneum. The vectors used were: WT mock, DKO mock, *BTK*p, UCOE *BTK*p, UCOE.*BTK*p.co and Eμ*BTK*p.

[0045] **Figure 33** shows B Cell Development Restoration of Mature B Cell Subsets. The black colored regions show that more mature peripheral B cell populations.

[0046] **Figure 34** shows B Cell Development Numerical Reconstitution of B Cell Populations (bone marrow, spleen and Peritoneum). As shown, the data summarize findings from up to 40 recipient mice per vector and similar numbers of controls.

[0047] **Figure 35** shows B cell proliferation in cells expressing four different types of lentiviral vectors (mock wt, DKO mock, lentiviral vector with UCOE.*BTK*p and

lentiviral vector Eμ.*BTK*p). The vital dye dilution vs Btk stain showed that UCOE led to very similar results to the WT mice in the experiments.

[0048] **Figure 36** shows B cell proliferation in cells with the following vectors: WT, WT mock, DKO, DKO mock, UCOE.*BTK*p and Eμ.*BTK*p.

[0049] **Figure 37** shows the results of IgM and IgG production in cells with the following vectors: WT, WT mock, DKO, DKO mock, *BTK*p, UCOE.*BTK*p and Eμ.*BTK*p. The bottom panel shows T independent immune responses in cells with the following vectors: WT, WT mock, DKO, DKO mock, UCOE.*BTK*p, WT-0 and KO-0. It is noted that the Eμ IgG levels actually slightly above WT mock recipients.

[0050] **Figure 38** shows T-dependent immune responses in cells with the following vectors: WT, WT mock, DKO, DKO mock, *BTK*p, UCOE.*BTK*p, UCOE.*BTK*p.co, WT-0, Eμ.*BTK*p and KO-0.

[0051] **Figure 39** shows T-dependent immunization: affinity maturation. Affinity maturation for individual UCOE animals and controls led to very similar results.

[0052] **Figure 40** shows evidence for auto-antibody production.

[0053] **Figure 41** shows evidence for auto-antibody production using a heat map of cells that have the vectors WT mock, UCOE.*BTK*p and Eμ.*BTK*p. This was performed for testing the production of IgM and IgG.

[0054] **Figure 42** shows association of antibody levels and percent mouse survival with BTK expression.

[0055] **Figure 43** shows long-term stem cell marking in neutrophils with BTK expression in secondary recipient mice.

[0056] **Figure 44** shows evidence for long-term stem cell marking in VCN in primary and secondary recipients that have the vectors: mock, *BTK*p, UCOE.*BTK*p, UCOE.*BTK*p.co, and Eμ.*BTK*p.

[0057] **Figure 45** shows the impact of LV therapy on long-term survival.

[0058] **Figure 46** shows the summary of testing of alternative enhancer elements within BTK promoter LV.

[0059] **Figure 47** shows that 0.7UCOE.BTKp and 0.7UCOE.IE.BTKp rescue BTK expression and splenic B cell counts.

[0060] **Figure 48** shows that 0.7UCOE.BTKp and 0.7UCOE.IE.BTKp rescue B cell function.

[0061] **Figure 49** shows that 0.7UCOE.IE exhibits an improved safety profile over 0.7UCOE.

[0062] **Figure 50** shows new BTK constructs with DNase Hypersensitive Sites.

[0063] **Figure 51** shows the identification of DNase Hypersensitive sites.

[0064] **Figure 52** shows a schematic of the constructs that were evaluated for BTK expression in cells.

[0065] **Figure 53** shows *in vivo* comparison of DHS constructs to 0.7UCOE and 0.7UCOE.IE.

[0066] **Figure 54** shows peripheral blood lymphocyte distribution in B cells, T cells, monocytes and neutrophils 15 weeks post-transplant. BTK reconstitution was also shown in lymphocyte subsets in cells with the following vectors: KO unirradiated, KO Mock, 0.7 UCOE, 0.7 UCOE.IE, 0.7 UCOEDHS4, 0.7 UCOE.DHS12, 0.7 UCOE.DHS124, 0.7 UCOE1-5, WT mock and WT unirradiated.

[0067] **Figure 55** shows BTK experimental summary in cells with the vectors: KO Mock, 0.7 UCOE, 0.7 UCOE.IE, 0.7 UCOEDHS4, 0.7 UCOE.DHS12, 0.7 UCOE.DHS124, 0.7 UCOE1-5 and WT mock.

[0068] **Figure 56** shows BTK expression in cells with vectors with either the UCOE element or DHS4 element.

[0069] **Figure 57** shows BTK expression experiments with cells that have the following vectors: 0.7UCOE.*BTK*p.co*BTK,* KO Mock, 0.7 UCOE, DHS4, DHS1-5 and WT Mock.

[0070] **Figure 58** shows peripheral blood lymphocyte distribution—12 weeks post transplantation with cells with the following vectors: KO Mock, WT Mock, 0.7 UCOE, DHS4 and DHS1-5.

[0071] **Figure 59** shows 6 week and 12 week peripheral blood lymphocyte distribution in B cells, monocytes and neutrophils that have the following vectors: KO unirradiated, KO Mock, 0.7 UCOE, DHS4, DHS1-5, WT Mock, and WT unirradiated.

[0072] **Figure 60** shows 6 week and 12 week BTK expression in B cells, monocytes and neutrophils that have the following vectors: KO unirradiated, KO Mock, 0.7 UCOE, DHS4, DHS1-5, WT Mock, and WT unirradiated.

[0073] **Figure 61** shows that BTK is expressed across cell subsets after a 12 week bleed following cell transplantation.

[0074] **Figure 62** shows the experimental set up for the *in vitro* comparison of original coBTK (codon optimized BTK) vs new coBTK.

[0075] **Figure 63** shows *in vitro* Comparison—TBK Lineage Negative Cells, Volume Matched Virus (day 7 BTK stain).

[0076] **Figure 64** shows the percent BTK expression in cells that received different concentrations of the lentivirus vectors for BTK expression. The vectors used were the following: KO Mock, 0.7 UCOE, DHS4, 0.7 UCOE.newcoBTK, 0.7 UCOE.newcoBTK, and WT spleen.

[0077] **Figure 65** shows *in vivo* comparison of original vs new coBTK.

[0078] **Figure 66** shows additional techniques for optimizing the UCOE elements to increase or enhance BTK expression.

[0079] **Figure 67** shows additional techniques for optimizing the UCOE elements to increase or enhance BTK expression for the 1.5kb UCOE.

[0080] **Figure 68** shows 0.7UCOE.BTKp vs. 0.7UCOEfwd.BTKp: *in vitro* test with matched volume virus.

[0081] **Figure 69** shows an outline for finalizing the clinical BTK LV construct.

[0082] **Figure 70** shows an outline for finalizing the clinical BTK LV construct and planned final *in vivo* testing for a codon optimized BTK.

[0083] **Figure 71** is a table showing approved apheresis of XLA patient's stem cells.

[0084] **Figure 72** shows a human chimera in NSG.

[0085] **Figure 73** shows human lymphocyte reconstitution in B cells of the bone marrow and the spleen.

[0086] **Figure 74** shows phenotype of engrafted XLA stem cell (spleen) such as the expression of IgD and IgM.

[0087] **Figure 75** shows a phenotype of engrafted XLA stem cell (spleen) such as the expression of CD24 and CD38.

[0088] **Figure 76** shows B cell developmental block (BM) indicating that there is an equivalent number of % ProB cells between the XLA group and the healthy group.

[0089] **Figure 77** shows B cell developmental block (BM) indicating that patients with XLA have a significantly higher % pre-B cells compared to a healthy control.

[0090] **Figure 78** shows B cell developmental block (BM) indicating that patients with XLA have cells that are blocked at the Pre B cell stage. These Pre B cells are able to migrate into the spleen. CD179a/CD179b surrogate light chain is disulfide-linked to membrane-bound Ig mu heavy chain in association with a signal transducer CD79a/CD79b heterodimer to form a B cell receptor-like structure, so-called preB cell receptor (preBCR).

[0091] **Figure 79** shows a B cell developmental block (BM). Development of XLA B cells are blocked at Pre B cell stage. Pre B cells are able to migrate to the spleen.

[0092] **Figure 80** shows that that B cells function by Ca^{2+} flux. However, the XLA B cells are unable to flux with IgM as compared to the control cells.

[0093] **Figure 81** shows the block of the pathway in B cell development, in which XLA causes the B cell development to be blocked at the Pre B cell stage.

[0094] **Figure 82** shows an outline of the results and conclusions from the experiments.

[0095] **Figure 83** shows a diagram outlining the human lentiviral transduction of stem cells.

[0096] **Figure 84** shows a diagram outlining preclinical modeling- human HSC.

[0097] **Figure 85** shows results from the Human lentiviral transduction of Stem cells. As shown there is 70% viability with 0.7UCOE.BTKp.BTK compare to DHS4.

[0098] **Figure 86** shows BTK expression at D15 with XLA P2. As shown, in a non-selective environment 0.7 UCOE.BTKpBTK leads to higher expression of BTK compare to DHS4.

[0099] **Figure 87** shows an outline of the conclusion from the experiments and follow up experiments.

[0100] **Figure 88** shows preclinical modeling for Human HSC. For these experiments, CD34+ cells are transduced with either mock vector or the vector: UCOE.*BTK*p.co.

[0101] **Figure 89** shows preclinical modeling- Human HSC. Cells were transduced with the vector UCOE.*BTK*pro.co-op*BTK* (UCOE.*BTK*p.co) GFP.

[0102] **Figure 90** shows a diagram of the experimental methods for transduction of the NSG recipient mice.

[0103] **Figure 91** shows the results from the transformed recipient mice: % GFP expression, viral copy expression in the cells of the bone marrow and the spleen, as well as, the expression in B cells and the myeloid cells.

[0104] **Figure 92** shows the analysis to identify conserved non-coding sequences by comparing mouse and human BTK gene sequences and all the vectors that are tested for expression of BTK. The regions identified and located were within the BTK promoter, upstream from the BTK promoter and proximal to the neighboring gene (BTK enhancer or BTKe), within part of intron 1, introns 4, 5, and 13.

[0105] **Figure 93** shows results from truncation of 1.5kb UCOE to 0.7kb and identification of potential DNA enhancer elements may improve titer and BTK expression in Lentiviral constructs. (a) Truncation of 1.5kb Ubiquitous Chromatin Opening Element (UCOE) to 0.7kb. The UCOE element spans a large, CpG-rich region across the divergently transcribed promoter regions for the housekeeping genes CBX3 and HNRPA2B1, and has traditionally been truncated to a 1.5-2.2kb region by various groups for use in protein expression constructs. The 1.5kb UCOE used here starts at Exon 1 of CBX3 and spans past CBX3 Alternate Exon 1. Truncation of this region to 0.7kb eliminates the region downstream of Alt. Ex. 1. (b) DNaseI Hypersensitive sites (DHS) from intronic regions of the BTK gene were identified from the ENCODE database and visualized using the UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly. Five DHS were identified, and were labeled consecutively as DHS1, DHS2, DHS3, DHS4, and DHS5 (blue boxes). ENCODE Genome Segmentation identified a predicted Enhancer element around DHS4 (yellow box). Exons are shown as black boxes. The sequence length is noted beneath each DHS. Various combinations of these DHS sequences were cloned into the 0.7UCOE.BTKp.coBTK construct and tested in vitro (data not shown). (c) An *in vitro*

transduction experiment of murine (TBK) lineage negative cells was performed to compare BTK expression levels in two versions of codon-optimized BTK: coBTK (Figures 1-2), and a codon-optimized BTK published by Staal et al. (Leukemia 2010), denoted here as co2BTK. Representative flow plots show BTK expression at 7 days post-transduction. (d) Based on the results of the *in vitro* testing of the DHS constructs and the coBTK vs co2BTK comparison, four constructs were identified to test *in vivo*. Shown here are diagrams of the lentiviral constructs with RRL backbone expressing either version of codon optimized human BTK (coBTK or co2BTK) with a 0.7 kb ubiquitous chromatin opening element (0.7UCOE), with or without addition of DHS4 downstream of the 0.7UCOE element.

[0106] **Figure 94** shows restoration of BTK expression in affected hematopoietic lineages and B cell development in gene therapy mice treated with 0.7UCOE vectors. The proportion of BTK+ cells and numerical reconstitution of B and myeloid cell subsets was assessed at 19-23 weeks post-transplant. (Figure 94A) Representative flow plots showing intracellular BTK staining in splenic B cells at endpoint analysis. (b-d) Percent of BTK+ cells in bone marrow (Figure 94B), spleen (Figure 94C), and peritoneal (Figure 94D) lymphocyte subsets from gene therapy treated groups, determined by flow cytometry. Cell subsets are defined as Neutrophils (CD11b+ GR1+), Monocytes (CD11b+), and B cells (B220+). (Figure 94E-F) Stacked bars show the average counts of B cell subsets in bone marrow (Figure 94E), spleen (Figure 94F), and peritoneum (Figure 94G). Early B cell development (bone marrow): Pro+Pre-B (IgM-, IgD-), Immature (IgM+ IgD-), and Mature (IgM+, IgD+). Late B cell development (spleen): transitional T1 (CD24hi, CD21-), transitional T2 (CD24hi, CD21int), marginal zone/precursor MZ/MZP (CD24hi, CD21hi), and follicular FM (CD24int, CD21int). Peritoneal B cell subsets: B1 (IgM+ CD43+), and B2 (CD43-). (Figure 94H) Rescue of BTK expression in B cell subsets, measured by flow cytometry. (Figure 94I) BTK+ MFI across B cell development, normalized to WT Mock in each individual experiment. Data represent mean ± SD from 4 unique experiments, n = 13 (WT Mock), 13 (KO Mock), 11 (0.7UCOE.BTKp.co), 11 (0.7UCOE.BTKp.co2), 16 (0.7UCOE.DHS4.BKTp.co), 11 (0.7UCOE.DHS4.BKTp.co2), and 6 (0.7UCOE.DHS1-5.BTKp.co). P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0107] **Figure 95** shows restoration of B cell function *in vivo* and *in vitro*. (Figure 95A) Mice were immunized with NP-CGG in Alum at 12 weeks post-transplant. Levels of NP-specific IgG in serum from immunized mice was measured by ELISA and expressed relative to an IgG standard. High-affinity NP-IgG was measured from serum prior to (-) and 10 days following primary immunization (1°). One month following primary challenge, mice were re-challenged with NP-CGG in PBS and serum was collected 10 days later (2°). (Figure 95B-C) Total serum IgG (Figure 95B) and IgM (Figure 95C) in serum from treated mice was measured by ELISA and endpoint analysis (21-23 weeks post-transplant). (Figure 95D-F) At endpoint analysis, B cells were isolated from splenocytes by CD43- magnetic separation, labeled with Cell Trace Violet and stimulated in vitro with IgM, LPS, or a media control. (Figure 95D) The percentage of BTK+ B cells that underwent ≥ 1 cell division 72 hours after incubation with anti-mouse IgM antibodies, LPS or media only (read out by flow cytometry). (Figure 95E) BTK+ MFI of cells after each division (D0-D4), normalized to WT Mock. (Figure 95F) Representative flow plots showing BTK staining and Cell Trace dilution in B cells 72 hours post-IgM stimulation, gated on live and B220+ BTK+ cells. Data represent mean ± SD from 4 unique experiments, n = 13 (WT Mock), 13 (KO Mock), 11 (0.7UCOE.BTKp.co), 11 (0.7UCOE.BTKp.co2), 16 (0.7UCOE.DHS4.BKTp.co), 11 (0.7UCOE.DHS4.BKTp.co2), and 6 (0.7UCOE.DHS1-5.BTKp.co). P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0108] **Figure 96** shows vector safety considerations. (Figure 96A-B) Levels of anti-dsDNA IgG (Figure 96A) and anti-dsDNA IgG2c (Figure 96B) in serum from treated mice were measured by ELISA and are depicted as absorbance readings (OD450). Serum from the known autoimmune-prone WAS chimeric mouse model and mice treated with Eu.BTKp were included as positive controls. (Figure 96C) Genomic DNA was isolated from total bone marrow and spleen at endpoint analysis and the number of viral integrations per cell (VCN) was quantified by qPCR. Data represent mean ± SD from 4 unique experiments, n = 13 (WT Mock), 13 (KO Mock), 11 (0.7UCOE.BTKp.co), 11 (0.7UCOE.BTKp.co2), 16 (0.7UCOE.DHS4.BKTp.co), 11 (0.7UCOE.DHS4.BKTp.co2), and 6 (0.7UCOE.DHS1-5.BTKp.co). P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0109] Figure 97 shows a schematic of a transfection protocol.

[0110] **Figure 98** shows equivalent bone marrow engraftment of human hematopoietic cells between treatment groups. Human stem cells from XLA patient, either with or without gene therapy treatments, engrafted into the bone marrow equivalently as those from a healthy donor. 98A. Representative flow plots showing various markers of human immune cells including human and mouse CD45 (a marker for hematopoietic cells) CD33 (myeloid cells) and CD19 (B cells), CD4 and CD8 (T cells). Human hematopoietic cells are hCD45+ and mCD45- from total live BM cells; CD33 and CD19 markers were analyzed from hCD45+gate; CD4 and CD8 were analyzed from the CD33-CD19- gate. 98B and 98C. % human CD45 and total number of hCD45 cells engrafted in BM; n= 4 for each cohort (XLA3, XLA3+LV 0.7UCOE.BTKp.BTKco2, XLA3 + LV 0.7UCOE.DHS4.BTKp.BTKco2, and healthy donor).

[0111] **Figure 99** shows Pre-clinical modeling XLA3: Spleen analysis 12 weeks post-transplant.

[0112] **Figure 100** shows Pre-clinical modeling XLA3: Spleen analysis 12 weeks post-transplant and results of mouse recipients of XLA3 HSC treated with gene therapy using 0.7UCOE.BTKp BTKco2 or 0.7UCOE.DHS4.BTKp.BTKco2.

[0113] **Figure 101** shows representative flow plot for B cell development subsets in spleen. A typical gating strategy for identifying human B cell developmental subsets is shown for each gene therapy cohort (listed at right). Markers used in each panel are shown at bottom (Hist = histogram); predecessor gates are shown at the top of each column if used.

[0114] **Figure 102** shows that recipients of LV transduced XLA3 HSC (using 0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4 BTKp.BTKco2) have an increased proportion of splenic immature B cells (including CD19+CD24+CD38+ B cells and CD19+CD24+CD38+IgM+ cells) compared to XLA controls. Graphs summarize the results from flow cytometry shown in Figure 4, looking at specific subpopulations of immature B cells. A,% of Immature B cells (CD24+ CD38+) in the spleen; B, % of immature B cells that are IgM+; C- D, Total number of immature B cells (CD24+ CD38+) and CD24+hCD38+ IgM+ cells in the spleen; E, overlay of CD10 histogram , showing the mean fluorescence intensity MFI shift in CD10 compared to healthy donor. n= 4 for each cohort; ***P = 0.0004; **P =0.0044; *P= 0.4 by one way ANOVA.

[0115] **Figure 103** shows that recipients of LV transduced XLA HSC (0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4 BTKp.BTKco2) have increased proportions of mature B cells ($CD19^{+}CD24^{low}CD38^{low}IgM^{+}$ and IgD^{+}) compared to XLA controls. 104A-C, % of mature B cells ($hCD24^{low}hCD38^{low}$) and the percent of mature B cells that are IgM^{+} and $IgM^{+}IgD^{+}$ in the spleen, respectively; 103D-F, Total number of splenic mature B cells and mature B cells that are IgM^{+} and $IgM^{+}IgD^{+}$, respectively; 103G, histogram overlay of CD10, showing similar MFI of CD10 as that of a healthy donor. N = 4 for each cohort; ***P= 0.0004; **P=0.0044; * P= 0.4 by one way ANOVA.

[0116] **Figure 104** shows a representative flow plot for B cell development subsets in the bone marrow.

[0117] **Figure 105** shows that recipients of LV transduced XLA HSC (using 0.7UCOE BTKp BTKco2 or DHS4 BTKpBTK.co2) exhibit an increased proportion of $CD19^{+}CD24^{+}CD38^{+}IgM^{+}$ immature B cells compared to XLA controls.

[0118] **Figure 106** shows that recipients of LV transduced XLA HSC (using LV 0.7UCOE BTKp BTKco2 or LV 0.7UCOE.DHS4 BTKp.BTK.co2) exhibit gene marking of 0.2-2 viral copy number (VCN)/cell *in vivo.*

[0119] **Figure 107** shows that recipients of XLA3 HSC that received gene therapy with LV 0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4.BTK.pBTKco2 produce B cells that secrete IgM *in vivo.*

[0120] **Figure 108** shows that recipients of XLA3 HSC transduced with LV 0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4.BTKp.BTKco2 exhibit a restored capacity for B cells to flux calcium in response to B cell receptor (BCR) engagement.

[0121] **Figure 109** shows the B cell differentiation protocol.

[0122] **Figure 110** shows a representative flow plot for *in vitro* B cell class switching.

[0123] **Figure 111** shows that recipients of LV transduced XLA HSC (using 0.7UCOE BTKp BTKco2 or DHS4 BTKpBTK.co2) generate B cells that are capable of responding to cytokine and T-cell dependent signals leading to antibody secretion.

Definitions

[0124] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

[0125] As used herein, "a" or "an" may mean one or more than one.

[0126] "About" as used herein when referring to a measurable value is meant to encompass variations of ±20% or ±10%, more preferably ±5%, even more preferably ±l%, and still more preferably ±0.1 % from the specified value.

[0127] **"**Polynucleotide," as described herein refers to "nucleic acid" or "nucleic acid molecule," such as deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), oligonucleotides, fragments generated by the polymerase chain reaction (PCR), and fragments generated by any of ligation, scission, endonuclease action, and exonuclease action. Nucleic acid molecules can be composed of monomers that are naturally-occurring nucleotides (such as DNA and RNA), or analogs of naturally-occurring nucleotides (e.g, enantiomeric forms of naturally-occurring nucleotides), or a combination of both. Modified nucleotides can have alterations in sugar moieties and/or in pyrimidine or purine base moieties. Sugar modifications include, for example, replacement of one or more hydroxyl groups with halogens, alkyl groups, amines, and azido groups, or sugars can be functionalized as ethers or esters. Moreover, the entire sugar moiety can be replaced with sterically and electronically similar structures, such as aza-sugars and carbocyclic sugar analogs. Examples of modifications in a base moiety include alkylated purines and pyrimidines, acylated purines or pyrimidines, or other well-known heterocyclic substitutes. Nucleic acid monomers can be linked by phosphodiester bonds or analogs of such linkages. Analogs of phosphodiester linkages include phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranilidate, phosphoramidate, and the like. The term "nucleic acid molecule" also includes so-called "peptide nucleic acids," which comprise naturally-occurring or modified nucleic acid bases attached to a polyamide backbone. Nucleic acids can be either single stranded or double stranded. In some alternatives, a nucleic acid sequence encoding a fusion protein is provided. In some alternatives, the nucleic acid is RNA or DNA.

[0128] Coding for" or "encoding" have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, the

property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other macromolecules such as a defined sequence of amino acids. Thus, a gene codes for a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system.

[0129] "Bruton's tyrosine kinase," (BTK) has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, an enzyme that in humans is encoded by the BTK gene. BTK is a kinase that plays a crucial role in B-cell development. For example, BTK plays a crucial role in B cell maturation as well as mast cell activation through the high-affinity IgE receptor. Mutations in the BTK gene are implicated in the primary immunodeficiency disease X-linked agammaglobulinemia (Bruton's agammaglobulinemia); sometimes abbreviated to XLA. Patients with XLA have normal pre-B cell populations in their bone marrow but these cells fail to mature and enter the circulation.

[0130] "X-linked agammaglobulinemia," (XLA) as described herein is a genetic disorder that affects the body's ability to fight infection. As the form of agammaglobulinemia that is X-linked, it is much more common in males. In people with XLA, the white blood cell formation process does not generate mature B cells, which manifests as a complete or near-complete lack of proteins called gamma globulins, including antibodies, in their bloodstream. X-linked agammaglobulinemia (XLA) is characterized by recurrent bacterial infections in affected males in the first two years of life. Recurrent otitis is the most common infection prior to diagnosis. Conjunctivitis, sinopulmonary infections, diarrhea, and skin infections are also frequently seen. Approximately 60% of individuals with XLA are recognized as having immunodeficiency when they develop a severe, life-threatening infection such as pneumonia, empyema, meningitis, sepsis, cellulitis, or septic arthritis.

[0131] A "promoter" is a region of DNA that initiates transcription of a specific gene. The promoters can be located near the transcription start site of a gene, on the same strand and upstream on the DNA (the 5'region of the sense strand). The promoter can be a conditional, inducible or a constitutive promoter. The promoter can be specific for bacterial, mammalian or insect cell protein expression. In some alternatives, wherein a nucleic acid encoding a fusion protein is provided, the nucleic acid further comprises a promoter

sequence. In some alternatives, the promoter is specific for mammalian protein expression. In some alternatives, the promoter is a conditional, inducible or a constitutive promoter.

[0132] "Ubiquitous chromatin opening elements (UCOE)" as described herein are regulatory elements that are derived from promoter-containing CpG islands of ubiquitously expressed housekeeping genes. It was proposed that regulatory elements from such promoters possess a chromatin-remodeling function allowing the maintenance of chromatin in a permissive configuration resulting in high and consistent expression of genes in their proximity. Although originally relatively large (up to 16 kb), new, smaller, synthetic UCOEs can lead to high expression of the transgene. Ubiquitous chromatin elements and their functions is described in **Figure 1.** In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0133] "Codon optimization" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, the design process of altering codons to codons known to increase maximum protein expression efficiency. In some alternatives, codon optimization for expression in human is preferred, wherein codon optimization can be performed by using algorithms that are known to those skilled in the art so as to create synthetic genetic transcripts optimized for high mRNA and protein yield in humans. Programs containing algorithms for codon optimization in humans are readily available. Such programs can include, for example, OptimumGene™ or GeneGPS® algorithms. Additionally human codon optimized sequences can be obtained commercially, for example, from Integrated DNA Technologies.

[0134] Optimization can also be performed to reduce the occurrence of secondary structure in a polynucleotide. In some alternatives of the method, optimization of the sequences in the vector can also be performed to reduce the total GC/AT ratio. Strict codon optimization can lead to unwanted secondary structure or an undesirably high GC content that leads to secondary structure. As such, the secondary structures affect transcriptional efficiency. Programs such as GeneOptimizer can be used after codon usage optimization, for secondary structure avoidance and GC content optimization. These additional programs can be used for further optimization and troubleshooting after an initial codon optimization to limit secondary structures that can occur after the first round of optimization. Alternative

programs for optimization are readily available. In some alternatives of the method, the vector comprises sequences that are optimized for secondary structure avoidance and/or the sequences are optimized to reduce the total GC/AT ratio and/or the sequences are optimized for expression in humans. In some alternatives herein, the gene encoding BTK is codon optimized. In some alternatives, the codon optimized BTK comprises a sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7.

[0135] "Enhancer elements," as described herein, are short regions of DNA that can be bound by proteins (activators) to increase the likelihood that transcription of a particular gene will occur. The activators can also be referred to as transcription factors. Enhancers can be either cis-acting, or Trans-acting (acting away from the gene) and can be located up to 1 Mbp (1,000,000 bp) away from the gene and can be upstream or downstream from the start site, and either in the forward or backward direction. The size of an enhancer can be of a size 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400 or 1500 bp or any number of base pairs in between a range defined by any two aforementioned values.

[0136] "Dnase I hypersensitive site" as described herein, is a region of chromatin that is sensitive to cleavage by the DNase I enzyme. In these specific regions of the genome, chromatin has lost its condensed structure, exposing the DNA and making it accessible. This raises the availability of DNA to degradation by enzymes, such as DNase I. These accessible chromatin zones are functionally related to transcriptional activity, since this remodeled state is necessary for the binding of proteins such as transcription factors. As described in the alternatives herein is "Dnase I hypersensitive site 4" (DHS4). DHS4 is an enhancer element that is located at -18 kb from a ϵ-globin promoter and can include binding sites for both erythroid specific and ubiquitous proteins and plays an important role as a regulatory element. In some alternatives herein, the vector for expression of BTK comprises at least one DNase Hypersensitive Site. In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5).

[0137] "Intron" as described herein, is any nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product. In some

alternatives of the vector herein, the vector comprises at least one intronic region. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter.

[0138] "Vector," "Expression vector" or "construct" is a nucleic acid used to introduce heterologous nucleic acids into a cell that has regulatory elements to provide expression of the heterologous nucleic acids in the cell. Vectors include but are not limited to plasmid, minicircles, yeast, and viral genomes. In some alternatives, the vector is a viral vector. In some alternatives, the viral vector is a lentiviral vector.

[0139] "B cells" as described herein are a type of white blood cell of the lymphocyte subtype. They are also known as B lymphocytes. B cells can function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells (APCs) and secrete cytokines. In some alternatives of the cells provided herein, the cells are B cells.

[0140] "Myeloid cells" has its plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a granulocyte or monocyte precursor cell in bone marrow or spinal cord, or a resemblance to those found in the bone marrow or spinal cord. The myeloid cell lineage includes circulating monocytic cells in the peripheral blood and the cell populations that they become following maturation, differentiation, and/or activation. These populations include non-terminally differentiated myeloid cells, myeloid derived suppressor cells, and differentiated macrophages. Differentiated macrophages include non-polarized and polarized macrophages, resting and activated macrophages. Without being limiting, the myeloid lineage can also include granulocytic precursors, polymorphonuclear derived suppressor cells, differentiated polymorphonuclear white blood cells, neutrophils, granulocytes, basophils, eosinophils, monocytes, macrophages, microglia, myeloid derived suppressor cells, dendritic cells and erythrocytes. For example, microglia can differentiate from myeloid progenitor cells. In some alternatives of the cells provided herein, the cells are myeloid cells.

[0141] "Hematopoietic stem cells" or "HSC" as described herein, are precursor cells that can give rise to myeloid cells such as, for example, macrophages, monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets,

dendritic cells and lymphoid lineages (such as, for example, T-cells, B-cells, NK-cells). HSCs have a heterogeneous population in which three classes of stem cells exist, which are distinguished by their ratio of lymphoid to myeloid progeny in the blood (L/M). In some alternatives of the cells provided herein, the cells are hematopoietic stem cells. "Subject" or "patient," have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, any organism upon which the alternatives described herein may be used or administered, e.g, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Subjects or patients include, for example, animals. In some alternatives, the subject is mice, rats, rabbits, non-human primates, and humans. In some alternatives, the subject is a cow, sheep, pig, horse, dog, cat, primate or a human. In some alternatives, the subject is a human male.

[0142] "Adoptive cellular therapy" or "adoptive cell transfer," as described herein refers to the transfer of cells, most commonly immune-derived cells, back into the same patient or into a new recipient host with the goal of transferring the immunologic functionality and characteristics into the new host. In some alternatives, adoptive cellular therapy or adoptive cell transfer comprises administering cells for expression of BTK to a subject in need.

DETAILED DESCRIPTION

[0143] BTK is expressed in both B cells and myeloid cells where it also contributes to normal functional responses in both lineages. Failure to express BTK leads to XLA. Conversely, overexpression of activated or wild type BTK can lead to cell transformation and/or developmental blockade ("Early arrest in B cell development in transgenic mice that express the E41K Bruton's tyrosine kinase mutant under the control of the CD19 promoter region" J Immunol. 1999 Jun 1;162(11):6526-33; "Correction of B-cell development in Btk-deficient mice using lentiviral vectors with codon-optimized human BTK." Leukemia. 2010 Sep;24(9):1617-30; incorporated by reference in their entireties herein) and dysregulated expression of wild-type BTK can promote autoantibody production and increase the risk for autoimmunity ("Enhanced Expression of Bruton's Tyrosine Kinase in B Cells Drives Systemic Autoimmunity by Disrupting T Cell Homeostasis." J Immunol.

2016 Jul 1;197(1):58-67; incorporated by reference in its entirety herein). Thus, safe and successful clinical gene therapy in XLA requires restoration of BTK expression in each cell lineage that normally expresses the protein as well as tightly regulated expression that does not lead to overexpression in developmental subsets that do not normally express the protein- and where expression might promote altered cell function. To address this challenge, candidate viral vectors in murine XLA animal models and novel human cell models using HSC derived from human subjects with XLA were comprehensively assessed, as described in the alternatives herein. Based upon iterative design and testing of candidate promoter, insulator, and enhancer elements and human codon-optimized BTK cDNA constructs, a novel lentiviral-based (LV) vector construct that mediates sustained BTK expression in B and myeloid cells derived from (murine or human) hematopoietic stem cells following *ex vivo* transduction and transplantation into BTK deficient hosts has been identified and is shown in the alternatives herein. The unique constructs of the alternatives herein, utilize a truncated UCOE element, a conserved enhancer element derived from intronic regions within the human BTK locus in association with the human BTK proximal promoter to drive expression of a human codon-optimized BTK cDNA. The optimal LV vectors of the one of the exemplary alternatives, is referred to as 0.7 UCOE.DHS4.BTKpro.coBTK. As part of the research described in the alternatives, a series of surprising and unpredicted results leading to this construct choice were identified, as shown: 1) the LV containing the BTK minimal promoter alone were not sufficient to restore B cell development or function as shown in several alternatives; 2) the LV utilizing the Eμ enhancer element (with either a B lineage restricted promoter or the BTK minimal promoter) lead to development of high titer autoantibodies including pathogenic class-switched IgG isotypes indicating that this enhancer created significant safety concerns as shown in several alternatives; 3) silencing of LV vector expression for multiple candidate LV platforms in secondary recipient animals was observed which led to utilization of a UCOE element to resist such silencing; 4) low titers with use of a large UCOE element was observed and therefore led to designing and testing of a novel truncated 0.7kb element that would lead to improved titer and function and retained resistance to silencing; 5) bioinformatic tools were utilized to identify and test multiple potential candidate enhancer elements derived from the BTK locus and after significant analysis this was used to identify an optimal element, DHS4, that lead to increased BTK

expression *in vivo* without reducing viral titer; 6) alternative human codon-optimized BTK cDNAs were tested and led to an identified construct that best restores BTK expression; 7) HSC was collected from multiple adult subjects with XLA and it was shown that when transplanted into immune deficient NSG mice these stem cells recapitulate the B cell developmental defects seen in XLA subjects and 8) in several alternatives herein, it was shown that XLA HSC can be efficiently transduced using the alternative optimized LV constructs described herein.

[0144] X-linked agammaglobulinemia (XLA) is a hereditary X-linked immunodeficiency disorder caused by a mutation in the BTK gene (Bruton's Tyrosine Kinase). This disease affects approximately 1 in 100,000 males. The clinical manifestations can include: lack mature B cells and serum immunoglobulins, susceptibility to lung, sinus, and skin infections with encapsulated bacteria, risks for sudden death due to bacteria sepsis, chronic and systemic infections with enteroviruses, chronic inflammatory bowel disease and increased risk for malignancy such as colon and other types of cancer.

[0145] The current treatment options for XLA can include lifelong pooled human immunoglobulin (IVIg or SCIg) every 3-4 weeks. However these treatments are expensive and the current treatments can also lead to risk for infection and sudden death.

[0146] The candidates for gene therapy can include those with single gene hematopoietic disorder.

[0147] Bruton's Tyrosine Kinase (BTK) is a cytoplasmic non-receptor protein tyrosine kinase whose main role is in B cell receptor signaling pathway. BTK promotes B cell survival, proliferation and differentiation. BTK can maintain sustained calcium signal following BCR (B cell receptor) engagement and promotes NFKB activation. Furthermore, BTK also plays role in cytokine, growth factor, and TLR signaling pathways. A role for BTK is shown in **Figure 21**, where BTK leads to the development of the B cells. As shown, XLA leads to a block at the Pre-B cell stage. BTK is expressed in B and myeloid lineages, and not expressed in T cells. The expression profile of endogenous BTK is shown in **Figure 16**.

[0148] No other investigators have described use of the BTK promoter or any of the additional modifications of the alternatives herein, in association with the BTK in LV vectors. While the BTK promoter and the BTK first intron have been partially evaluated in previous studies of promoter function, no group has described or tested candidate enhancer

elements derived from the human BTK locus including the DHS4 element or others ("Analysis of the Bruton's tyrosine kinase gene promoter reveals critical PU.1 and SP1 sites." Blood. 1996 Feb 1;87(3):1036-44; "Cell specific expression of human Bruton's agammaglobulinemia tyrosine kinase gene (Btk) is regulated by Sp1- and Spi-1/PU.1-family members." Oncogene. 1996 Nov 7;13(9):1955-64; "Large-scale comparative sequence analysis of the human and murine Bruton's tyrosine kinase loci reveals conserved regulatory domains." Genome Res. 1997 Apr;7(4):315-29.; "Synergistic activation of the human Btk promoter by transcription factors Sp1/3 and PU.1." Biochem Biophys Res Commun. 1999 Jun 7;259(2):364-9; "Btk expression is controlled by Oct and BOB.1/OBF.1." Nucleic Acids Res. 2006 Mar 31;34(6):1807-15; "Proteasome-dependent autoregulation of Bruton tyrosine kinase (Btk) promoter via NF-kappaB." Blood. 2008 May 1;111(9):4617-26.; all references hereby expressly incorporated by reference in their entireties).

[0149] An independently derived codon-optimized BTK cDNA has been identified ("Correction of B-cell development in Btk-deficient mice using lentiviral vectors with codon-optimized human BTK." Leukemia. 2010 Sep;24(9):1617-30' incorporated by reference in its entirety). Other investigators have studied the use of UCOE element alone or in association with a lineage specific or ubiquitous promoter in LV vectors but none have applied this technology to BTK ("Lentiviral vectors containing an enhancer-less ubiquitously acting chromatin opening element (UCOE) provide highly reproducible and stable transgene expression in hematopoietic cells." Blood. 2007 Sep 1;110(5):1448-57.; "A ubiquitous chromatin opening element (UCOE) confers resistance to DNA methylation-mediated silencing of lentiviral vectors." Mol Ther. 2010 Sep;18(9):1640-9; "Physiological regulation of transgene expression by a lentiviral vector containing the A2UCOE linked to a myeloid promoter." Gene Ther. 2012 Oct;19(10):1018-29; "Correction of murine Rag2 severe combined immunodeficiency by lentiviral gene therapy using a codon-optimized RAG2 therapeutic transgene." Mol Ther. 2012 Oct;20(10):1968-80; "Promoter and lineage independent anti-silencing activity of the A2 ubiquitous chromatin opening element for optimized human pluripotent stem cell-based gene therapy." Biomaterials. 2014 Feb;35(5):1531-42.; "A ubiquitous chromatin opening element prevents transgene silencing in pluripotent stem cells and their differentiated progeny." Stem Cells. 2013 Mar;31(3):488-99; "Lentiviral MGMT(P140K)-mediated in vivo selection employing a ubiquitous

chromatin opening element (A2UCOE) linked to a cellular promoter." Biomaterials. 2014 Aug;35(25):7204-13; "Detailed comparison of retroviral vectors and promoter configurations for stable and high transgene expression in human induced pluripotent stem cells." Gene Ther. 2017 Mar 27; all references hereby expressly incorporated by reference in their entireties herein).

[0150] The optimized lentiviral vectors, as described in the alternatives herein, will be used in gene therapy for subjects with X-linked agammaglobulinemia (XLA) designed to lead to long-term curative therapy for this disease. Shown in **Figure 22** is an exemplary alternative in the development of the optimal BTK lentiviral gene therapy vector. This alternative would lead to a safe viral delivery platform and the expression of desired lineages with optimal levels of protein expression.

[0151] In some alternatives, the optimized BTK lentiviral vector comprises a ubiquitous chromatin opening element (UCOE). The UCOE can provide stable expression of transgenes regardless of integration site and can also confer resistance to silencing in an adjacent promoter (see **Figure 1).**

[0152] The optimized LV vectors for BTK expression were also shown to increase BTK expression in cells. A few exemplary vectors that were used in several alternatives are shown in **Figure 23.** As shown in **Figure 24,** the lentiviral vectors comprising Eμ*BTK*p promoters also had an increase of BTK in myeloid cells.

[0153] Cells transduced with DKO mock, BTKp, UCOE.*BTK*p and Eμ.*BTK*p were tested for BTK expression. As shown in the FACS assay, incorporation of Eμ into the LV vector for BTK expression was also shown to boost BTK expression the most in both B cells and myeloid cells as compared to the *BTK*p promoter alone and with the UCOE elements. (**Figure 25).** The results of the BTK expression in the transduced cells are comparable to the wild type cells that express the BTK naturally as shown in **Figure 26**, which shows the comparison between a knock out cell and wild type cell in both B cells and monocytes.

[0154] It is contemplated that this LV vector will lead to curative therapy, in particular XLA gene therapy.

[0155] In the alternatives described herein, the gene delivery platform was specialized for XLA therapy. This would allow restoration of endogenous BTK expression in

B cells and myeloid cells, and rescue of immunological responses in those suffering from XLA. The vector safety profile was further evaluated. Previously investigated lentiviral vectors for XLA included those with promoter and transcription elements such as the BTK minimal promoter, the Ig heavy chain μ intronic enhancer, as well as the 1.5 kb ubiquitous chromatin opening element. However, as shown in the alternatives herein, there were further modifications needed in order to improve the BTK expression in B and myeloid cells.

Optimization of the gene delivery platform for XLA

[0156] In order to improve the lentiviral vector for gene therapy, several steps were taken, as shown in the alternatives herein: 1) improvement of viral titer by decreasing the size of the UCOE element to 0.7 kb; 2) identifying transcriptional elements within the endogenous human *BTK* that would improve expression in B and myeloid cells and test the expression with conserved non-coding sequences (CNS) that are included upstream from the *BTK* promoter (**Figure 1**). The lentiviral vectors tested in the pre-clinical models in the alternatives described herein include 0.7 UCOE.BTKp.BTK and 0.7 UCOE.I-4,5.BTKp.BTK. (see **Figure 2**). As shown in **Figure 3**, blood was taken from XLA mice, in which Lin negative cells were harvested. The cells were then transduced with LC-huBTK-LV. The cells were then administered to the XLA mice, which were analyzed at 20-25 weeks post cell transfer. The BTK expression was analyzed by flow cytometry. A secondary cellular transfer was also performed for long term repopulation of the stem cells (See **Figure 3**). A schematic showing the preclinical murine model for XLA gene therapy is shown in **Figure 3.**

[0157] Both vectors (.7UCOE and 0.7UCOE-I4,5) expressing human BTK, restored BTK expression to affected hematopoietic cells, rescued B cell development and function and restored immune responses (**Figures 4-7**). However it was shown that 0.7UCOE.I-45.BTIpBTK expressed BTK as effectively as 0.7UCOE.BTKp.BTK, but with fewer viral integrations (**Figure 8**). Thus several conclusions were drawn.

[0158] The LV vector that included conserved BTK regulatory elements (derived from *BTK* introns 4 and 5) in association with the endogenous BTK improves BTK

expression per viral integration. Also 0.7UCOE.I4,5.BTKpBTK LV comprises an efficient candidate for XLA gene therapy.

[0159] For expanded pre-clinical studies the following are performed: a) murine modeling to fully evaluate toxicity, safety and efficacy (including use of secondary transplantation and integration site analysis); b) *in-vitro* immortalization and transactivation assays; c) refine genetic elements within introns 4 and 5 for improving BTK expression in B and myeloid cells; and d) evaluation of 0.7UCOE.I-4,5.BTKp.BTK in healthy control and XLA subject CD34+ stem cells *in vitro* and in NSG recipient mice.

Improved safety and efficacy of lentiviral gene therapy in a murine XLA model using a UCOE-insulated BTK promoter

[0160] Experiments were performed in order to optimize the safety and efficacy of a lentiviral gene therapy in mice using a UCOE insulated BTK promoter. For the experiments several vector constructs were used: WT Mock, KO Mock, BTKp, 1.5.UCOE.BTKp, and Eμ.BTKp.

[0161] Shown in **Figure 9** are the expression profiles of four LV constructs and rescue of B cell development and function in primary recipient mice. The vectors used were BTKpro.BTK, 1.5UCOE.BTKpro.BTK, 1.5UCOE.BTKpro.coBTK (human codon optimized BTK) and Eμ.BTKpro.BTK. The vector, the Eμ.BTKp.hBTK was shown to increase BTK expression in all cells as shown in **Figure 9.** The vector, the Eμ.BTKp.hBTK was also shown to increase IgG expression in all cells as shown in **Figure 10**. Increased BTK expression was also seen for the vector Eμ.BTKp.hBTK in granulocytes, bone marrow and spleen B cells as seen in **Figure 11**. The 1.5kbUCOE.BTKp and 1.5kbUCOE.BTKp.co vectors were shown to lead to sustained BTK expression with lower copy numbers in primary and secondary recipients (**Figure 11).**

[0162] Restoration of BTK expression was shown in affected hematopoietic lineages and B cell development in gene therapy mice treated with 0.7kb UCOE.BTKpro.coBTK LV (**Figure 12**).

[0163] Proliferation of B cells, increase of IgM and IgG secretion were also seen in cells following 0.7.UCOE.BTK.co LV gene therapy in primary recipients (**Figure 12**).

[0164] Reconstitution of B cell function was also seen following 0.7.UCOE.Bkp.co LV gene therapy in primary recipients (**Figure 13**).

[0165] VCN and BTK expression are maintained after serial passage of gene therapy-treated bone marrow cells into secondary $TBK^{-/-}$ recipients (**Figure 14**). As shown, cells transduced with the 0.7UCOE.BTKp.co led to expression of BTK in the neutrophils, monocytes, B cells of the bone marrow and the spleen. Methylation of DNA was also measured, which is a modification for suppressing gene transcription.

[0166] The vector 0.7UCOE.BTKp.co was shown to lead to sustained BTK expression and lower copy numbers in XLA CD34 cells (**Figure 15**). XLA and control CD34 cells were transduced with 0.7UCOE.BTKp.co at various multiplicities of infection (MOI) and cultured in vitro for 15 days. As shown, the XLA transduced cells had similar viability as the healthy control cells.

[0167] The BTK promoter in the lentiviral vectors were also used to evaluate BTK expression in wild type mice. As shown, the BTK promoter mimics BTK's endogenous expression pattern in mice (**Figure 16**).

[0168] The Eμ promoter was then tested for expression enhancement in the lentiviral vectors. Two vectors were tested, which had the Eμ promoter as shown in **Figure 17** panel a (Eμ enhancer and human BTK cDNA, either wild type or human codon-optimized, with a T2A-linked GFP). Chicken BTK-/- DT40 cells were transduced with BTK-GFP or coBTK-GFP constructs; histograms show GFP and BTK expression (**Figure 17** panel b). BTK-GFP and coBTK-GFP transduced cells were stained with an Indo-1 Ester AM fluorescent dye and stimulated with anti-IgM; calcium mobilization was monitored via flow cytometry. As shown, lentiviral constructs under control of the BTK promoter with Eμ enhancer and human BTK cDNA led to controlled expression of the BTK-GFP in the chicken cells.

[0169] Representative plots of BTK expression after flow cytometry of peripheral blood B cells and myeloid cells from gene therapy-treated KO mice was also performed (**Figure 18**). The vectors tested were: WT Mock, KO Mock, BTKp, 1.5kb.UCOE.BTKp, 1.5kb.UCOE.BTKp.co, and Eμ.BTKp. Shown in **Figure 18** panel c are the representative flow cytometry plots from bone marrow of gene therapy treated mice, stained with markers for early B cell development. **Figure 18** panel d shows graphs that depict the percentage of B cells following Hardy fractions of decreasing maturity: Fr I (IgMlo, IgDhi), Fr II (IgMhi, IgDhi), FrIII (IgMhi, IgDlo), each ring represents one mouse and the mean percent of B cells

in each fraction is shown inside the graphic. Data represent mean ± SEM from 11 independent experiments, n = 18 (WT Mock), 14 (KO Mock), 7 (BTKp), 43 (1.5 kb.UCOE.BTKp), 18 (1.5kb.UCOE.BTKp.co), 23 (Eμ.BTKp). As shown, the vector with the Eμ enhancer led to the higher expression of BTK in both the B cells and the myeloid cells as well as an increase in IgG secretion.

[0170] As shown in **Figure 19,** Eμ.BTKp primary transplant mice also had increased survival as compared to the control XLA mice treated with cells that were transduced with the mock vectors.

[0171] Sera from the mice treated with the cells transduced with the WT Mock, 1.5kb.UCOE.BTKp and Eμ.BTKp vectors were analyzed by autoantigen array for levels of IgM and IgG reactive to 88 murine antigens. Data from each row was subject to z-transformation and Z-scores are displayed on a colorimetric scale from lowest reactivity (red) to highest (blue). As shown in **Figure 20**, the sera with the most reactivity were from the cells transduced with lentiviral vectors that had the Eμ promoter (Eμ.BTKp.)

Designing vectors for increasing BTK expression in B cells and monocytes

[0172] B cell specific promoters were also examined for their influence on BTK production. In an exemplary alternative, a lentivector was manufactured, which comprised the Eμ enhancer element and a B cell specific promoter, B29, fused to a gene encoding human BTK (huBTK) (**Figure 27).** As shown, the vector led to an increase of BTK expression in B cells; however, the BTK expression in the monocyte was comparable to the knockout cells (**Figure 27**).

[0173] The BTK promoter region was also examined in another alternative, to evaluate the influence of the BTK promoter in a lentiviral vector for BTK expression. As shown in **Figure 28,** a lentiviral vector was manufactured, which comprised the BTK promoter (BTKpro) fused to the gene encoding human BTK (huBTK). As shown, the BTK promoter led to increased BTK expression in B cells. However, BTK expression was not comparable to the expression in wild type cells. In the monocytes, the lentiviral vector comprising the BTK promoter region was unable to lead to increased expression of BTK and the expression of BTK was comparable to the knock out cells.

[0174] A lentiviral vector was manufactured, which comprised a ubiquitous chromatin opening element and a BTK promoter (BTKpro) fused to a gene encoding human BTK (**Figure 29).** As shown, the enhancer element along with the promoter led to increase of BTK expression in both B cells, as well as, monocytes. However, the expression was not comparable to the expression in the wild type cells.

[0175] A lentiviral vector was manufactured, which comprised a Eμ enhancer and a BTK promoter (BTKpro) fused to a gene encoding human BTK (**Figure 30).** As shown, the enhancer element along with the promoter led to increase of BTK expression in both B cells and monocytes. The results show that the expression BTK in the transduced cells exceeded the amounts of BTK in the wild type cells. The data shows that the Eμ enhancer led to the most BTK expression of the vectors that were tested.

[0176] Provided below are exemplary constructs used herein:

1. 0.7UCOE.BTKp.coBTK.
2. 0.7UCOEfwd.BTKp.coBTK
3. 0.7UCOE.DHS4.BTKp.coBTK
4. 0.7UCOEfwd.DHS4.BTKp.coBTK
5. 0.7UCOE.IE.BTKp.coBTK
6. 0.7UCOEfwd.IE.BTKp.coBTK
7. 0.7UCOE.BTKp.co2BTK
8. 0.7UCOEfwd.BTKp.co2BTK
9. 0.7UCOE.DHS4.BTKp.co2BTK
10. 0.7UCOEfwd.DHS4.BTKp.co2BTK
11. 0.7UCOE.IE.BTKp.co2BTK
12. 0.7UCOEfwd.IE.BTKp.co2BTK

Generally, these constructs represent various iterations of 3 different elements (0.7UCOE, Enhancer, or BTK coding sequence, all having the same BTK promoter):

0.7UCOE:		ENHANCER:			PROMOTER	BTK human codon optimization:	
0.7UCOE	0.7UCOEfwd	none	DHS4	IE	BTKp	coBTK	co2BTK

Human Codon optimized BTK

[0177] Human codon optimization of the gene encoding BTK was performed. Human codon optimization can be performed by using algorithms that are known to those skilled in the art so as to create synthetic genetic transcripts optimized for high mRNA and protein yield in humans. As shown in **Figure 17,** two constructs were tested for their ability to lead to increased BTK expression in cells. The lentiviral constructs comprised the Eμ

element and the BTK promoter region. The genes for expression were BTK and a human codon optimized BTK, both fused to GFP gene transcripts. As shown in **Figure 17,** human codon optimized BTK led to an increase in GFP (MFI 2288), as well as, an increase in GFP.

Expression profiles of the BTK lentiviral vector

[0178] The expression profile of several vectors were examined: WT mock, DKO mock, *BTK*p (BTK promoter), UCOE. *BTK*p (ubiquitous chromatin opening element plus BTK promoter), UCOE.*BTK*p.co (ubiquitous chromatin opening element, BTK promoter plus human codon optimized BTK) and Eμ.*BTK*p (Eμ element plus BTK promoter). As shown in **Figure 31** and **32**, the lentiviral vector for BTK expression with the Eμ element and BTK promoter led to the highest expression of BTK in bone marrow, spleen and peritoneum from the B cells and the myeloid cells.

B cell development and restoration of mature B cell subsets

[0179] The restoration of mature B cell subsets were also examined in the cells transduced with the vectors: WT mock, DKO mock, *BTK*p (BTK promoter), UCOE. *BTK*p (ubiquitous chromatin opening element plus BTK promoter), UCOE.*BTK*p.co (ubiquitous chromatin opening element, BTK promoter plus codon optimized BTK) and Eμ.*BTK*p (Eμ element plus BTK promoter). In XLA, development stops at the pre B cell. Accordingly, the cells were examined for further development, in which development of the B cell is dependent on the levels of BTK. As shown, the lentivector comprising the Eμ element plus BTK promoter for BTK expression led to cells that were of the mature peripheral B cell population, indicating that the levels of BTK produced from the transduced cell would lead to restoration of mature B cell subsets in the mice (**Figure 33**).

[0180] The numerical reconstitution of B cell populations were also examined in BTK deficient mice that were administered cells expressing BTK. The cells were transduced with the following vectors: WT mock, DKO mock, *BTK*p (BTK promoter), UCOE. *BTK*p (ubiquitous chromatin opening element plus BTK promoter), UCOE.*BTK*p.co (ubiquitous chromatin opening element, BTK promoter plus human codon optimized BTK) and Eμ.*BTK*p (Eμ element plus BTK promoter). Shown in **Figure 34** are the data that summarize the finding from 40 recipient mice that received the transduced cells for BTK expression. Mice that received the cells that were transduced with the BTK expression vector comprising

UCOE.*BTK*p.co , Eμ.*BTK*p or UCOE. *BTK*p were able to develop mature B cells in the bone marrow, spleen and peritoneum. Accordingly, aspects of the invention concern a lentiviral vector that comprises ubiquitous chromatin opening element, BTK promoter, and human codon optimized BTK, which can be used in methods to promote mature B cell development in subjects suffering from XLA.

[0181] B cell proliferation was also shown in mice that were treated with cells transduced with the lentiviral vectors that comprised the ubiquitous chromatin opening element and BTK promoter (UCOE.*BTK*p) and a lentiviral vector that comprise the Eμ element fused to the BTK promoter region (Eμ.*BTK*p) (**Figure 35)**. Controls include the WT mock as well as the DKO mock cells. Fluorescence activated cell sorting was performed on the cells using anti-IgM antibodies. As shown, the cells with expressing BTK from the two lentiviral vectors UCOE.*BTK*p and Eμ.*BTK*p had expression of IgM, which is a basic antibody produced by B cells.

[0182] The cells were also treated with PMA and lonomycin. PMA is used for activating PKC, while lonomycin, is used to trigger calcium release, which is needed for NFAT signaling (**Figure 35)**.

[0183] As shown in **Figure 36,** the cells that were transduced with the two lentiviral vectors UCOE.*BTK*p and Eμ.*BTK*p had an increase in cell division as compared to the wild type, when treated with anti-IgM and PMA/Ionomycin. Additionally, these cells were also shown to have an increase in total IgM and IgG secretion as compared to the vectors that had only the BTK promoter and the BTK promoter with the UCOE element (**Figure 37)**.

T cell dependent immune responses

[0184] The transduced cells were administered to mice and further tested for T cell dependent immune responses. The cells were transduced with the following lentiviral vectors: WT mock, DKO, DKO mock, *BTK*p, UCOE.*BTK*p, and UCOE.BTKp.co (human codon optimized BTK), Eμ.*BTK*p.co (human codon optimized BTK), and Eμ.*BTK*p. T cell immune responses were then evaluated. As shown, the cells transduced with Eμ.*BTK*p lentiviral vectors led to increased IgG and IgM expression (**Figure 38 -41**).

[0185] The antibody levels were also associated with BTK expression, as well as, survival of the mice. As shown in **Figure 42,** mice that were administered cells transduced with Eμ.*BTK*p lentiviral vectors led to increased mouse survival, as compared to the mice that were administered the DKO mock cells.

[0186] BTK expression was also evaluated in neutrophils and secondary recipient mice. As shown in **Figure 43,** administered cells transduced with Eμ.*BTK*p lentiviral vectors led to increased BTK expression in secondary recipient mice. However, there was increased viral copy number in secondary recipients in mice that were administered the viral vector *BTK*p (**Figure 44).** Evaluation of the lentiviral therapy on long term survival provided evidence that the vectors UCOE.*BTK*p.co, UCOE.*BTK*p and Eμ.*BTK*p led to increased mouse survival.

[0187] Overall the BTK promoter studies demonstrated that the BTK promoters in the lentiviral vectors exhibit significant BTK expression in B and myeloid cells. UCOE.BTKpro and Eμ.BTKpro rescue B cell development, absolute B cell numbers, B cell proliferation, and immune responses. Myeloid expression is also rescued with UCOE.BTKpro and Eμ.BTKpro. Unexpectedly, Eμ-containing vectors lead to high-titer autoantibody production, thus, making them potentially unsafe for clinical use. UCOE-Btkp-Btk vectors exhibit functional rescue at much lower viral copy number compared with non-UCOE vectors. UCOE-Btkp-Btk vectors exhibit sustained marking in both murine and human HSC. Thus, the UCOE.BTKp-coBTK lentiviral vector represents an improved and unique clinical vector platform for additional modification.

Alternative enhancer elements

[0188] Alternative enhancer elements within the BTK promoter were evaluated for their abilities to improve BTK expression in cells. The lentiviral constructs used are shown in **Figure 46.** As shown, the 1.5kb UCOE gave improvement over the BTK promoter in B cells. However, additional improvement was sought for decreasing the large vector size and the low viral titers (**Figure 46).**

[0189] The 1.5 kb UCOE was truncated to 0.7UCOE to create the lentiviral vector 0.7UCOE.*BTK*p (**Figure 2).** Potential human BTK enhancer elements were also added

to create 0.7UCOE.IE.*BTK*p as shown in **Figure 2.** The intronic regions included intron 4 and 5 from a human BTK locus that is in association with a human BTK proximal promoter.

[0190] The 0.7UCOE.*BTK*p and 0.7UCOE.IE.*BTK*p were transduced into cells and the methods outlined in **Figure 3** were used for administering the cells into the mouse. As shown in **Figure 47,** the cells transduced with 0.7UCOE.*BTK*p and 0.7UCOE.IE.*BTK*p rescue BTK expression and splenic B cell counts. The cells were also shown to rescue B cell function (**Figure 48).**

[0191] The cells transduced with 0.7UCOE.IE exhibited an improved safety profile over 0.7UCOE, as well (see **Figure 49).** As shown, 0.7UCOE and 0.7UCOE.IE both produce low autoantibody titers compared to autoimmune controls (and previous non-Btk promoter vectors, while 0.7UCOE.IE exhibits similar efficacy with few viral integrations per cell.

Testing of BTK constructs comprising DNase Hypersensitive sites

[0192] Lentiviral constructs for expression of BTK were designed with DNase Hypersensitive sites (**Figure 50)**. The vectors were the following: 0.7UCOE.*BTK*p.coBTK (0.7 UCOE enhancer, BTK promoter, and human codon optimized BTK) and 0.7UCOE.IE4,5,.*BTK*p.coBTK (0.7UCOE element, intron 4 and 5 of the human BTK locus that is in association with the human BTK proximal promoter, BTK promoter and the human codon optimized BTK).

[0193] The DNAse hypersensitivity sites were identified as shown in **Figure 51.**

[0194] Base on the identification of the introns and the DNAse hypersensitivity sites, constructs with candidate introns and DNAse hypersensitive sites were constructed (**Figure 52).** Constructs were the following: 0.7UCOE.BTKp.coBTK, 0.7UCOE.IE.BTKp.coBTK, 0.7UCOE.DHS4.BTKp.coBTK, 0.7UCOE.DHS1,2.BTKp.coBTK, 0.7UCOE.DHS1,2,4.BTKp.coBTK, and 0.7UCOE.**DHS1-5**.BTKp.coBTK.

[0195] *In vivo* comparisons of the DHS constructs to the 0.7UCOE and 0.7UCOE.IE vectors were performed. In an experimental set up, 40ul virus per $1x10^6$ cells (optimized for matched viral count numbers (VCN) for an overnight transduction. This was followed by RO injection of $1x10^6$ cells/condition into TBKBP mice (900 rads irradiation

prior to transplant). As shown, the cells that were transduced with the 0.7UCOE.BTKp.coBTK led to higher expression of BTK with higher VCN (**Figure 53).**

[0196] After 15 weeks post-transplant, B cell development was evaluated and a peripheral blood lymphocyte distribution was examined. As shown in **Figure 54,** the cells transduced with the vectors led to an increase of B cells over the KO mock cells with 0.7UCOE lentivector showing an increase in B cells. However, higher levels of BTK reconstitution in lymphocyte subsets was seen with cells transduced with the lentiviral vector comprising the 0.7UCOE elements.

[0197] Experiments were performed to compare the lentiviral constructs, which had the UCOE and intronic elements to the new DHS constructs. The volumes were matched for 40uL virus/million cells. As shown in **Figure 55,** the input VCN was increased in the cells transduced with the lentiviral vector comprising the 0.7UCOE element, as compared to the vectors comprising the DHS elements. There was also no significant difference in BTK expression between UCOE and DHS4 in these experiments; however the BTK/VCN of DHS4 was significantly higher than UCOE in spleen (**Figure 56)**.

[0198] In another alternative, BTK expression *in vivo* was examined using the following vectors: 0.7UCOE.BTKp.coBTK, 0.7UCOE.DHS4.BTKp.coBTK and 0.7UCOE.DHS1-5.BTKp.coBTK. For the experiment, Lin-cells were harvested from TBK donor mice. For the transduction: a matched volume was achieved by10ul virus/million cells (target: matched input VCN of ~3, as predicted by in vitro test) followed by a 16 hour transduction, $4x10e^6$ cells/ml in SCGM transduction media (mSCF, mTPO) + polybrene. The cells were then transplanted in which $1.5x10e^6$ cells were administered per mouse (recipients: TBK, 900 rads irradiation) (**Figure 57)**. As shown in **Figure 57,** cells transduced with the 0.6UCOE construct had a higher VCN; however the levels of BTK expression were similar to the lentiviral construct comprising the DHS4 element. Additionally, analysis of the peripheral blood lymphocyte distribution at 12 weeks showed that cell transduced with the lentiviral vectors 0.7UCOE, 0.7UCOE.DHS4 and 0.7UCOE.DHS1-4 had an increase in B cells indicating that the lentiviral vectors allowed expression of BTK thus leading to mature B cell development in the mice (**Figure 58)**. The 6 week peripheral blood lymphocyte distribution is shown in **Figure 59.** As shown, the cells expressing BTK from 0.7UCOE, 0.7UCOE.DHS4 and 0.7UCOE.DHS1-4 had an increase in B cell production (**Figure 59).**

Additionally, BTK expression was shown in the B cells, monocytes and neutrophils at the evaluation at 6 weeks and 12 weeks in mice that were administered the cells comprising the 0.7UCOE, 0.7UCOE.DHS4 and 0.7UCOE.DHS1-4 lentiviral vectors (**Figure 60).** At the 12 week bleed experiments, BTK was shown to be expressed across all the subsets (**Figure 61**).

Testing alternative Human Codon Optimized BTK Constructs

[0199] Experiments were performed to examine the effect of human codon optimized BTK constructs on cellular expression of BTK. Human codon optimized BTK is described in Ng *et al.* ("Correction of B cell development in Btk-deficient mice using lentiviral vectors with codon-optimized human BTK." Leukemia. 2010 Sep;24(9):1617-30; incorporated by reference in its entirety).

[0200] The objective of the following experiments was to compare the BTK expression/staining of two different versions of human codon optimized BTK. The set-up included: Isolated Lin- cells from TBK mice, Transduction media: complete SCGM + mSCF + mTPO + polybrene, addition of 5, 10, or 20ul virus to 1x106 cells (4x106 cells/ml), 7-day *in vitro* culture, then BTK stain and VCN at Day 7. The lentiviral constructs were: 0.7UCOE.BTKp.coBTK (Titer: $1.17E^{+09}$), 0.7UCOE.DHS4.BTKp.coBTK (Titer: $1.09E^{+09}$), 0.7UCOE.BTKp.newcoBTK (Titer: $1.81E^{+08}$), and 0.7UCOE.DHS4.BTKp.newcoBTK (Titer: $1.13E^{+08}$) (**Figure 62)**.

[0201] As shown in **Figure 63,** BTK expression was increased in the cells transduced with the 0.7COE.newcoBTK and the DHS4.newcoBTK at 5, 10 and 20 uL of virus additions. Increased MFI was also shown for the cells that were transduced with .7COE.newcoBTK and the DHS4.newcoBTK at 5, 10 and 20 uL of virus additions (**Figure 64).** The optimal viral copy number/cell was shown in cells that were transduced with 10uL additions of both .7COE.newcoBTK and the DHS4.newcoBTK lentiviral vectors (**Figure 64).**

[0202] *In vivo* comparison of original vs new human codon optimized BTK is also contemplated. The experimental groups include: 0.7UCOE.BTKp.coBTK (Titer: $1.17E^{+09}$) (5 mice), 0.7UCOE.DHS4.BTKp.coBTK (Titer: $1.09E^{+09}$) (5 mice), 0.7UCOE.BTKp.newcoBTK (Titer: $1.81E+^{+08}$) (5 mice), 0.7UCOE.DHS4.BTKp.newcoBTK (Titer: $1.13E^{+08}$) (5 mice), KO Mock (3 mice), WT Mock (5 mice) and Unirradiated controls

(1 mouse). Transduction set-up includes: Volume match with 10ul/million cells (for consistency with current *in vivo* experiments) **(Figure71)**.

Testing alternative orientations with the UCOE elements in the lentiviral vector

[0203] Experiments were performed to examine the effect of UCOE element orientation on cellular expression of BTK **(Figure 66)**. Constructs were manufactured as shown in **Figure 67,** to evaluate whether the orientation of the UCOE would affect the expression of BTK.

[0204] For the experiments, 4 lentiviral vectors were tested: KO mock, 0.7UCOE.BTKp ($7.52E^{+07}$), 0.7UCOEfwd.BTKp col4 ($6.79E^{+08}$), 0.7UCOEfwd.BTKp col6 ($1.79E^{+09}$), and WT mock. As shown in **Figure 68,** the levels of BTK between the lentiviral vectors 0.7UCOE.BTKp ($7.52E^{+07}$), 0.7UCOEfwd.BTKp col4 ($6.79E^{+08}$), 0.7UCOEfwd.BTKp col6 ($1.79E^{+09}$) were similar, however VCN was increased at increased volume of virus.

[0205] As shown from the experiments, the BTK promoter is a robust promoter. In regards to the UCOE elements, 0.7kb UCOE effectively prevents silencing of BTK expression and leads to increased vector titer. Furthermore, placing the UCOE in the forward orientation increases titer significantly, but does not alter BTK expression. This indicates that the reverse UCOE orientation performs equivalent to high titer constructs. In regards to enhancer elements, it was shown that 0.7UCOE.IE.Btkp exhibits rescue of BTK expression function with fewer viral integrations compared to 0.7UCOE.Btkp and the addition of smaller enhancer elements (DHS sites) has not increased titer compared to larger IE construct.

[0206] UCOE in the forward orientation increases IE titer by >1 log indicating that the forward orientation of the UCOE will increase titer in all constructs.

[0207] For example, it was shown that 0.7UCOE.DHS4.Btkp exhibits increased BTK expression in B and myeloid cells as compared to 0.7UCOE.IE.Btkpro indicating that 0.7UCOE.DHS4.Btkp vector is a particularly robust vector.

[0208] In regards to the human codon optimized BTK, the new construct leads to a significant increase in BTK expression as compared to the previous co-Btk construct.

Testing IgG, IgM and NP specific Ig/M Human HSC studies-control and XLA subjects:

[0209] The rescue of B cell development and function of XLA cells *in vivo* were examined using a lentiviral vector. The experiments were performed to evaluate whether it would be feasible to recapitulate XLA patient's B cell phenotype in NSG mice. Also contemplated was whether the methods would rescue the B cell development *in vivo* by transducing XLA stem cells with the clinical LV vector. Shown in **Figure 71Figure 71** is a table of XLA patients selected to receive therapy.

[0210] The XLA B cell phenotype in the periphery include a markedly reduced percentage of B cells, higher percentage of transition/ immature B cells (CD38+ CD24+ CD10 high), and a lack of mature B cells (CD38- CD24- $CD10^{low}$).

[0211] The human chimera in NSG was shown in patient XLA P2, P3 and P4 in **Figure 72.** As shown, there was an equivalent engraftment of hCD45 cells in bone marrow, however, a significantly lower percentage of differentiated hCD45 cells were in the periphery.

[0212] For the human lymphocyte reconstitution, the percentage of B cells was equivalent in bone marrow, however, a significantly lower percentage in spleen with a relative increase in myeloid and T cells was seen in all XLA patients P2, P3 and P4 (**Figure 73)**.

[0213] The phenotype of the engrafted XLA stem cell (spleen) is shown in **Figure 74** for patients XLA P2, P3 and P4. As shown, the patients exhibited low levels of mature B cells; however, the patients had similar levels of immature B cells (**Figure 75)**.

[0214] The phenotype of the engrafted XLA stem cell (spleen) is shown in **Figure 76** for patients XLA P2, P3 and P4. As shown, the patients exhibited equivalent %Pro B cell between the XLA and healthy group.

[0215] The B cell developmental block was examined for all XLA patients. As shown in **Figure 77,** BTK allows development of Pro B cell to a mature B cell. The cells were analyzed for hCD19+, CD22+ and CD179a+. As shown, the XLA patients had a significantly higher percentage of pre-B cells as compared to the healthy control. These XLA B cells are thus blocked at the Pre B cell stage in which they are then able to migrate to the spleen (**Figure 78 and 85).**

[0216] The B cell function by Ca^{2+} was also examined in the XLA cells (**Figure 80.** As shown, the XLA B cells were not able to flux with IgM as compared to the control.

[0217] From the evaluation of the XLA B cells, it was shown the XLA cells have B cell development blocked at the Pre B cell stage (**Figure 81)**.

[0218] As shown, XLA patients have a lower number and percentage of B cells in spleen. Additionally, the B cell development is arrested at the pre-B cell stage in the bone marrow. The next step was to recapitulate the XLA patient's B cell phenotype in NSG mice to examine the effects of the BTK expressing lentiviral vector system.

[0219] Human lentiviral transduction of stem cells was performed with the following vectors: 0.7 UCOE.BTKp.coBTK and 0.7UCOE.DHS4.BTKp.coBTK according to the methods shown in **Figure 83 and 90.**

[0220] The human lentiviral transduction of the stem cells led to 70% viability with the 0.7UCOEBTKp.BTK, as compared to the vector with the DNAse hypersensitivity site 4 region (**Figure 85).**

[0221] BTK expression was also seen in the cells derived from patient XLA P2 transduced with the 0.7UCOE.BTK.pBTK lentiviral vector. As shown in a non-selective environment, 0.7UCOE.BTKpBK leads to a higher expression of BTK, as compared to the lentiviral vector comprising the DNAse hypersensitivity site 4 region (**Figure 86).**

[0222] In view of the above experimentation, it was concluded that the XLA stem cells transduced with 0.7UCOE.BTKp.BTK and 0.7UCOE. DHS4.BTKp.BTK at MOI10, leads to clinically relevant viral copy 1-2. As such, it is contemplated that lentiviral transduction of XLA stem cells *in vivo* will lead to rescue of B cell development.

Preclinical modeling of Human HSC

[0223] The preclinical modeling of human HSC was examined using a lentiviral vector expressing human codon optimized BTK fused to a GFP protein, which was self-cleavable with a T2A linker (**See Figure 88)**. As shown, the test construct comprises the UCOE element, a BTK promoter, a human codon optimized BTK gene, as well as, the T2A-GFP marker protein. *In vitro* transduction of the CD34+ HSC indicated an increase of GFP in the cells transduced with the lentivector (**Figure 88).** Cells were then administered to NSG

recipient mice as shown in **Figure 90.** *In vivo* analysis after 6 months showed that there was an increase in B cells, as well as, myeloid cells (**Figure 89 and 97).**

[0224] Further tests are contemplated with constructs as shown in **Figure 92**. A bioinformatics approach was undertaken utilizing the ENCODE genome-wide database information on regulatory markers in specific cell lineages. The flow of the discovery was the use of conserved non-coding sequence information to identify candidate enhancers

[0225] In effort to improve tissue specific BTK expression, conserved non-coding sequences were identified by comparing human vs. mouse non-coding sequences and identifying areas that are highly conserved. Conserved non-coding sequences were cloned in front of BTKp and see if they improve the expression in conjunction with the BTK promoter (BTKp). The first pass read-out used GFP reporter to track expression- improved expression would increase the GFP signal or "MFI". Introns 4 and 5 were identified as improving MFI, as well as a contig of introns 4, 5, and 13. GFP was encoded by the sequence set forth in SEQ ID NO: 8. Sequences that are shown in Set 1 of Figure 92 are in SEQ ID NO's 23-30. The tested sequences that encoded the GFP are set forth in SEQ ID NO's: 31, 32, and 36-40.

[0226] The contig containing introns 4, 5 and 13 vs. a contig with introns 4 and 5 only were next tested again *in vitro* with GFP. The Intron 4,5 together had better MFI.

[0227] Intron 4 and 5 contig were tested in vivo in mouse gene therapy model, calling it intronic enhancer 4, 5 or IE4-5. These studies used the enhancer/promoter elements to drive expression of a codon-optimized human BTK coding sequence, and showed that inclusion of IE4-5 improved expression of BTK per viral copy number.

[0228] The polypeptides that encode the sequences for the BTK for expression are set forth in SEQ ID NO's 33-35, and 41-45.

Refining candidate enhancers using information from encode database

[0229] **[0228]** To more narrowly define DNA elements mediating enhancer activities in IE4-5, the ENCODE database was used to find DNase hypersensitive sites located in these introns, and one was found in each intron that were both in B cells and in myeloid cells, but not always present in non-relevant tissues. These were called DHS 4 and 5, and were 725 bp and 1077 bp less than the sizes of the previous intronic regions that were included. There were also DNase hypersensitive sites in B and myeloid cells identified

within intron 1 (DHS1, 2, and 3) that were also for testing, due to some evidence that intron 1 may improve MFI in vitro. DHS 3 and 4 were identified as having properties of transcriptional enhancers in B cells by the ENCODE segmentation analysis; DHS5 was identified as a CTCF binding site/candidate insulator.

[0230] Various combinations of DHS sites 1 through 5 were also tested.

[0231] As shown in **Figure 92**, "1kb" and "3kb" are non-conserved intron 1 sequences to control for the size of the enhancers.

Truncation of 1.5kb UCOE to 0.7kb and identification of potential DNA enhancer elements may improve titer and BTK expression in Lentiviral constructs.

[0232] Shown in **Figure 93A,** are the results from truncation of 1.5kb Ubiquitous Chromatin Opening Element (UCOE) to 0.7kb. The UCOE element spans a large, CpG-rich region across the divergently transcribed promoter regions for the housekeeping genes CBX3 and HNRPA2B1, and has traditionally been truncated to a 1.5-2.2kb region by various groups for use in protein expression constructs. The 1.5kb UCOE used here starts at Exon 1 of CBX3 and spans past CBX3 Alternate Exon 1. Truncation of this region to 0.7kb eliminates the region downstream of Alt. Ex. 1. (93B) DNaseI Hypersensitive sites (DHS) from intronic regions of the BTK gene were identified from the ENCODE database and visualized using the UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly. Five DHS were identified, and were labeled consecutively as DHS1, DHS2, DHS3, DHS4, and DHS5 (blue boxes). ENCODE Genome Segmentation identified a predicted Enhancer element around DHS4 (yellow box). Exons are shown as black boxes. The sequence length is noted beneath each DHS. Various combinations of these DHS sequences were cloned into the 0.7UCOE.BTKp.coBTK construct and tested in vitro as follows (data not shown). Murine $Btk^{-/-}Tec^{-/-}$bone marrow cells were transduced with LV containing the various expression cassettes shown below. Mean fluorescence intensity of transgene expression was then compared by flow cytometry. (93C) An *in vitro* transduction experiment of murine (TBK) lineage negative cells was performed to compare BTK expression levels in two versions of codon-optimized BTK: coBTK (Figures 1-2), and a codon-optimized BTK published by Staal et al. (Leukemia 2010), denoted here as co2BTK. Representative flow plots show BTK expression at 7 days post-transduction. (93D) Based on

the results of our in vitro testing of the DHS constructs and the coBTK vs co2BTK comparison, we identified four constructs to test in vivo. Shown here are diagrams of the lentiviral constructs with RRL backbone expressing either version of codon optimized human BTK (coBTK or co2BTK) with a 0.7 kb ubiquitous chromatin opening element (0.7UCOE), with or without addition of DHS4 downstream of the 0.7UCOE element.

[0233] Shown in **Figure 94**: are the results from restoration of BTK expression in affected hematopoietic lineages and B cell development in gene therapy mice treated with 0.7UCOE vectors. The proportion of BTK+ cells and numerical reconstitution of B and myeloid cell subsets was assessed at 19-23 weeks post-transplant. (**Figure 94A**) Representative flow plots showing intracellular BTK staining in splenic B cells at endpoint analysis. (**Figure 94**B-D) Percent of BTK+ cells in bone marrow (**Figure 94**B), spleen (**Figure 94**C), and peritoneal (**Figure 94**D) lymphocyte subsets from gene therapy treated groups, determined by flow cytometry. Cell subsets are defined as Neutrophils (CD11b+ GR1+), Monocytes (CD11b+), and B cells (B220+). (**Figure 94**E-F) Stacked bars show the average counts of B cell subsets in bone marrow (**Figure 94**E), spleen (**Figure 94F**), and peritoneum (**Figure 94**G. Early B cell development (bone marrow): Pro+Pre-B (IgM-, IgD-), Immature (IgM+ IgD-), and Mature (IgM+, IgD+). Late B cell development (spleen): transitional T1 (CD24hi, CD21-), transitional T2 (CD24hi, CD21int), marginal zone/precursor MZ/MZP (CD24hi, CD21hi), and follicular FM (CD24int, CD21int). Peritoneal B cell subsets: B1 (IgM+ CD43+), and B2 (CD43-). (**Figure 94H**) Rescue of BTK expression in B cell subsets, measured by flow cytometry. (**Figure 94I**) BTK+ MFI across B cell development, normalized to WT Mock in each individual experiment. Data represent mean ± SD from 4 unique experiments, n = 13 (WT Mock), 13 (KO Mock), 11 (0.7UCOE.BTKp.co), 11 (0.7UCOE.BTKp.co2), 16 (0.7UCOE.DHS4.BKTp.co), 11 (0.7UCOE.DHS4.BKTp.co2), and 6 (0.7UCOE.DHS1-5.BTKp.co). P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0234] **Figure 95** shows the restoration of B cell function *in vivo* and *in vitro*. **(Figure 95A)** Mice were immunized with NP-CGG in Alum at 12 weeks post-transplant. Levels of NP-specific IgG in serum from immunized mice was measured by ELISA and expressed relative to an IgG standard. High-affinity NP-IgG was measured from serum prior to (-) and 10 days following primary immunization (1°). One month following primary

challenge, mice were re-challenged with NP-CGG in PBS and serum was collected 10 days later (2^o). **(Figure 95B-C)** Total serum IgG **(Figure 95B)** and IgM **(Figure 95C)** in serum from treated mice was measured by ELISA and endpoint analysis (21-23 weeks post-transplant). **(Figure 95D-F)** At endpoint analysis, B cells were isolated from splenocytes by CD43- magnetic separation, labeled with Cell Trace Violet and stimulated in vitro with IgM, LPS, or a media control. **(Figure 95D)** The percentage of BTK+ B cells that underwent ≥ 1 cell division 72 hours after incubation with anti-mouse IgM antibodies, LPS or media only (read out by flow cytometry). **(Figure 95E)** BTK+ MFI of cells after each division (D0-D4), normalized to WT Mock. **(Figure 95F)** Representative flow plots showing BTK staining and Cell Trace dilution in B cells 72 hours post-IgM stimulation, gated on live and B220+ BTK+ cells. Data represent mean ± SD from 4 unique experiments, n = 13 (WT Mock), 13 (KO Mock), 11 (0.7UCOE.BTKp.co), 11 (0.7UCOE.BTKp.co2), 16 (0.7UCOE.DHS4.BKTp.co), 11 (0.7UCOE.DHS4.BKTp.co2), and 6 (0.7UCOE.DHS1-5.BTKp.co). P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

[0235] **Figure 96** shows some vector safety considerations. Levels of anti-dsDNA IgG **(Figure 96A)** and anti-dsDNA IgG2c **(Figure 96B)** in serum from treated mice were measured by ELISA and are depicted as absorbance readings (OD450). Serum from the known autoimmune-prone WAS chimeric mouse model and mice treated with Eu.BTKp were included as positive controls. **(Figure 96C)** Genomic DNA was isolated from total bone marrow and spleen at endpoint analysis and the number of viral integrations per cell (VCN) was quantified by qPCR. Data represent mean ± SD from 4 unique experiments, n = 13 (WT Mock), 13 (KO Mock), 11 (0.7UCOE.BTKp.co), 11 (0.7UCOE.BTKp.co2), 16 (0.7UCOE.DHS4.BKTp.co), 11 (0.7UCOE.DHS4.BKTp.co2), and 6 (0.7UCOE.DHS1-5.BTKp.co). P value was determined using the One way Anova: Sidak test: ***P < .001; **P = .001-.01; *P = .01-.05.

Pre-clinical modeling LV vectors in human HSC from XLA patients

[0236] The aim of the following experiments was to determine if gene therapy vectors can rescue the development of B cells from XLA HSCs when transplanted into immunodeficient NSG mice. CD34 cell source: XLA Patient 3 (missense mutation) and healthy donor #15. The transduction protocol comprises one hit of LV after a 48 hour

prestimulation in SCGM (TPO, FLT3 and SCF at 100ng/ml) .The MOI used: 5. The lentivirus used was 0.7 UCOE. BTKp.BTK .co2 (titer: 7 X 10^8) and DHS4.co2 (titer: 1 X 10^9)

[0237] Experimental mice: 4 mice = Healthy donor #15 (HD)

[0238] 3 mice = XLA P3 mock treated (XLAP3)

[0239] 5 mice = 0.7 UCOE.BTKp.BTK.co2 (0.7UCOE)

[0240] 4 mice = 0.7 UCOE.DHS4.BTKp.BTK.co2 (DHS4)

[0241] Analyzed at: 12 week post transfer (**Figure 97).**

[0242] Shown in **Figure 98** are the results from an equivalent bone marrow engraftment of human hematopoietic cells between treatment groups. Human stem cells from XLA patient, either with or without gene therapy treatments, engrafted into the bone marrow equivalently as those from a healthy donor. Representative flow plots showing various markers of human immune cells including human and mouse CD45 (a marker for hematopoietic cells) CD33 (myeloid cells) and CD19 (B cells), CD4 and CD8 (T cells). Human hematopoietic cells are hCD45+ and mCD45- from total live BM cells; CD33 and CD19 markers were analyzed from hCD45+gate; CD4 and CD8 were analyzed from the CD33-CD19- gate. **Figures 98**B and **98**C. % human CD45 and total number of hCD45 cells engrafted in BM; n= 4 for each cohort (XLA3, XLA3+LV 0.7UCOE.BTKp.BTKco2, XLA3 + LV 0.7UCOE.DHS4.BTKp.BTKco2, and healthy donor).

[0243] Shown in **Figure 99,** are the results of mouse recipients of XLA3 HSC given gene therapy using 0.7UCOE.BTKp BTKco2 or 0.7UCOE.DHS4.BTKp.BTKco2 showing significantly increased numbers of splenic human hematopoietic cells. **Figure 99**A. Representative flow plots showing markers of human immune cells including human and mouse CD45 (a marker for hematopoietic cells) CD33 (myeloid cells) and CD19 (B cells), CD4 and CD8 (T cells). Human hematopoietic cells are both hCD45+ and mCD45-; CD33 and CD19 markers were analyzed from the hCD45+gate; CD4 and CD8 were analyzed from the CD33-CD19- gate. **Figures 99**B and **99**C: % and total number of splenic cells that were hCD45+. n= 4 for each cohort; ** P = 0.004 by one way ANOVA. Shown in **Figure 100,** are the results of recipients of LV transduced XLA HSC (using 0.7UCOE BTKp BTKco2 or DHS4 BTKpBTK.co2), which exhibit an increased proportion of splenic B cells (CD19+ cells) relative to non-treated XLA patient cells Here the results from flow cytometry shown

in Figure 2 are summarized, looking at specific categories of human immune cells: A-C, % of human CD45+ cells in the spleen that are B cells (CD19+), myeloid cells (CD33+) and T cells (CD4+ or CD8+); D-F, Total number of human CD45+ cells in the spleen that are B cells (CD19+), myeloid cells (CD33+) and T cells (CD4+ or CD8+); n= 4 for each cohort. **P =0.0044 by one way ANOVA.

[0244] Shown in **Figure 101,** is a representative flow plot for B cell development subsets in spleen. A typical gating strategy for identifying human B cell developmental subsets is shown for each gene therapy cohort (listed at right). Markers used in each panel are shown at bottom (Hist = histogram); predecessor gates are shown at the top of each column if used. Human CD24 and hCD38 cells were gated from human CD19+cells. Immature B cells (hCD24+hCD38+) are IgM+ IgD – CD10high; mature B cells (CD24low CD38low) are IgM+IgD+ CD10 low.

[0245] Shown in **Figure 102** are the results of recipients of LV transduced XLA3 HSC (using 0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4 BTKp.BTKco2). As shown, the recipients have an increased proportion of splenic immature B cells (including CD19+CD24+CD38+ B cells and CD19+CD24+CD38+IgM+ cells) compared to XLA controls. Graphs summarize the results from flow cytometry shown in Figure 4, looking at specific subpopulations of immature B cells. A,% of Immature B cells (CD24+ CD38+) in the spleen; B, % of immature B cells that are IgM+; C- D, Total number of immature B cells (CD24+ CD38+) and CD24+hCD38+ IgM+ cells in the spleen; E, overlay of CD10 histogram , showing the mean fluorescence intensity MFI shift in CD10 compared to healthy donor. n= 4 for each cohort; ***P = 0.0004; **P =0.0044; *P= 0.4 by one way ANOVA.

[0246] As shown in **Figure 103**, recipients of LV transduced XLA HSC (0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4 BTKp.BTKco2) have increased proportions of mature B cells ($CD19^{+}CD24^{low}CD38^{low}IgM^{+}$ and IgD^{+}) compared to XLA controls. **Figures 104A-C**, % of mature B cells ($hCD24^{low}hCD38^{low}$) and the percent of mature B cells that are IgM^{+} and $IgM^{+}IgD^{+}$ in the spleen, respectively; Figures **103D-F**, Total number of splenic mature B cells and mature B cells that are IgM^{+} and $IgM^{+}IgD^{+}$, respectively; **Figure 103**G, histogram overlay of CD10, showing similar MFI of CD10 as that of a healthy donor. N = 4 for each cohort; ***P= 0.0004; **P=0.0044; * P= 0.4 by one way ANOVA.

[0247] Shown in **Figure 104** is a representative flow plot for B cell development subsets in the bone marrow. Flow plots and gating strategy for identifying human B cell developmental subsets in the bone marrow is shown for each gene therapy cohort (listed at right). Markers used in each panel are shown at bottom (Hist = histogram); predecessor gates are shown at the top of each column if used. Human CD24 and hCD38 cells were gated from human CD19 + cells. Immature B cells in the bone marrow (hCD24+hCD38+) are IgM+ IgD – CD10high.

[0248] As shown in **Figure 105,** recipients of LV transduced XLA HSC (using 0.7UCOE BTKp BTKco2 or DHS4 BTKpBTK.co2) exhibit an increased proportion of $CD19^{+}CD24^{+}CD38^{+}IgM^{+}$ immature B cells compared to XLA controls. Graphs summarize flow analysis based on gating strategy shown in figure 7**.** Each dot represents individual mice **A-D**, Percent and number of immature B cells ($CD24^{+}CD38^{+}$) and immature B cells that are IgM^{+} , respectively; E, Overlay of CD10 histogram showing the MFI shift in CD10 compared to healthy donor. Blue color represents individual mice treated with LV 0.7.UCOE.BTKp.BTKco2, and orange color individual mice treated with LV 0,7UCOE.DHS4.UCOE.BTKp.BTKco2. n= 4 for each cohort. Statistical significance were determined by one way ANOVA; ***P= 0.0004; **P=0.0044; * P= 0.4.

[0249] As shown in **Figure 106,** recipients of LV transduced XLA HSC (using LV 0.7UCOE BTKp BTKco2 or LV 0.7UCOE.DHS4 BTKp.BTK.co2) exhibit gene marking of 0.2-2 viral copy number (VCN)/cell in vivo. The number of viral integrations per cell were calculated in BM (A) and Spleen (B), as well as the original CD34 cells prior to transplantation (C) as determined by quantitative PCR. No significant difference between 0.7UCOE.Co2.BTKp.BTK and DHS4.BTKp.BTKCo2. Each dot represents individual mice (N = 4 for each in A and B; N = 1 in C)

[0250] As shown in **Figure 107,** recipients of XLA3 HSC that received gene therapy with LV 0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4.BTK.pBTKco2 produce B cells that secrete IgM *in vivo*. Total IgM levels were quantified by ELISA from serum obtained 12 weeks post- transplant. The value of IgM (μg/mL) were determined using a human IgM standard. Each dot represents the result from an individual mouse; N = 4 for each cohort.

[0251] As shown in **Figure 108,** recipients of XLA3 HSC transduced with LV 0.7UCOE.BTKp.BTKco2 or 0.7UCOE.DHS4.BTKp.BTKco2 exhibit a restored capacity for B cells to flux calcium in response to B cell receptor (BCR) engagement. Pooled 5 x 10^6 total splenic cells from mice within each cohort were analyzed for their ability to flux calcium in response to BCR signaling, an important event downstream of BTK activation. **Figure 108A,** provides a representative flow plots showing the gating strategy for human CD19+ cells evaluated for the calcium flux. **Figure 108B** provides a kinetic analysis of intracellular calcium levels by flow cytometry after BCR engagement with human IgM antibodies.

[0252] Shown in **Figure 110,** is a representative flow plot for *in vitro* B cell class switching. Splenic cells from recipient mice were cultured in B cell differentiation protocol (previous slide) then stained for markers allowing the identification of plasma B cells. Media supernatant was also collected for determining human IgM and IgG levels by ELISA.

[0253] As shown in **Figure 111,** recipients of LV transduced XLA HSC (using 0.7UCOE BTKp BTKco2 or DHS4 BTKpBTK.co2) generate B cells that are capable of responding to cytokine and T-cell dependent signals leading to antibody secretion. 0.5x 10^6 total splenic cells (pooled from mice in each cohort) were cultured in IMDM + 10% FBS + 2-mercaptoethanol media. In Phase I cells were cultured for 7 days with MegaCD40L (100ng/ml) + CpG ODN 2006 (1μg/ml) + IL-2 (50ng/ml) + IL-10 (50ng/ml) + IL-15 (10ng/ml). After phase I cells were washed with PBS 2x and cultured for 3 days in PhaseII media (IMDM+ 10% FBS + BME supplemented with IL-2 (50ng/ml) + IL-6 (50ng/ml) + IL-10 (50ng/ml) + IL-15 (10ng/ml), then switched to Phase III media (IMDM+ 10% FBS + BME supplemented with IL-6 (50ng/ml) + IL-15 (10ng/ml) + IFN-α 2B (100U/ml) for 4 days. At this time point media supernatants were collected and the levels of human IgG (**A**) and IgM (**B**) were determined by ELISA using a human IgM and IgG standard.

Additional alternatives

[0254] As described herein, a polynucleotide for sustained Bruton's tyrosine kinase (BTK) expression is provided. The polynucleotide can comprise a first sequence encoding a ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter and a third sequence encoding BTK. In some alternatives, the UCOE is 2kb, 1.5kb,

1kb, 0.75kb, 0.5kb or 0.25 kb or any number of kilobases in between a range defined by any two afore mentioned values. In some alternatives, the first sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 1, and/or SEQ ID NO: 2. In some alternatives, the promoter is a BTK promoter. In some alternatives, the BTK promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5. In some alternatives, the third sequence is codon optimized for expression in humans. In some alternatives, the third sequence comprises the sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7. In some alternatives, the promoter is a B cell specific promoter. In some alternatives, the B cell specific promoter comprises the B cell specific promoter, B29. In some alternatives, the B29 promoter sequence comprises a sequence set forth in SEQ ID NO: 46. In some alternatives, the B cell specific promoter is an endogenous promoter. In some alternatives, the polypeptide further comprises one or more enhancer elements. In some alternatives, the one or more enhancer elements comprise at least one DNase Hypersensitive Site (DHS). In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5). In some alternatives, the DNase Hypersensitive Site comprises a sequence set forth in SEQ ID NO: 3. In some alternatives, the one or more enhancer elements comprise at least one intronic region. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter. In some alternatives, the at least one intronic region is intron 4, intron 5 and/or intron 13 of the human BTK locus that is in association with the human BTK proximal promoter. In some alternatives, the intronic region comprises the sequence set forth in SEQ ID NO: 9 (intron 4), SEQ ID NO: 10 (intron 5) and/or SEQ ID NO: 11 (intron 13). In some alternatives, the one or more enhancer elements comprise the sequence set forth in SEQ ID NO: 4, SEQ ID NO: 14 or SEQ ID NO: 15. In some alternatives, the UCOE is in a reverse orientation or forward orientation. In some alternatives, the UCOE is in a forward orientation. In some alternatives, the one or more enhancer elements comprises the sequences set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and/or SEQ ID NO: 20. In some alternatives, the polynucleotide further comprises a gene upstream of a BTK promoter. In some alternatives, the gene upstream of a BTK promoter is a BTK enhancer. In some alternatives, the BTK enhancer comprises the sequence set forth in SEQ

ID NO: 21 or SEQ ID NO: 22. In some alternatives, the polypeptide comprises a sequence set forth in SEQ ID NO's: 33, 34, 35, 41, 42, 43, 44 or 45. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 1. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0255] A vector for sustaining BTK expression in cells is also provided. The vector can comprise a first sequence encoding an ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter, and a third sequence encoding BTK. In some alternatives, the first sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 1, and/or SEQ ID NO: 2. In some alternatives, the promoter is a BTK promoter. In some alternatives, the promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5. In some alternatives, the third sequence is codon optimized for expression in humans. In some alternatives, the third sequence comprises the sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7. In some alternatives, the vector further comprises a B cell specific promoter. In some alternatives, the B cell specific promoter comprises the B cell specific promoter, B29. In some alternatives, the B29 promoter sequence comprises a sequence set forth in SEQ ID NO: 46. In some alternatives, the B cell specific promoter is an endogenous promoter. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the one or more enhancer elements comprise at least one intronic region. In some alternatives, the one or more enhancer elements comprise a DNase Hypersensitive Site (DHS). In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5). In some alternatives, the DNase Hypersensitive Site comprises a sequence set forth in SEQ ID NO: 3. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter. In some alternatives, the at least one intronic region is intron 4 intron 5 and/or intron 13of the human BTK locus that is in association with the human BTK proximal promoter. In some alternatives, the intronic region comprises the sequence set forth in SEQ ID NO: 9 (intron 4), SEQ ID NO: 10 (intron 5) and/or SEQ ID NO: 11 (intron 13). In some alternatives, the one or more enhancer elements comprise the sequence set forth in SEQ ID NO: 4, SEQ ID NO: 14 or SEQ ID NO: 15. In

some alternatives, the UCOE is in a reverse orientation or forward orientation. In some alternatives, the UCOE is in a forward orientation. In some alternatives, the vector is a lentiviral-based vector of a B lineage specific lentiviral vector. In some alternatives, the cells are B cells. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells. In some alternatives, the one or more enhancer elements comprise the sequences set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and/or SEQ ID NO: 20. In some alternatives, the polynucleotide further comprises a gene upstream of a BTK promoter. In some alternatives, the gene upstream of a BTK promoter is a BTK enhancer. In some alternatives, the BTK enhancer comprises the sequence set forth in SEQ ID NO: 21 or SEQ ID NO: 22. In some alternatives, the polypeptide or vector comprises a sequence set forth in SEQ ID NO's: 33, 34, 35, 41, 42, 43, 44 or 45. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0256] In some alternatives, a cell for expression of BTK is provided, the cell comprising: a polynucleotide, which comprises a first sequence encoding an ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter and a third sequence encoding BTK. In some alternatives, the polynucleotide is in a vector. The vector can comprise a first sequence encoding a ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter, and a third sequence encoding BTK. In some alternatives, the first sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 1, and/or SEQ ID NO: 2. In some alternatives, the promoter is a BTK promoter. In some alternatives, the promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5 In some alternatives, the third sequence is codon optimized for expression in humans. In some alternatives, the third sequence comprises the sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7. In some alternatives, the vector further comprises a B cell specific promoter. In some alternatives, the B cell specific promoter comprises the B cell specific promoter, B29. In some alternatives, the B29 promoter sequence comprises a sequence set forth in SEQ ID NO: 46. In some alternatives, the B cell specific promoter is an endogenous promoter. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the one or more enhancer elements comprise at least one intronic region. In

some alternatives, the one or more enhancer elements comprises a DNase Hypersensitive Site (DHS). In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5). In some alternatives, the DNase Hypersensitive Site comprises a sequence set forth in SEQ ID NO: 3. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter. In some alternatives, the at least one intronic region is intron 4 intron 5 and/or intron 13 of the human BTK locus that is in association with the human BTK proximal promoter. In some alternatives, the intronic region comprises the sequence set forth in SEQ ID NO: 9 (intron 4), SEQ ID NO: 10 (intron 5) and/or SEQ ID NO: 11 (intron 13). In some alternatives, the one or more enhancer elements comprise the sequence set forth in SEQ ID NO: 4 (SEQ ID NO: 4: intron 4-5), SEQ ID NO: 14 or SEQ ID NO: 15. In some alternatives, the UCOE is in a reverse orientation or forward orientation. In some alternatives, the UCOE is in a forward orientation. In some alternatives, the vector is a lentiviral-based vector of a B lineage specific lentiviral vector. In some alternatives, the cells are B cells. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells. In some alternatives, the one or more enhancer elements comprises the sequences set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and/or SEQ ID NO: 20. In some alternatives, the polynucleotide further comprises a gene upstream of a BTK promoter. In some alternatives, the gene upstream of a BTK promoter is a BTK enhancer. In some alternatives, the BTK enhancer comprises the sequence set forth in SEQ ID NO: 21 or SEQ ID NO: 22. In some alternatives, the vector is a lentiviral vector. In some alternatives, the cell is a B cell. In some alternatives, the cells are myeloid cells. In some alternatives, the cell is a hematopoietic stem cell. In some alternatives, the cell is a CD34+ hematopoietic stem cell. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0257] In some alternatives, a method of promoting B cell survival, proliferation and/or differentiation in a subject in need thereof is provided, the method comprising administering the cell of any one of the alternatives herein to the subject or a cell comprising

the polynucleotide of any one of the alternatives herein or the vector of any one of the alternatives herein to the subject in need and, optionally identifying the subject as one that would benefit from receiving a therapy that would promote B cell survival, proliferation and/or differentiation in advance of administering the cell and/or, optionally, measuring B cell survival, proliferation and/or differentiation in said subject or in a biological sample obtained from said subject. The vector can comprise a first sequence encoding a ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter, and a third sequence encoding BTK. In some alternatives, the first sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 1, and/or SEQ ID NO: 2. In some alternatives, the promoter is a BTK promoter. In some alternatives, the promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5. In some alternatives, the third sequence is codon optimized for expression in humans. In some alternatives, the third sequence comprises the sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7. In some alternatives, the vector further comprises a B cell specific promoter. In some alternatives, the B cell specific promoter comprises the B cell specific promoter, B29. In some alternatives, the B29 promoter sequence comprises a sequence set forth in SEQ ID NO: 46. In some alternatives, the B cell specific promoter is an endogenous promoter. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the one or more enhancer elements comprise at least one intronic region. In some alternatives, the one or more enhancer elements comprise a DNase Hypersensitive Site (DHS). In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5). In some alternatives, the DNase Hypersensitive Site comprises a sequence set forth in SEQ ID NO: 3. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter. In some alternatives, the at least one intronic region is intron 4 intron 5 and/or intron 13of the human BTK locus that is in association with the human BTK proximal promoter. In some alternatives, the intronic region comprises the sequence set forth in SEQ ID NO: 9 (intron 4), SEQ ID NO: 10 (intron 5) and/or SEQ ID NO: 11 (intron 13). In some alternatives, the one or more enhancer elements comprise the sequence set forth in SEQ ID NO: 4 (SEQ ID NO: 4: intron 4-5), SEQ ID NO: 14 or SEQ ID NO: 15. In some

alternatives, the UCOE is in a reverse orientation or forward orientation. In some alternatives, the UCOE is in a forward orientation. In some alternatives, the vector is a lentiviral-based vector of a B lineage specific lentiviral vector. In some alternatives, the cells are B cells. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells. In some alternatives, the one or more enhancer elements comprises the sequences set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and/or SEQ ID NO: 20. In some alternatives, the polynucleotide further comprises a gene upstream of a BTK promoter. In some alternatives, the gene upstream of a BTK promoter is a BTK enhancer. In some alternatives, the BTK enhancer comprises the sequence set forth in SEQ ID NO: 21 or SEQ ID NO: 22. In some alternatives, the cell is from the subject and, wherein the cell is genetically modified by introducing the polynucleotide or the vector of any one of alternatives described above into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a B cell. In some alternatives, the cells are myeloid cells. In some alternatives, the cell is a hematopoietic stem cell. In some alternatives, the cell is a CD34+ hematopoietic stem cell. In some alternatives, the subject is male. In some alternatives, the subject is suffering from X linked agammaglobulinemia (XLA). In some alternatives, the subject is selected to receive immunoglobulin replacement therapy. In some alternatives, the subject is selected to receive targeted anti-microbial agents. In some alternatives, the polypeptide or vector comprises a sequence set forth in SEQ ID NO's: 33, 34, 35, 41, 42, 43, 44 or 45. In some alternatives, the polypeptide or vector comprises a sequence set forth in SEQ ID NO's: 33, 34, 35, 41, 42, 43, 44 or 45. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

[0258] In some alternatives, a method of treating, inhibiting, or ameliorating X linked agammaglobulinemia (XLA) or disease symptoms associated with XLA in a subject in need thereof is provided, the method comprising: administering the cell of any one of the alternatives herein to the subject or a cell comprising the polynucleotide of any one of the alternatives herein or the vector of any one of the alternatives herein to the subject in need and, optionally identifying the subject as one that would benefit from receiving a therapy for XLA or disease symptoms associated with XLA and/or, optionally, measuring an

improvement in the progression of XLA or an improvement in a disease symptom associated with XLA in said subject. The vector can comprise a first sequence encoding a ubiquitous chromatin opening element (UCOE), a second sequence encoding a promoter, and a third sequence encoding BTK. In some alternatives, the first sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 1 and/or SEQ ID NO: 2. In some alternatives, the promoter is a BTK promoter. In some alternatives, the promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5. In some alternatives, the third sequence is codon optimized for expression in humans. In some alternatives, the third sequence comprises the sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7. In some alternatives, the vector further comprises a B cell specific promoter. In some alternatives, the B cell specific promoter comprises the B cell specific promoter, B29. In some alternatives, the B29 promoter sequence comprises a sequence set forth in SEQ ID NO: 46. In some alternatives, the B cell specific promoter is an endogenous promoter. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the one or more enhancer elements comprise at least one intronic region. In some alternatives, the one or more enhancer elements comprise a DNase Hypersensitive Site (DHS). In some alternatives, the DNase Hypersensitive Site is DNase Hypersensitive Site 1 (DHS1), DNase Hypersensitive Site 2, (DHS2) DNase Hypersensitive Site 3 (DHS3), DNase Hypersensitive Site 4 (DHS4) and/or DNase Hypersensitive Site 5 (DHS5). In some alternatives, the DNase Hypersensitive Site comprises a sequence set forth in SEQ ID NO: 3. In some alternatives, the at least one intronic region is from a human BTK locus that is in association with a human BTK proximal promoter. In some alternatives, the at least one intronic region is intron 4 intron 5 and/or intron 13of the human BTK locus that is in association with the human BTK proximal promoter. In some alternatives, the intronic region comprises the sequence set forth in SEQ ID NO: 9 (intron 4), SEQ ID NO: 10 (intron 5) and/or SEQ ID NO: 11 (intron 13). In some alternatives, the one or more enhancer elements comprise the sequence set forth in SEQ ID NO: 4 (SEQ ID NO: 4: intron 4-5), SEQ ID NO: 14 or SEQ ID NO: 15. In some alternatives, the UCOE is in a reverse orientation or forward orientation. In some alternatives, the UCOE is in a forward orientation. In some alternatives, the vector is a lentiviral-based vector of a B lineage specific lentiviral vector. In some alternatives, the cells are B cells. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are

hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells. In some alternatives, the one or more enhancer elements comprises the sequences set forth in SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and/or SEQ ID NO: 20. In some alternatives, the polynucleotide further comprises a gene upstream of a BTK promoter. In some alternatives, the gene upstream of a BTK promoter is a BTK enhancer. In some alternatives, the BTK enhancer comprises the sequence set forth in SEQ ID NO: 21 or SEQ ID NO: 22. In some alternatives, the vector is a lentiviral-based vector of a B lineage specific lentiviral vector. In some alternatives, the cells are B cells. In some alternatives, the cells are myeloid cells. In some alternatives, the cells are hematopoietic stem cells. In some alternatives, the cells are CD34+ hematopoietic stem cells. In some alternatives, the cell is from the subject, wherein the cell is genetically modified by introducing the polynucleotide of any one of the alternatives herein or the vector of any one of the alternatives herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a B cell. In some alternatives, the cells are myeloid cells. In some alternatives, the cell is a hematopoietic stem cell. In some alternatives, the cell is a CD34+ hematopoietic stem cell. In some alternatives, the subject is male. In some alternatives, the subject is selected to receive immunoglobulin replacement therapy. In some alternatives, the subject is selected to receive targeted anti-microbial agents. In some alternatives, the polypeptide or vector comprises a sequence set forth in SEQ ID NO's: 33, 34, 35, 41, 42, 43, 44 or 45. In some alternatives, 0.7UCOE comprises a sequence set forth in SEQ ID NO: 2. In some alternatives, the enhancer comprises a sequence set forth in SEQ ID NO: 3 or 4.

Sequences

[0259] Listed below are sequences used in the alternatives herein:

0.7UCOE:		ENHANCER:			PROMOTER	BTK optimization:	codon
0.7UCOE	0.7UCOEfwd	one	HS4	IE4-5	BTKp	coBTK	co2BTK

>0.7UCOE (SEQ ID NO: 1)

[0260] (SEQ ID # 1)

Cgcgtgtggcatctgaagcaccaccagcgagcgagagctagagagaaggaaagccaccgacttcaccgcctccgagctgctccg
ggtcgcgggtctgcagcgtctccggccctccgcgcctacagctcaagccacatccgaaggggagggagccgggagctgcgcgc
ggggccgctgggggggaggggtggcaccgcccacgccgggcggccacgaagggcggggcagcgggcgcgcgcccggcgggg
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tcgcggcgtggcgcccggtggtccccaaggggagggaaggggggaggcggggcgaggacagtgaccggagtctcctcagcggt
ggcttttctgcttggcagcctcagcggctggcgccaaaaccggactccgcccacttcctcgcccctgcggtgcgagggtgtggaatc
ctccagacgctgggggaggggggagttgggagcttaaaaactagtacccctttgggaccactttcagcagcgaactctcctgtacacca
ggggtcagttccacagacgcgggccaggggtgggtcattgcggcgtgaacaataatttgactagaagttgattcgggtgttt

>0.7UCOEfwd (SEQ ID NO: 2)

[0261] (SEQ ID NO: 2)

Cgcaaacacccgaatcaacttctagtcaaattattgttcacgccgcaatgacccacccctggcccgcgtctgtggaactgacccctgg
tgtacaggagagttcgctgctgaaagtggtcccaaaggggtactagtttttaagctcccaactccccctcccccagcgtctggaggatt
ccacaccctcgcaccgcaggggcgaggaagtgggcggagtccggttttggcgccagccgctgaggctgccaagcagaaaagcca
ccgctgaggagactccggtcactgtcctcgccccgcctcccccttccctcccctttggggaccaccgggcgccacgccgcgaacggt
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ggcgcgcgcccgctgccccgcccttcgtggccgcccggcgtgggcggtgccacccctcccccccagcggcccgcgcgcagctc
ccggctccctcccccttcggatgtggcttgagctgtaggcgcggagggccggagacgctgcagacccgcgacccggagcagctcg
gaggcggtgaagtcggtggctttccttctctctagctctcgctcgctggtggtgcttcagatgccacac

>DHS4

[0262] (SEQ ID NO: 3)

aattctatcatagtgtgtcttgtctatgataactgcattgagaaagatgctctgcttgttgagtgagcatttcacttccttctggttctgactatc
tgtctaatagtggtcatgtgggttgaaaagatagaaaaggggagtagtattaggaagttcagtatgaggaagacttattagacttatgcat
aaacctaaattctgttgtaatctggaagagctgaagtgccacatatgcatctgtttaggagagcaagaactacaaatttggtcttcagtttg
gcttgcttacatcctgagaactctgtaggccacatgtcgtgaatatagcagcctctgcaacagtgaaagccagaaaaggaagtggaaa
gtctcaggggaggggggctttctgtcatggatttatgagcacagcaagactaacaagcaaaaagaaaaatgtaaaaggatcttgttcgt

>IE4-5

[0263] (SEQ ID NO: 4)

acatctttgagcttcagtttcctcatctgtaaataggggaataatacatacttcttaaggctactgcaaagatcaaataagtaatacatttga
agcacttgggacagagcctgctacatagtaagtgctcattaagtgttagttatcattgttgttgtttttaggccaaggttgttgtgaaaattaa
atgagataatatataaaaggtatttagctcaatatctggcacatagcaataattgaatagatgatccttcatcttcgttcctcctgttccctttc
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agaatctaaatgtttattaagacaaagggctgtcatgcaataacccaaccataccattatcagtctgccatccttcctgtttctctaggcag
cctttcctgatgtcaactcaaccagttaatctctcagtcacttgacatgtggctatatatacacacaaatatgtgtgcatgcatcctgtgctg
caagcatttacagtcaagtttatctgaacacactgtatggttgatgtgaaatgctgaaactgttcaagtttaggtcctcacaaagcaagga
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>BTKp

[0264] (SEQ ID NO: 5)

Tgcatttcctaggagaatccctgggggaatcattgcagttggagcataatgtaggggggcccctgagaaaacctccaggcttcaagtg

acatacctagtctgctttaccggtttacaggactcaagagaaaggtggacattgagagttaatccctgaggccaaatcttaaatggagaa
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cagaggtcccaagcaaatgaagggcggggacagttgaggggggtggaatagggacggcagcagggaaccagatagcatgctgct
gagaagaaaaaaagacattggtttaggtcaggaagcaaaaaaagggaactgagtggctgtgaaagggtggggtttgctcagactgtc
cttcctctctggactgtaagaattagtctc

>coBTK

[0265] (SEQ ID NO: 6)

atggccgctgtgatcctggagagcattttcctgaagaggtcccagcagaaaaagaaaacctctcccctgaactttaagaaaagactgtt
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ctgtttagtacaatcccagagctgattaactaccaccagcacaattctgccggcctgatcagcaggctgaagtatcccgtctcccagca
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tgggctctaagtttcctgtgagatggtctccacccgaggtgctgatgtatagcaagttctcctctaagagcgatatctgggcctttggcgt
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gcgcctgtaccggccacatctggcctctgagaaggtgtacaccatcatgtacagctgttggcacgagaaggccgacgagagaccca
cattcaagatcctgctgtccaacattctagatgtgatggacgaggagagctga

>co2BTK

[0266] (SEQ ID NO: 7)

atggccgccgtgatcctggaaagcatcttcctgaagcggagccagcagaagaagaaaaccagccccctgaacttcaagaagcggct
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atggacgaggaaagctga

[0267] Sequence elements relative to Figure 92 (if not already shown above)- these are constructs that were tested as part of the process of identifying the above sequences as our top candidates for clinical gene therapy vectors:

>GFP

[0268] (SEQ ID NO: 8)

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>Intron 4

[0269] (SEQ ID NO: 9)

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>Intron 5

[0270] (SEQ ID NO: 10)

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[0272]

>CONTIG

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[0275]

>ABCD

[0276] (SEQ ID NO: 16)

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>AB

[0278] (SEQ ID NO: 18)

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>A

[0279] (SEQ ID NO: 19)

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>B

[0280] (SEQ ID NO: 20)
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>BTKe

[0281] (SEQ ID NO: 21)
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>BTKeΔMyc

[0282] (SEQ ID NO: 22)
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[0283] The sequences of gene expression cassettes below are cloned into pRRL backbone of pRRLSIN.cppt.PGK-GFP.WPRE [PGK-GFP removed] Addgene #12252;

[0284] The nucleic acid comprising the promoter with GFP sequence is below **(BTKp.GFP) : (SEQ ID NO: 23)**

[0285]

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INT4.BTKp.GFP (SEQ ID NO: 24)

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AGACTTATTAGACTTATGCATAAACCTAAATTCTGTTGTAATCTGGAAGA
GCTGAAGTGCCACATATGCATCTGTTTAGGAGAGCAAGAACTACAAATTT
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GCTTCAAGTGACATACCTAGTCTGCTTTACCGGTTTACAGGACTCAAGAG
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TCAGCACGGGGAAGTCTTGTCTCTACCTCTGTCTTGTTTTGTCCTTTGGGG
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CAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGACC
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CGTGCTGCTGCCCGACAACCACTACCTGAGCACCCAGTCCGCCCTGAGCA
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INT5.BTKp.GFP (SEQ ID NO: 25)

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ATTTCTCTATTTATTAAGAAAAGTCCCATTTTTTGCACTGAATACAAGGGT
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INT13.BTKp.GFP (SEQ ID NO: 26)

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CGTGCTGCTGCCCGACAACCACTACCTGAGCACCCAGTCCGCCCTGAGCA
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1kb.BTKp.GFP (SEQ ID NO: 27)

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CAATGTTTCTGGAAACTATTTTGGCAGTATGTATCAAAATGCAAAATGCA
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CGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGACCCTG
AAGTTCATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCGT
GACCACCCTGACCTACGGCGTGCAGTGCTTCAGCCGCTACCCCGACCACA
TGAAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAG
GAGCGCACCATCTTCTTCAAGGACGACGGCAACTACAAGACCCGCGCCGA
GGTGAAGTTCGAGGGCGACACCCTGGTGAACCGCATCGAGCTGAAGGGC
ATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGGAGTACA
ACTACAACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGG

CATCAAGGTGAACTTCAAGATCCGCCACAACATCGAGGACGGCAGCGTG
CAGCTCGCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGT
GCTGCTGCCCGACAACCACTACCTGAGCACCCAGTCCGCCCTGAGCAAAG
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TTTCCTAGGAGAATCCCTGGGGGAATCATTGCAGTTGGAGCATAATGTAG
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TTTATCAGCTAGTGGAGGAGGCTGACGGAGGGTGGGAGTGTCATCAGCAC
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CCCTTCTGTCAAATAGTGCTTGAAGACTCAATAGGGATACATGGGTCAAT
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GCGACGGCCCCGTGCTGCTGCCCGACAACCACTACCTGAGCACCCAGTCC
GCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTGG
AGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAG
TAA

B.BTKp.GFP (SEQ ID NO: 40)

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ACCCTGGTGAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACG
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GGGCCTTTGGCGTGCTGATGTGGGAAATCTACAGCCTGGGCAAGATGCCT
TACGAGCGGTTCACAAATTCCGAGACAGCTGAGCACATCGCCCAGGGCCT
GCGCCTGTACCGGCCACATCTGGCCTCTGAGAAGGTGTACACCATCATGT
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GCTGTCCAACATTCTAGATGTGATGGACGAGGAGAGCTGA

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AGATGTGATGGACGAGGAGAGCTGA

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[0286]

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CGAGGAGAGCTGA

[0287] SEQ ID NO: 46: The B29 promoter sequence:

[0288]

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TGGGGGAGAGAGTTTGCCCTGAGAGACCCAGCAGGCAACTGTGTGCACTTTGTG
GCAGAGGAGCAGGACTGA

[0289] It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (*e.g,* bodies of the appended claims) are generally intended as "open" terms (*e.g,* the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (*e.g,* "a" and/or "an" should be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should be interpreted to mean at least the recited number (*e.g,* the bare recitation of "two recitations," without other modifiers, means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g,* " a

system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g,* " a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

[0290] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0291] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0292] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as, an acknowledgement or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

WHAT IS CLAIMED IS:

1. A polynucleotide for sustained Bruton's tyrosine kinase (BTK) expression, the polynucleotide comprising:

(i) a first sequence encoding a ubiquitous chromatin opening element (UCOE), wherein the UCOE consists of a fragment from a human CBX3 gene, wherein the fragment comprises an exon 1 and an alternative exon 1 of the CBX3 gene, and a 3′ end of the alternative exon 1, and wherein the UCOE has a length in a range from 0.668 kb to 1 kb;

(ii) a second sequence encoding a BTK promoter; and

(iii) a third sequence encoding BTK.

2. The polynucleotide of claim 1, wherein the UCOE has a length of 0.75 kb or less.

3. The polynucleotide of any one of claims 1-3, wherein the UCOE lacks a cryptic splice acceptor site located between an exon 1 and an alternative exon 1 in a wild type CBX3 gene.

4. The polynucleotide of any one of claims 1-4, wherein the UCOE lacks a splice acceptor site located at the 3′ end of exon 1 in the wild type CBX3 gene.

5. The polynucleotide of claim 1 or 2, wherein the first sequence comprises the nucleotide sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 2.

6. The polynucleotide of any one of claims 1-5, wherein the BTK promoter comprises the nucleotide sequence set forth in SEQ ID NO: 5.

7. The polynucleotide of any one of claims 1-6, wherein the third sequence is codon optimized for expression in humans.

8. The polynucleotide of any one of claims 1-7, wherein the third sequence comprises the nucleotide sequence set forth in SEQ ID NO: 6 or SEQ ID NO: 7.

9. A vector comprising the polynucleotide of any one of claims 1-8.

10. The vector of claim 9, wherein the vector is a lentiviral-based vector.

11. A cell comprising the polynucleotide of any one of claims 1-8 or the vector of claim 9 or 10.

12. The cell of claim 11, wherein the cell is a B cell.

13. The cell of claim 11, wherein the cell is a myeloid cell.

14. The cell of claim 11, wherein the cell is a hematopoietic stem cell.

15. The cell of claim 11, wherein the cell is a CD34+ hematopoietic stem cell.

16. A pharmaceutical composition comprising the cell of any one of claims 11-15, and a pharmaceutically acceptable carrier.

17. A method of promoting B cell survival, proliferation and/or differentiation in a subject in need thereof, the method comprising administering the cell of any one of claims 11-15 or the pharmaceutical composition of claim 16 to the subject.

18. The method of claim 17, wherein the subject has a BTK deficiency.

19. A method of treating, inhibiting, or ameliorating X linked agammaglobulinemia (XLA) in a subject in need thereof, the method comprising administering the cell of any one of claims 11-15 or the pharmaceutical composition of claim 16 to the subject.

20. The method of any one of claims 17-19, wherein the cell is derived from the subject.

21. The method of any one of claim 17-20, wherein the administering is performed by adoptive cell transfer.

22. Use of the cell of any one of claims 11-15 in the manufacture of a medicament for treating a subject having a BTK deficiency.

23. The use of claim 22, wherein the subject has X linked agammaglobulinemia.

24. An *in vitro* or *ex vivo* method of modifying a cell, comprising introducing into the cell the polynucleotide of any one of claims 1-8.

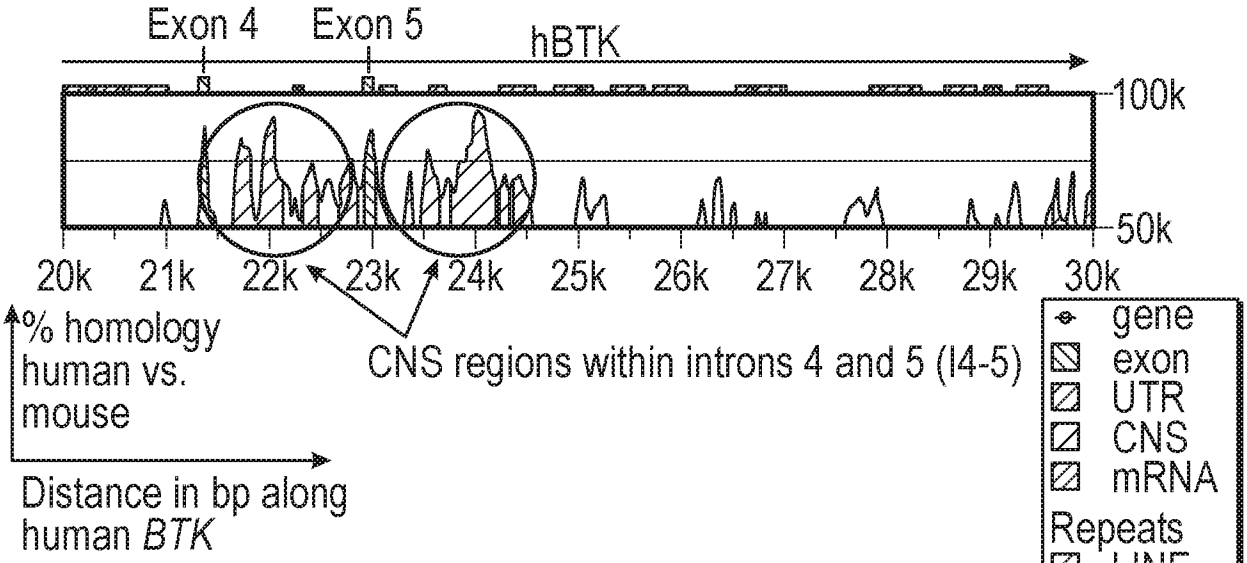
GOAL: Optimize gene delivery platform for XLA
Restore endogenous BTK expression in B and myeloid cells
Rescue immunological responses
Optimize vector safety profile
Previously Investigated Lentiviral vectors for XLA
Promoter and transcription regulatory elements
coding sequence
Restored BTK expression in B and myeloid cells
Effective with Low number Viral integrations per cell
BTKp
BTK
BTK minimal Promoter
X
✓
Eμ
BTKp
BTK
Ig heavy chain μ intronic enhancer
✓
X
1.5 kb UCOE
BTKp
BTK
Ubiquitous Chromatin opening element
✓/X
✓
Need to further optimization to improve BTK expression in B and myeloid cells.

FIG. 1

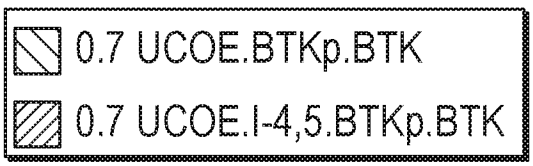
Optimizing Lentiviral Vector for Gene Therapy of XLA

1) Improve viral titer by decreasing size of the UCOE element to 0.7 kb.

2) Identify transcriptional elements within the endogenous human *BTK* that improve expression in B and myeloid cells. Test expression with conserved non-coding sequences (CNS) included upstream of *BTK* promoter



Lentiviral vectors tested in pre-clinical model:



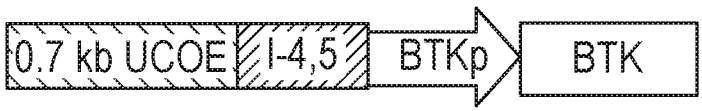


FIG. 2

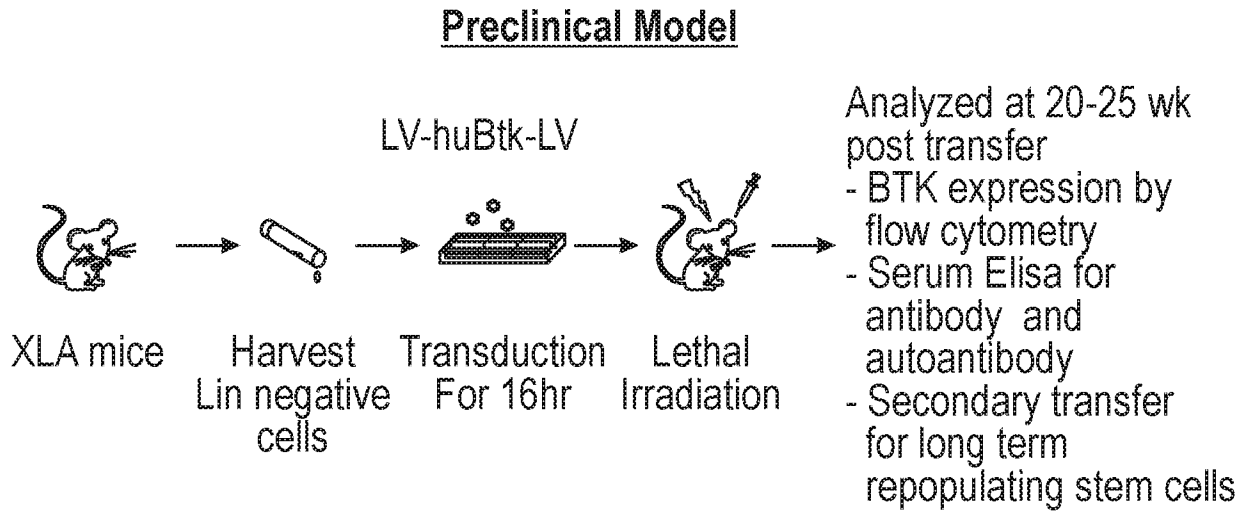

Preclinical Model
LV-huBtk-LV
Analyzed at 20-25 wk post transfer
- BTK expression by flow cytometry
- Serum Elisa for antibody and autoantibody
- Secondary transfer for long term repopulating stem cells
XLA mice
Harvest Lin negative cells
Transduction For 16hr
Lethal Irradiation

FIG. 3

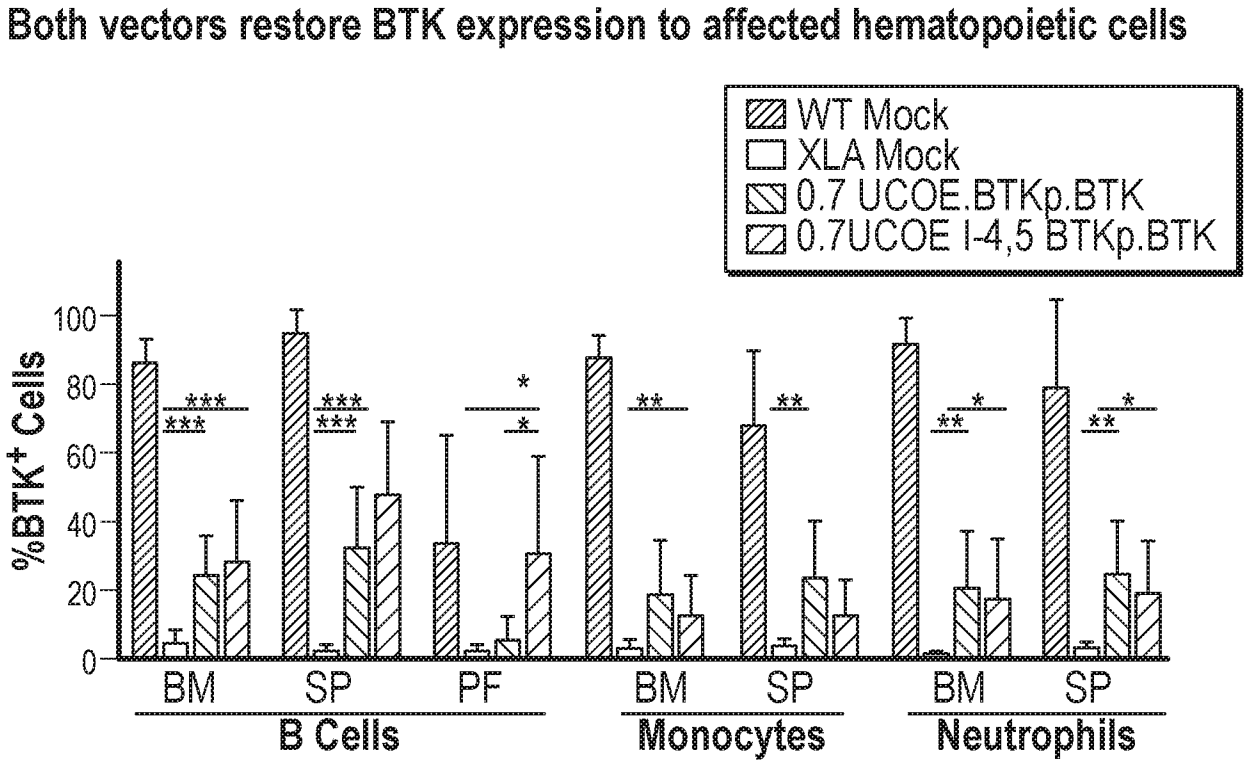

Both vectors restore BTK expression to affected hematopoietic cells
WT Mock
XLA Mock
0.7 UCOE.BTKp.BTK
0.7UCOE I-4,5 BTKp.BTK
%BTK+ Cells
100
80
60
40
20
0
BM
SP
PF
BM
SP
BM
SP
B Cells
Monocytes
Neutrophils

FIG. 4

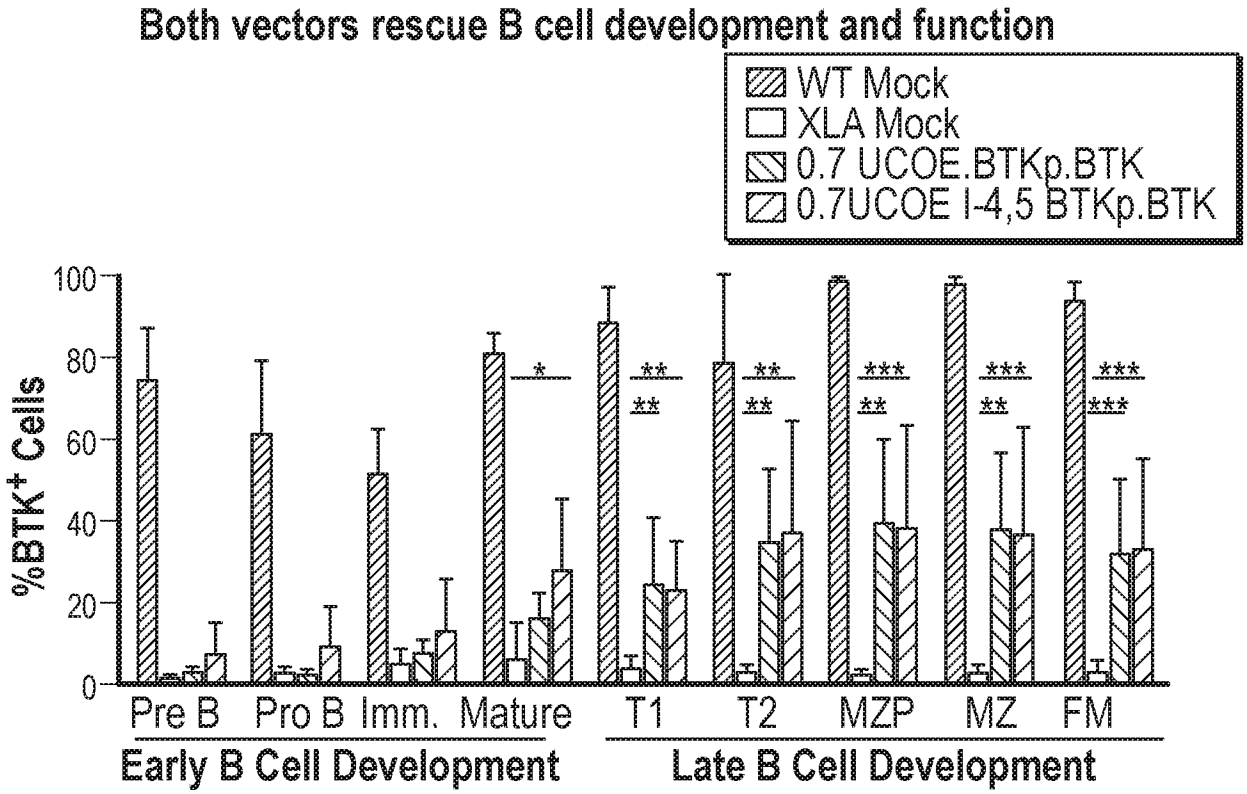


FIG. 5

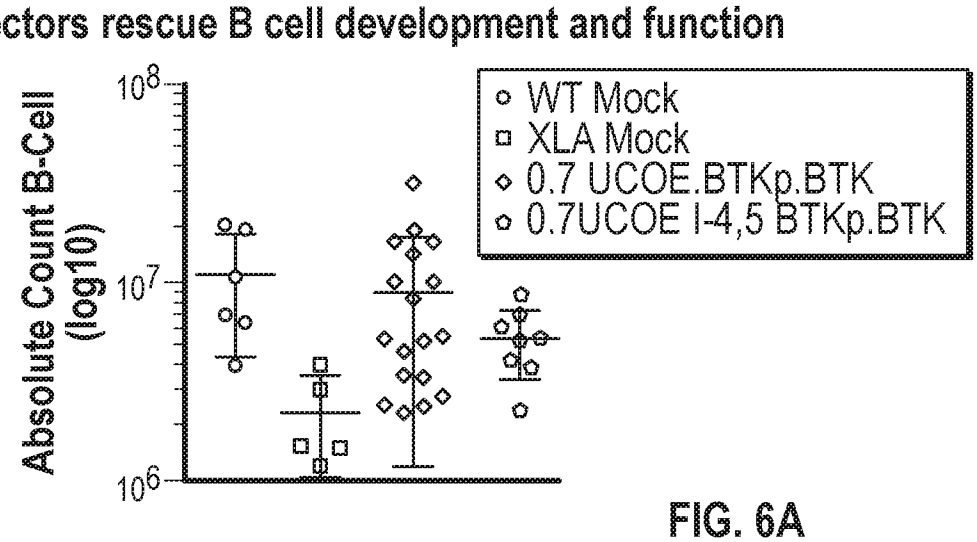


FIG. 6A

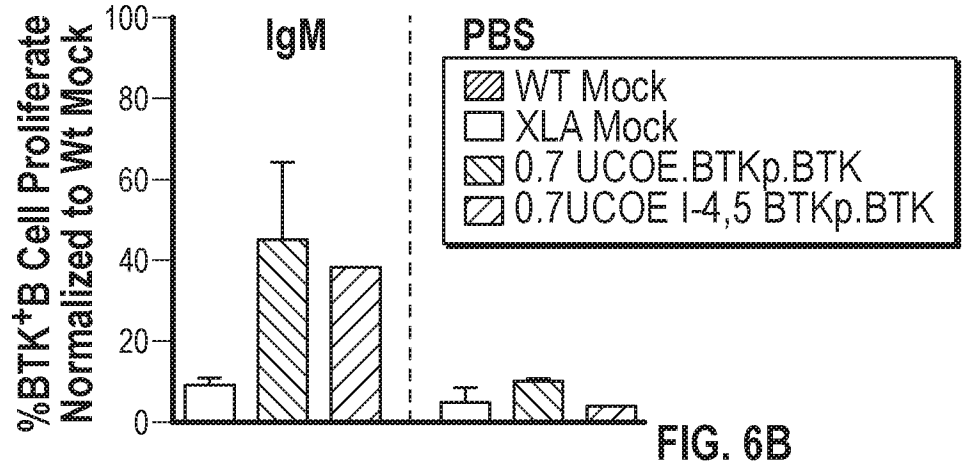


FIG. 6B

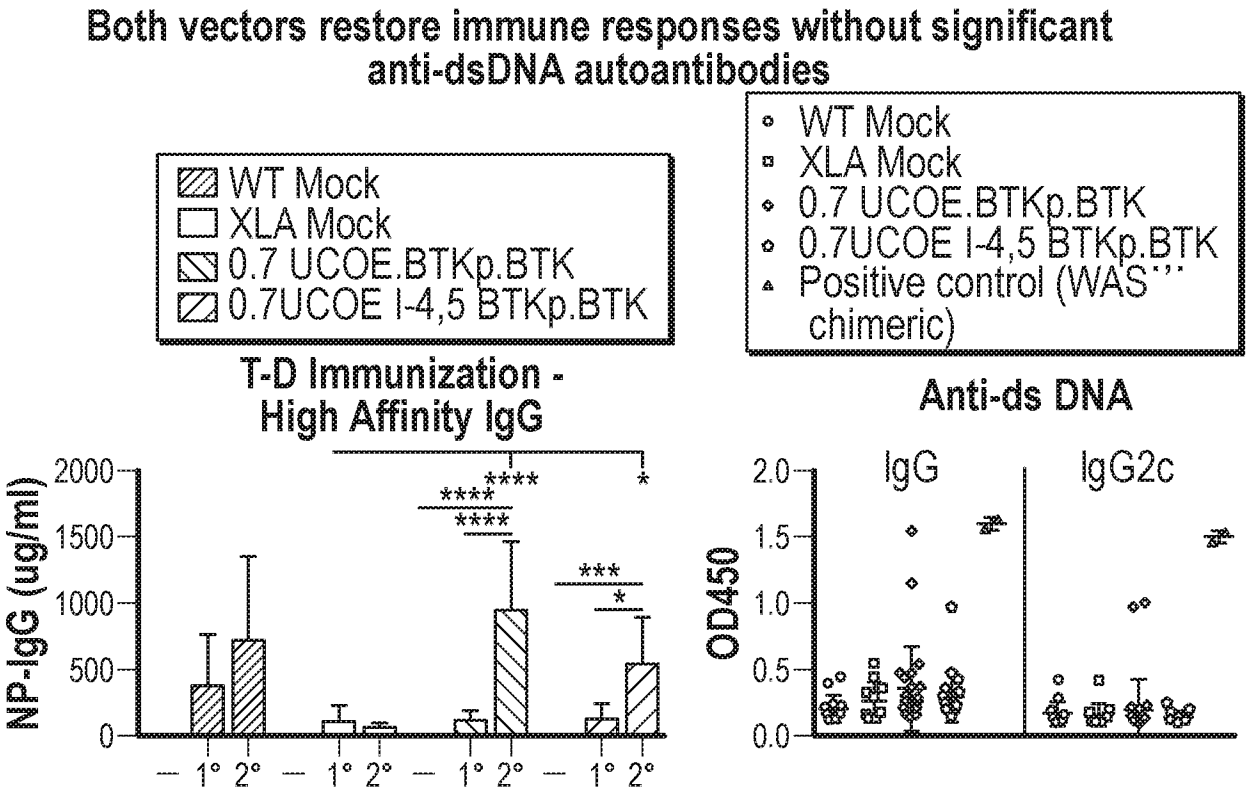


FIG. 7A

FIG. 7B

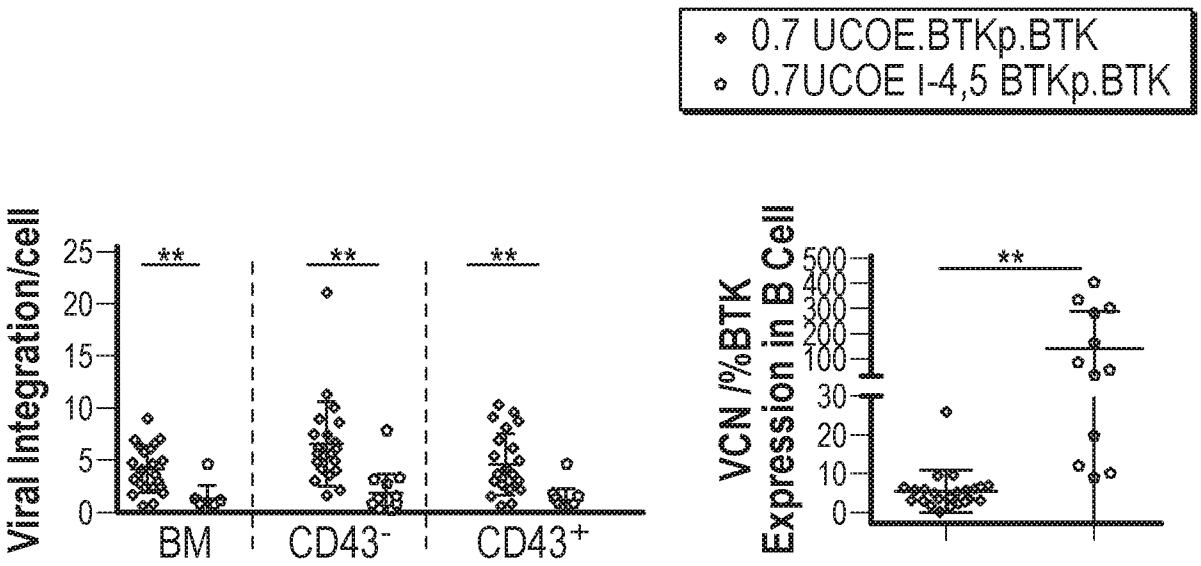


FIG. 8A

FIG. 8B

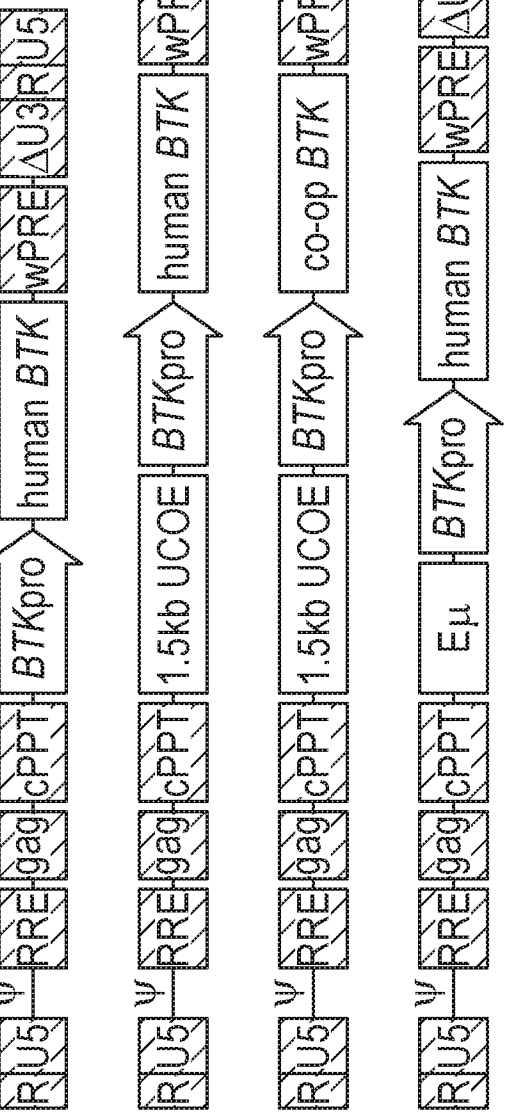

BTKpro.BTK (5.4kb)
1.5UCOE.BTKpro.BTK (6.9kb)
.5UCOE.BTKpro.coBTK (6.9kb)
Eμ.BTKpro.BTK (6.4kb)
RU5
Ψ
RRE
gag
cPPT
1.5kb UCOE
Eμ
BTKpro
human BTK
co-op BTK
wPRE
ΔU3RU5

FIG. 9A

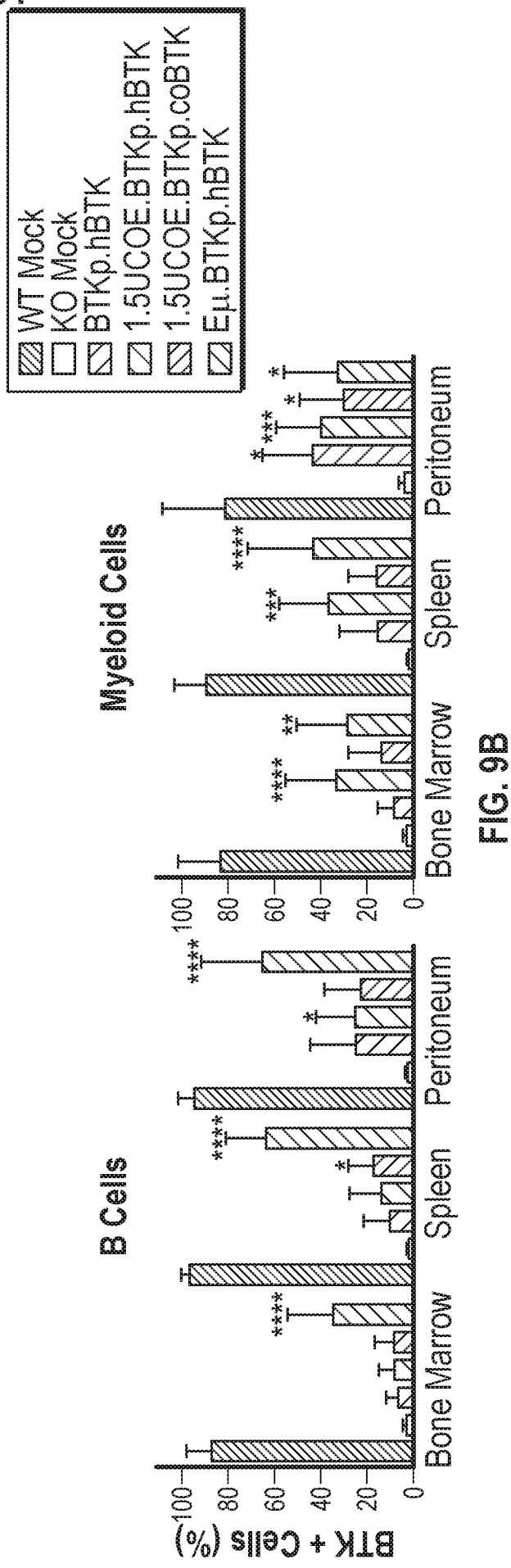

WT Mock
KO Mock
BTKp.hBTK
1.5UCOE.BTKp.hBTK
1.5UCOE.BTKp.coBTK
Eμ.BTKp.hBTK
B Cells
Myeloid Cells
BTK + Cells (%)
Bone Marrow
Spleen
Peritoneum

FIG. 9B

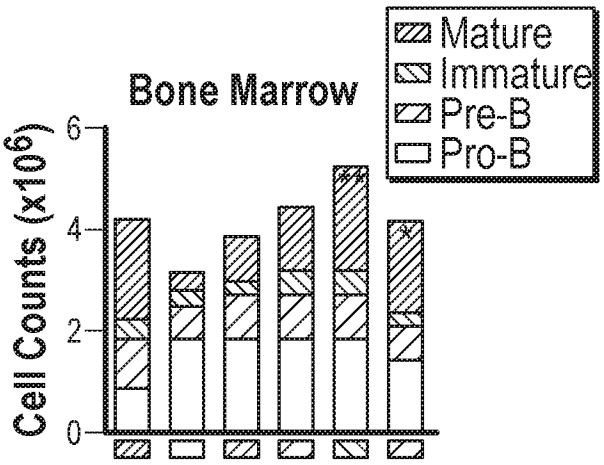


FIG. 9C

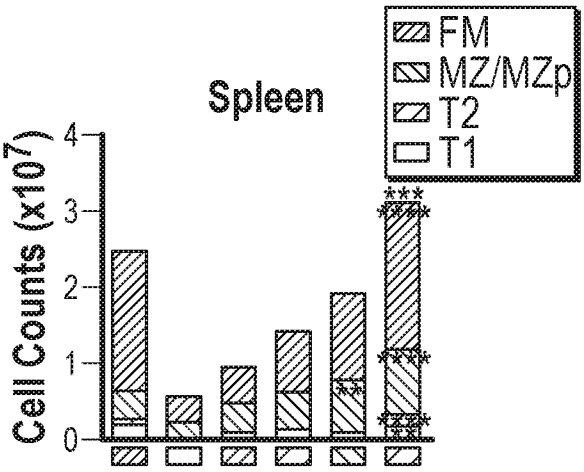


FIG. 9D

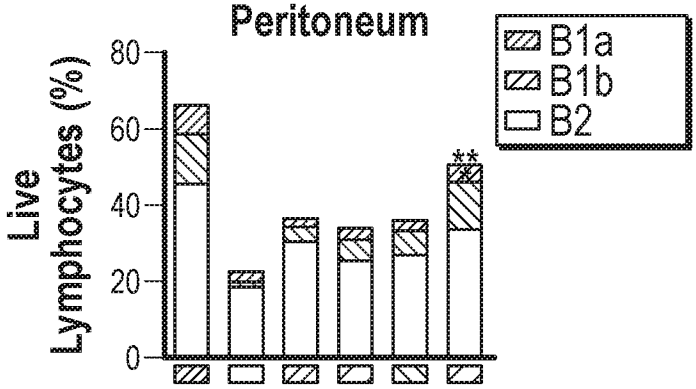


FIG. 9E

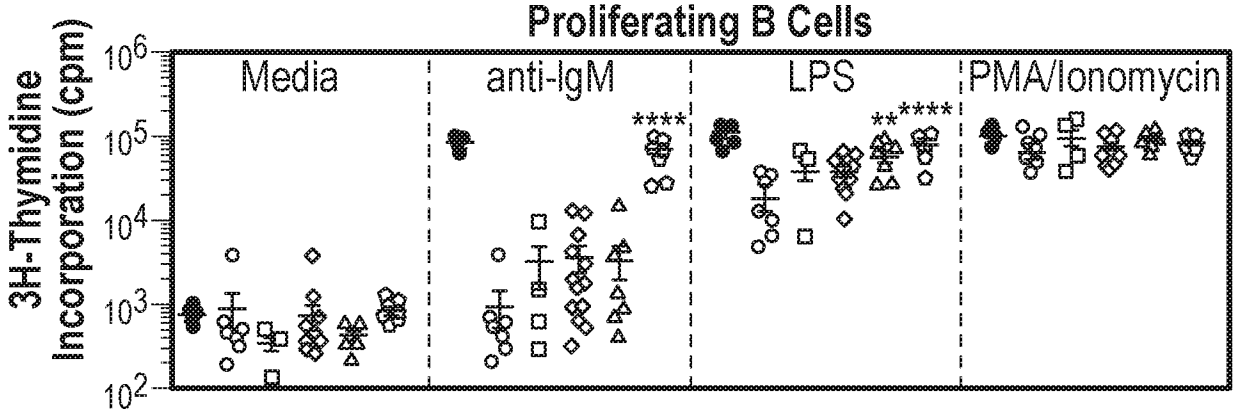


FIG. 9F

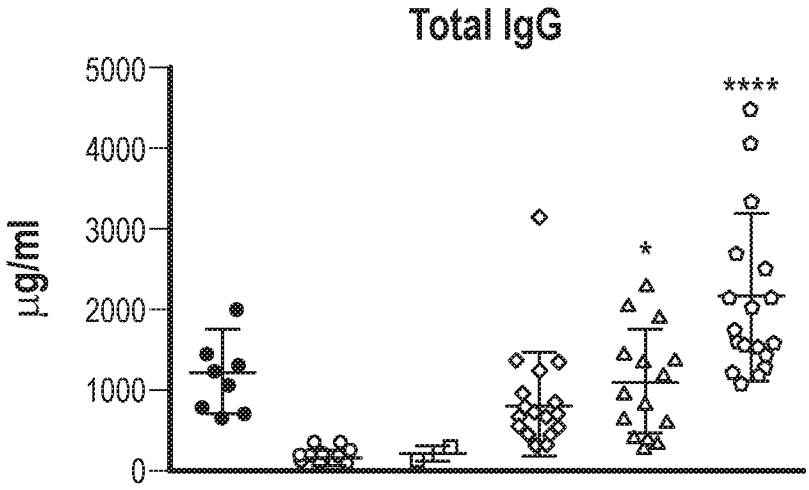


FIG. 9G

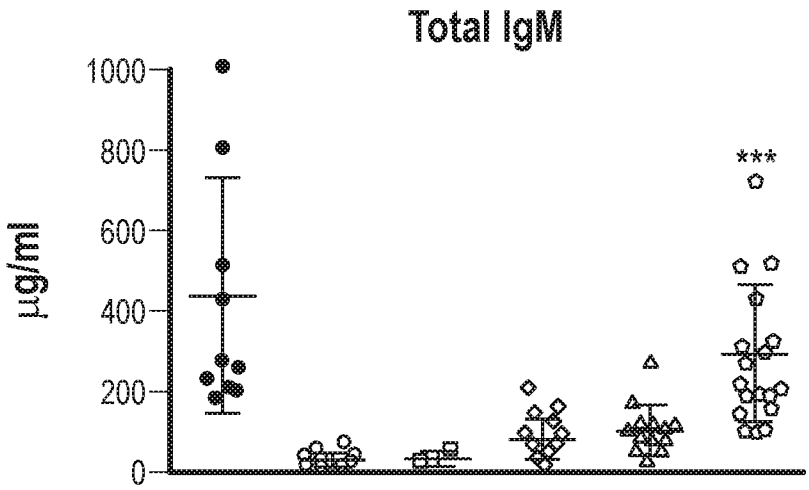


FIG. 9H

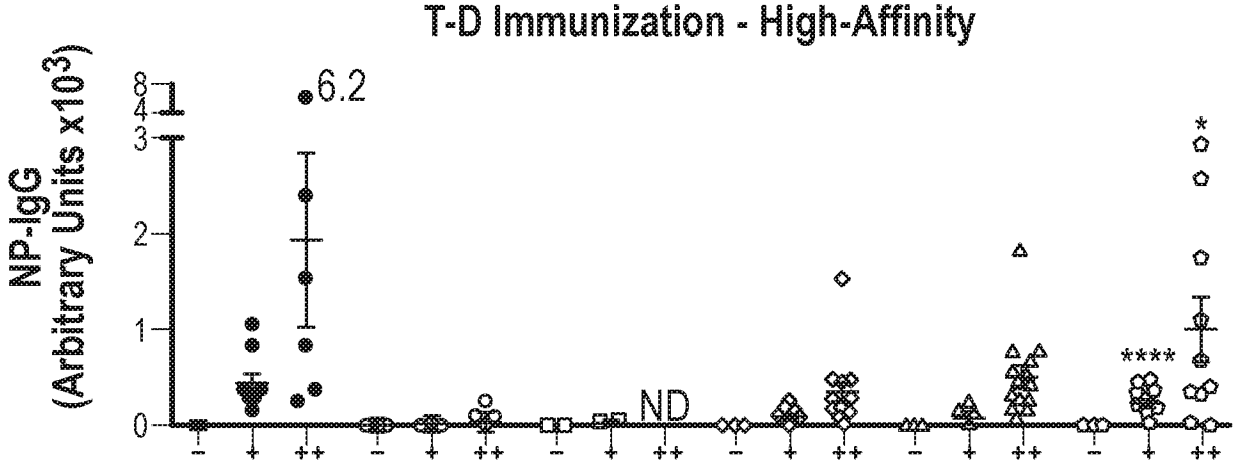


FIG. 9I

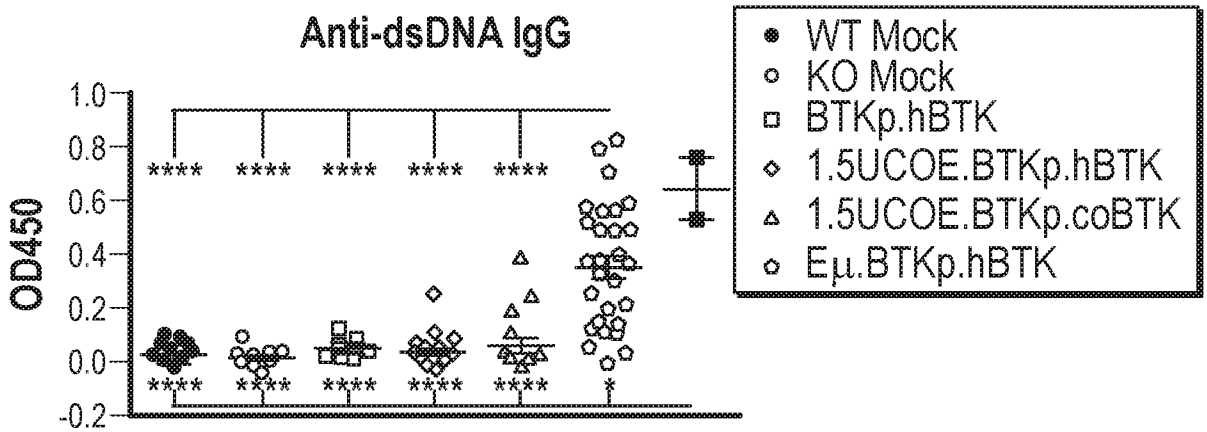


FIG. 10A

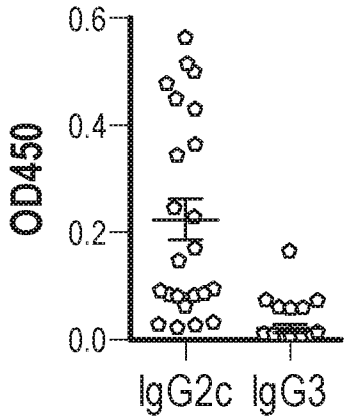


FIG. 10B

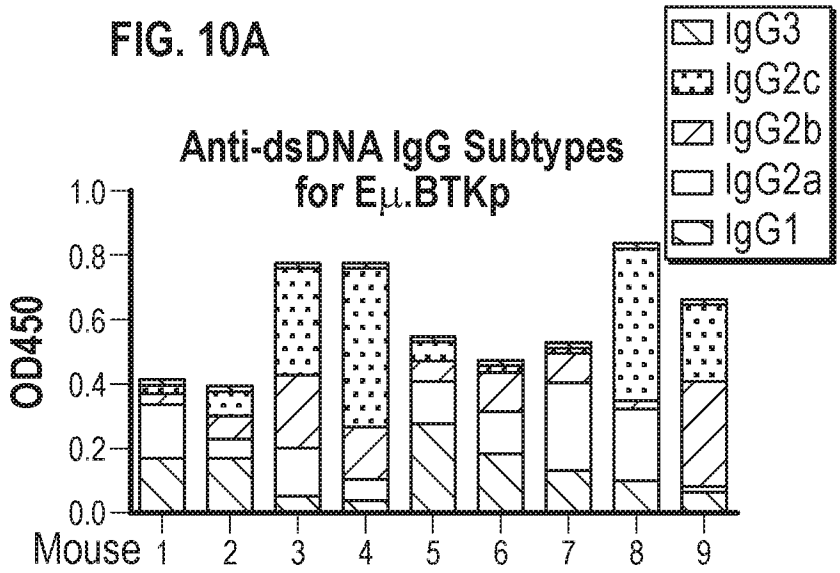


FIG. 10C

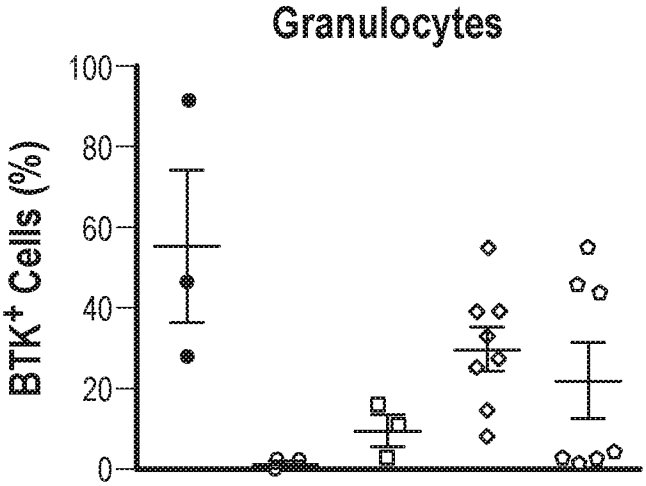


FIG. 11A

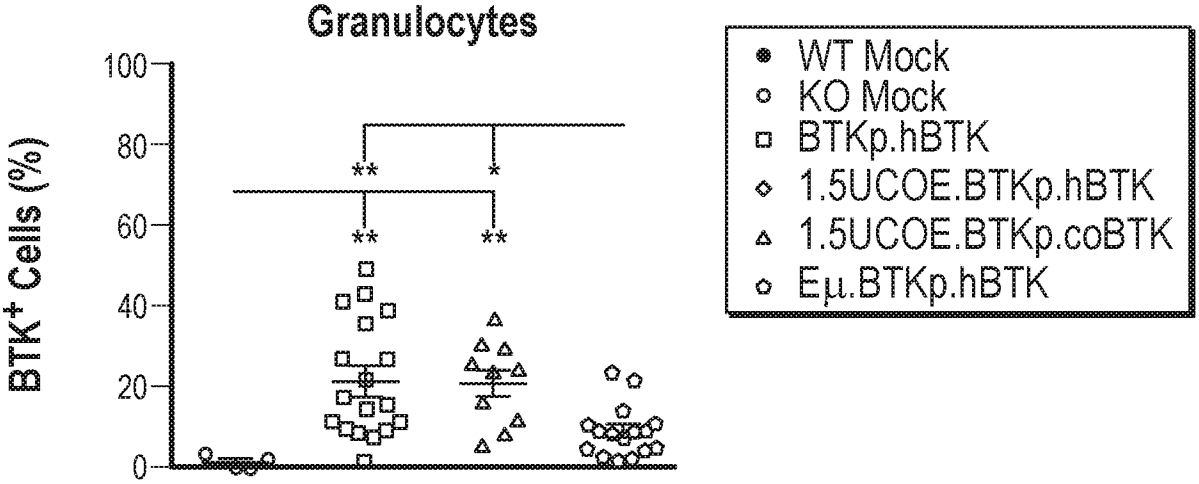


FIG. 11B

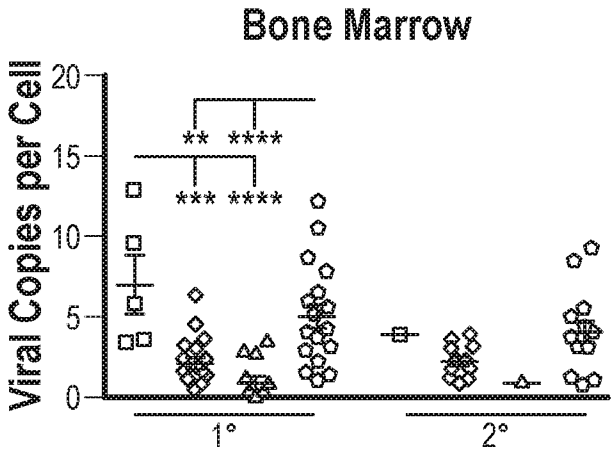


FIG. 11C

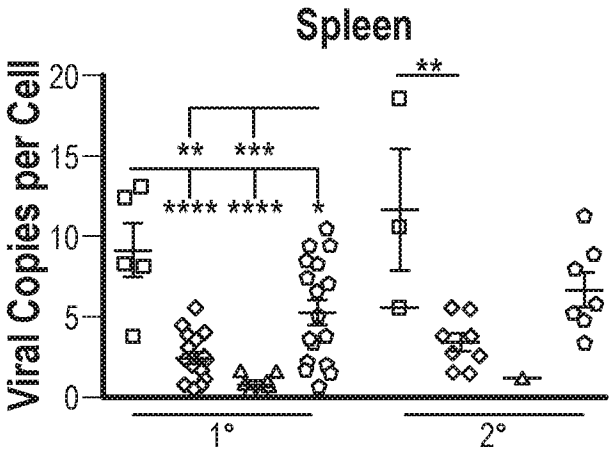


FIG. 11D

FIG. 12A

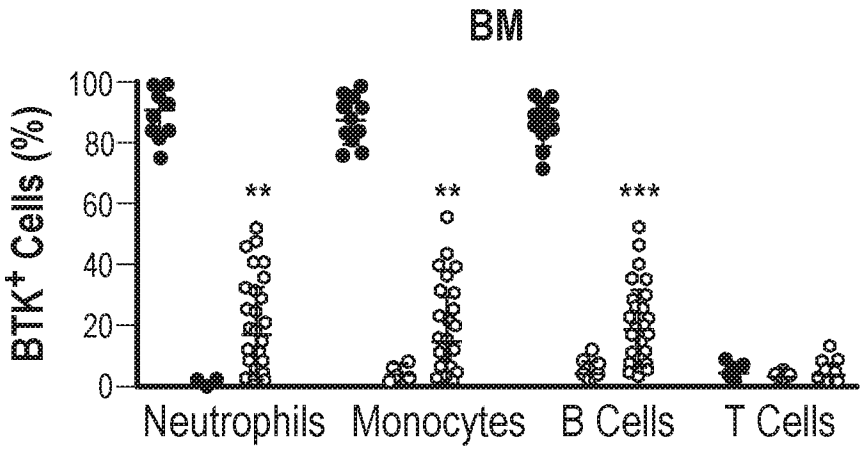


FIG. 12B

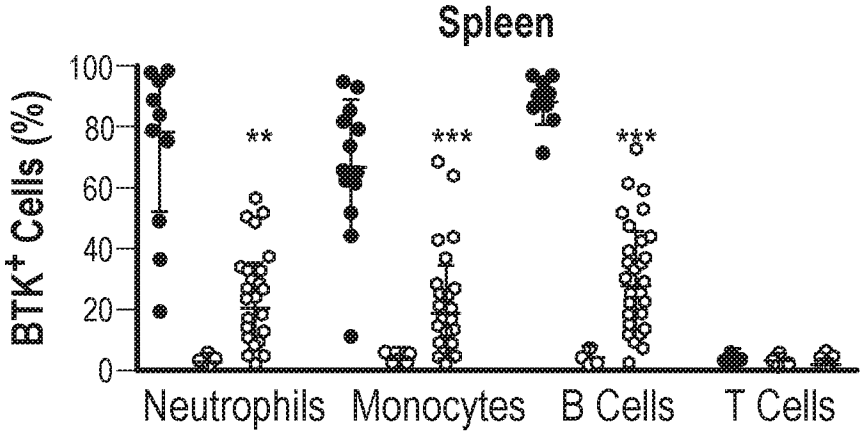


FIG. 12C

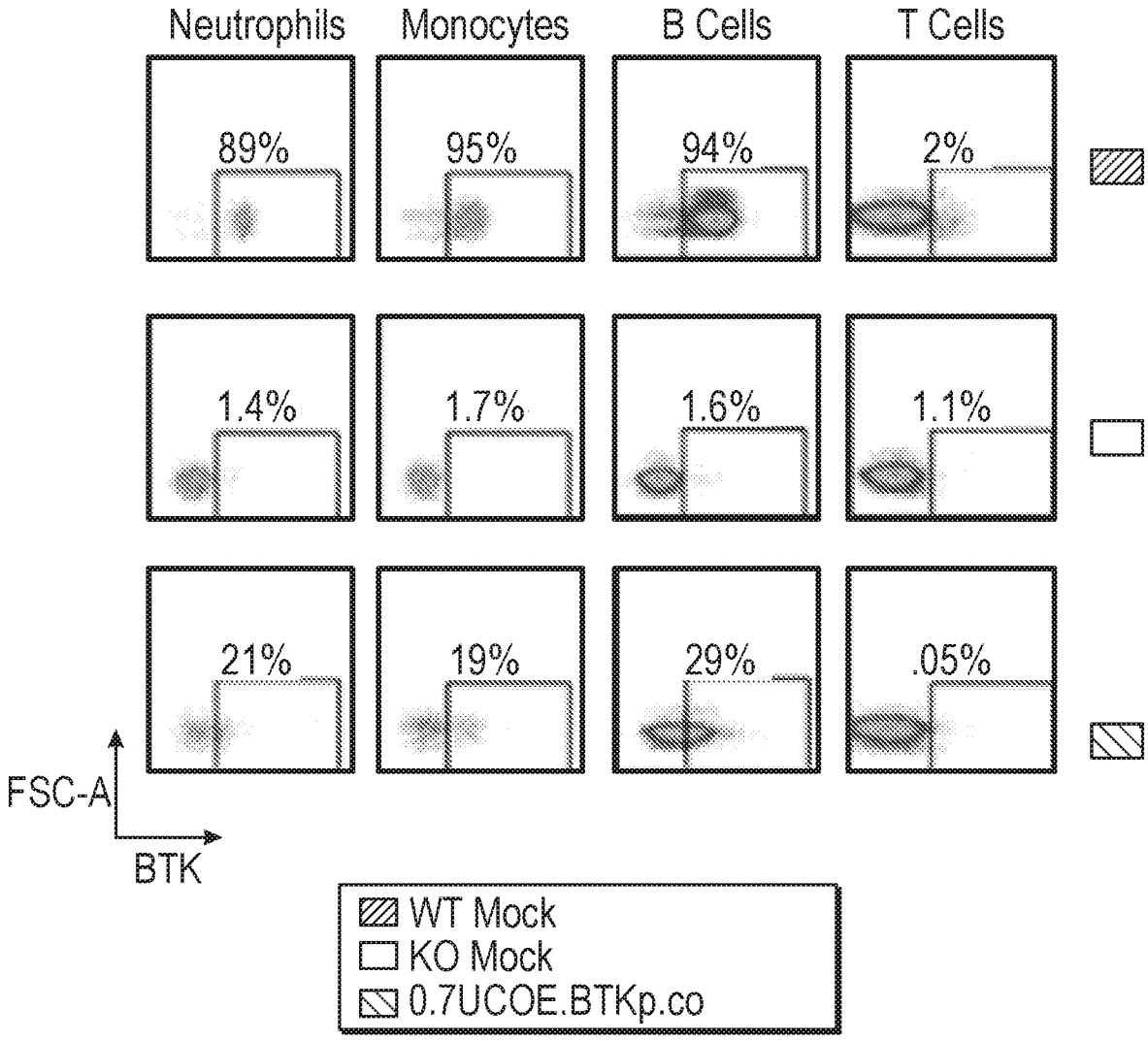


FIG. 12D

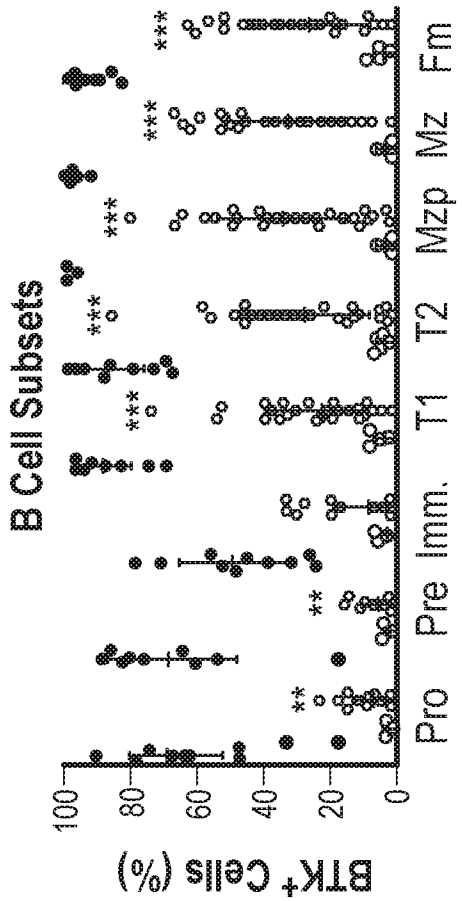


FIG. 12F

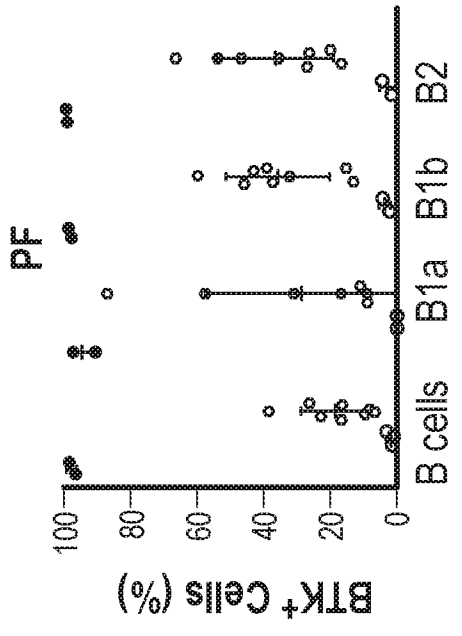


FIG. 12E

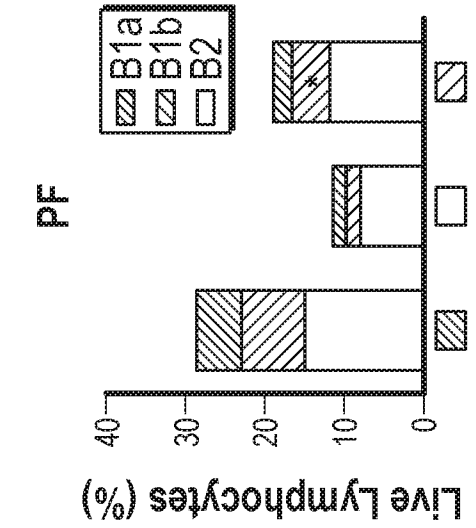


FIG. 12I

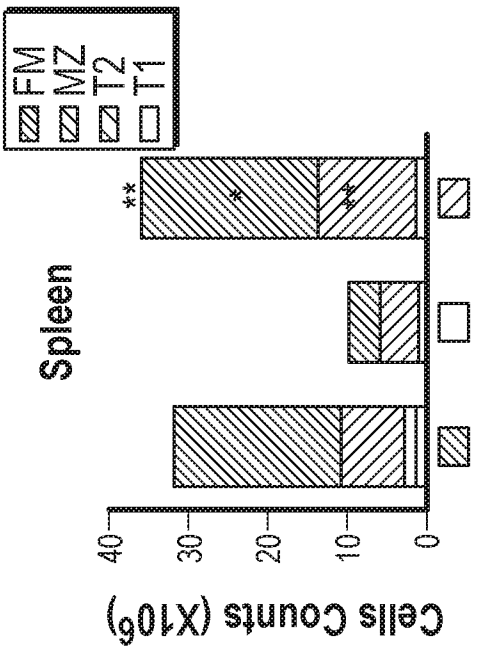


FIG. 12H

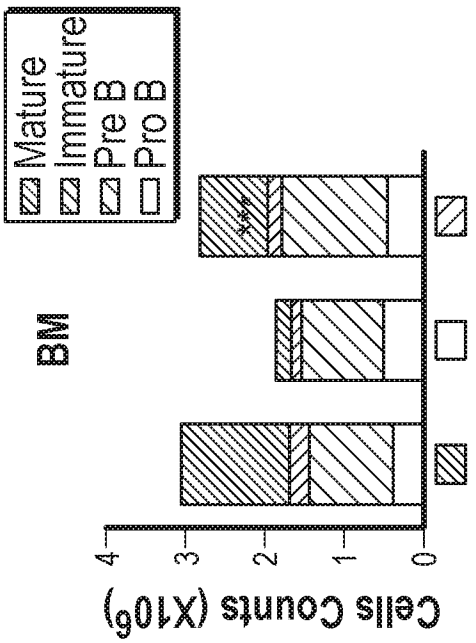


FIG. 12G

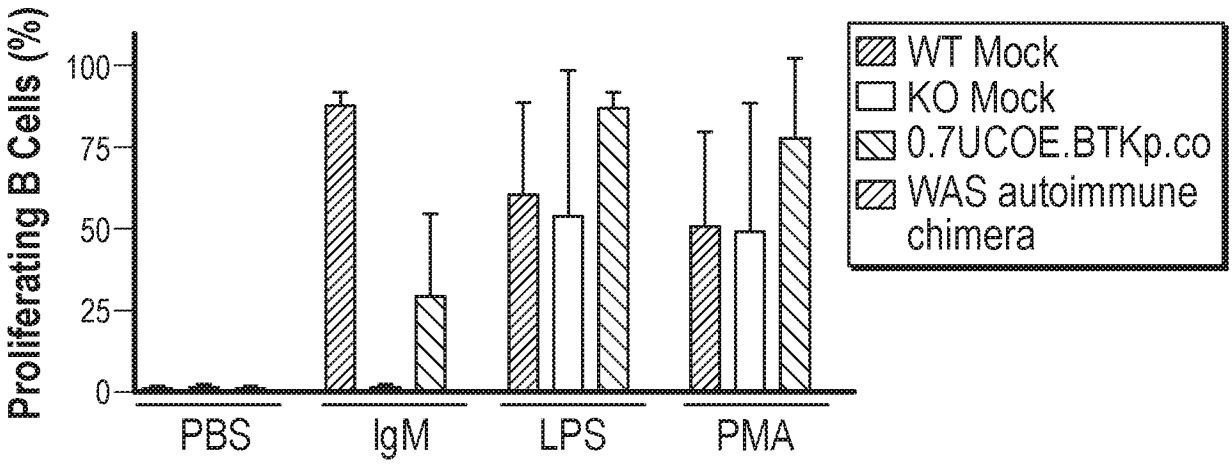


FIG. 13A

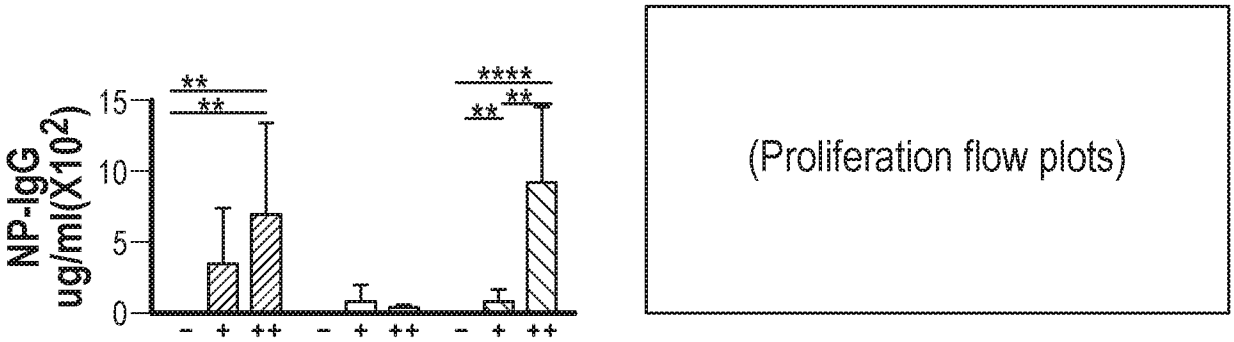


FIG. 13C

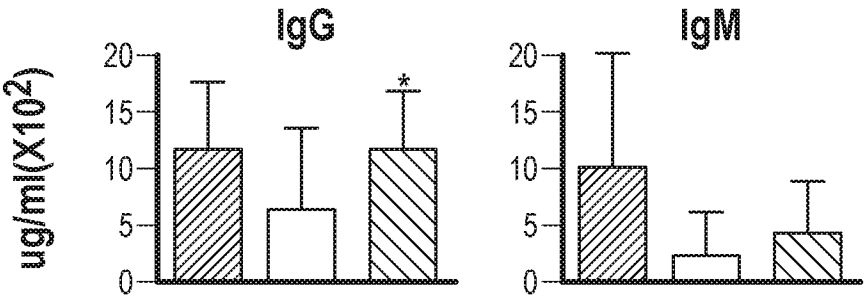


FIG. 13D

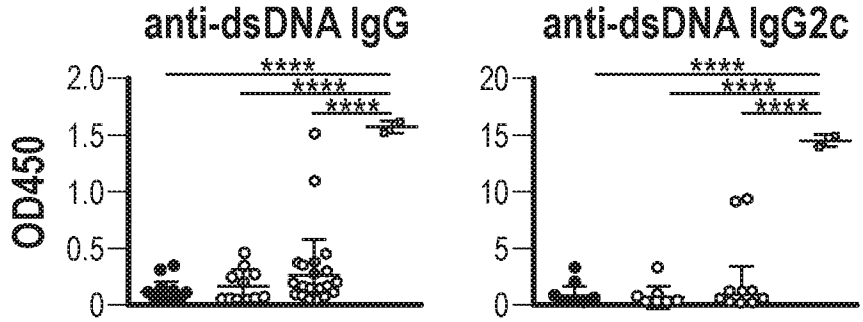


FIG. 13E

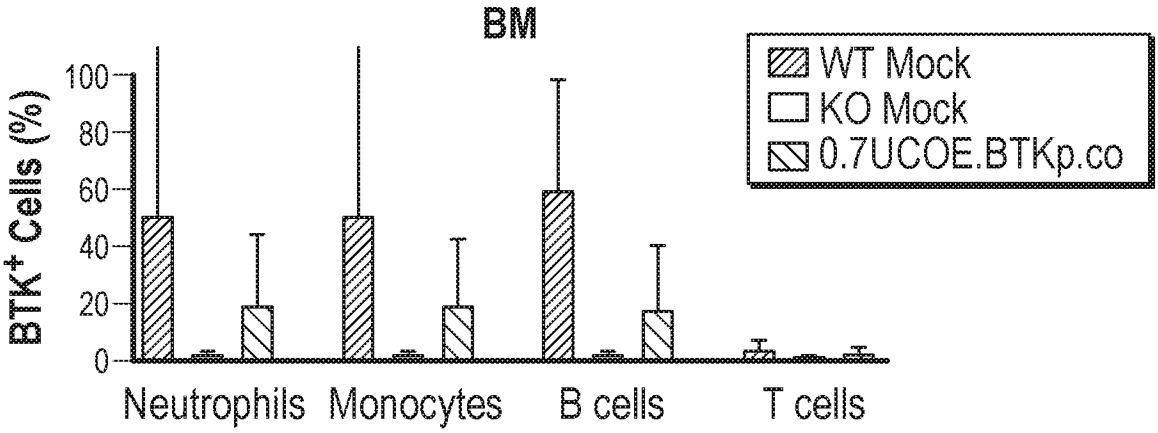


FIG. 14A

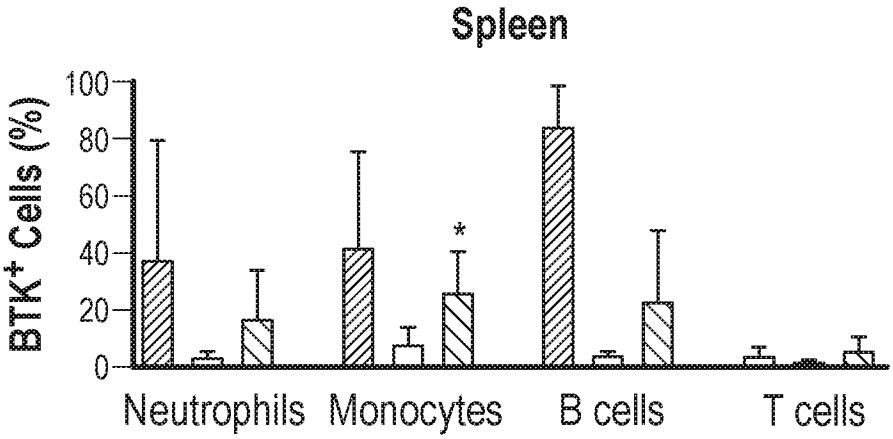


FIG. 14B

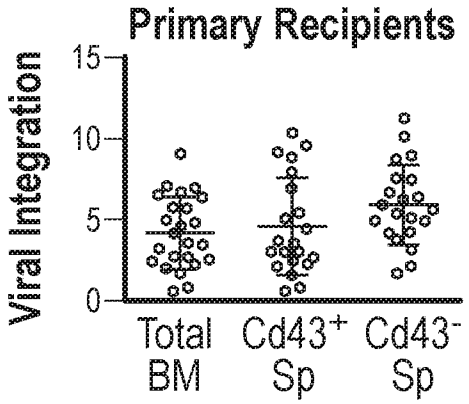


FIG. 14C

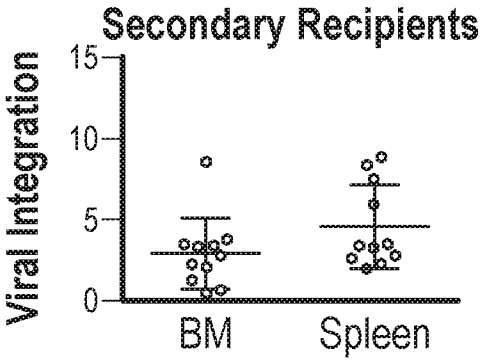


FIG. 14D

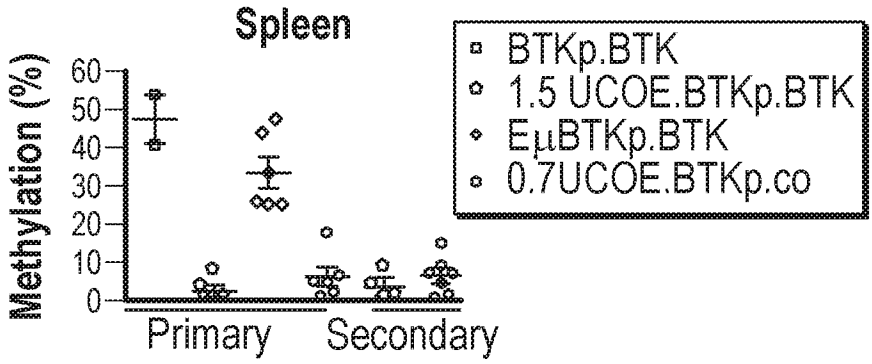


FIG. 14E

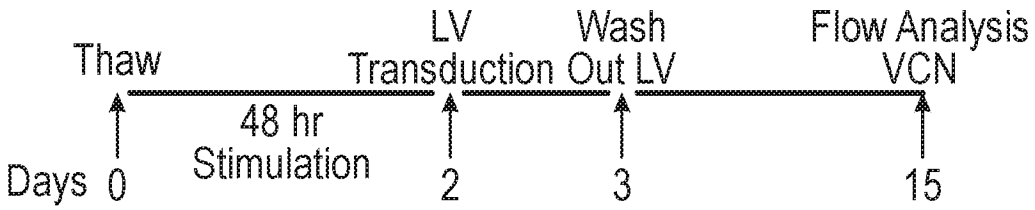


FIG. 15A

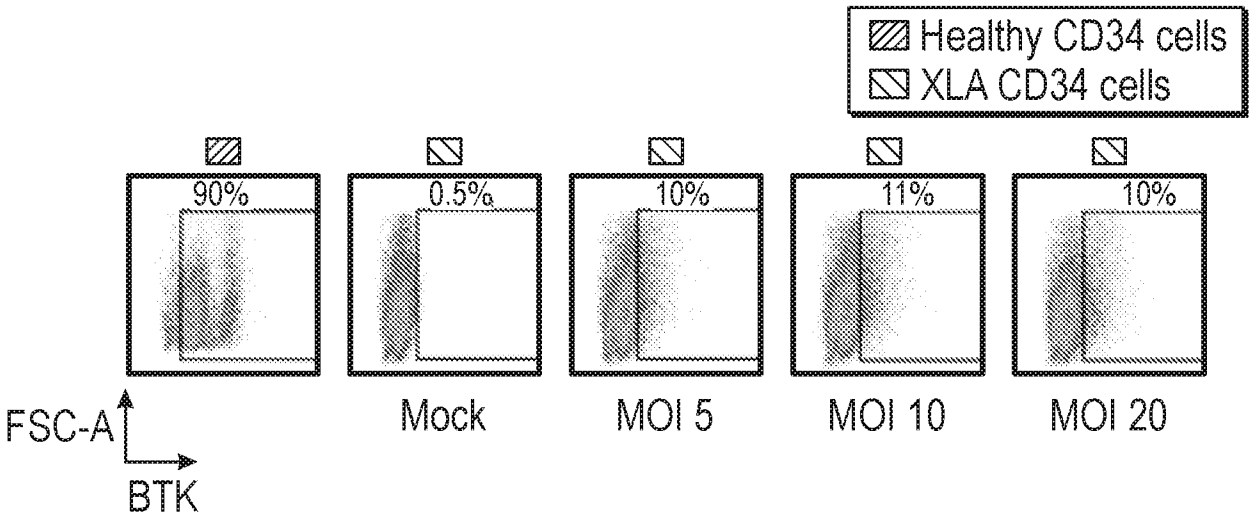


FIG. 15B

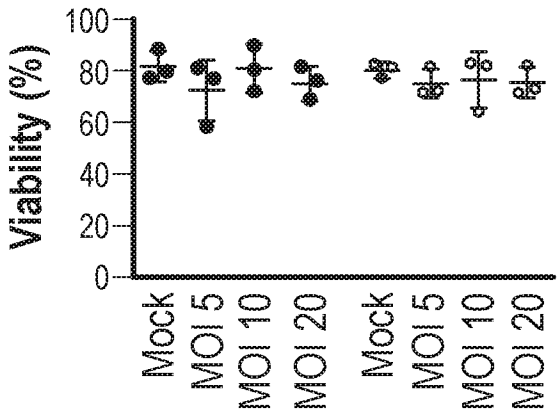


FIG. 15C

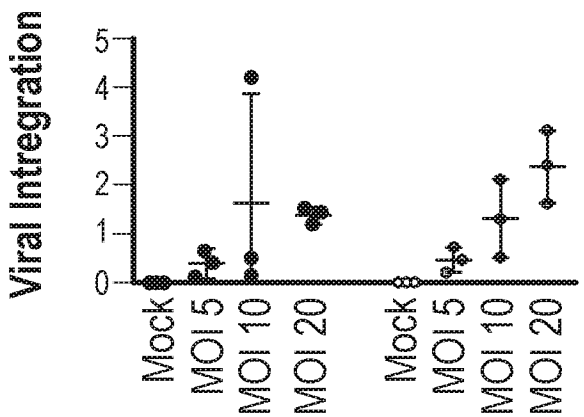


FIG. 15D

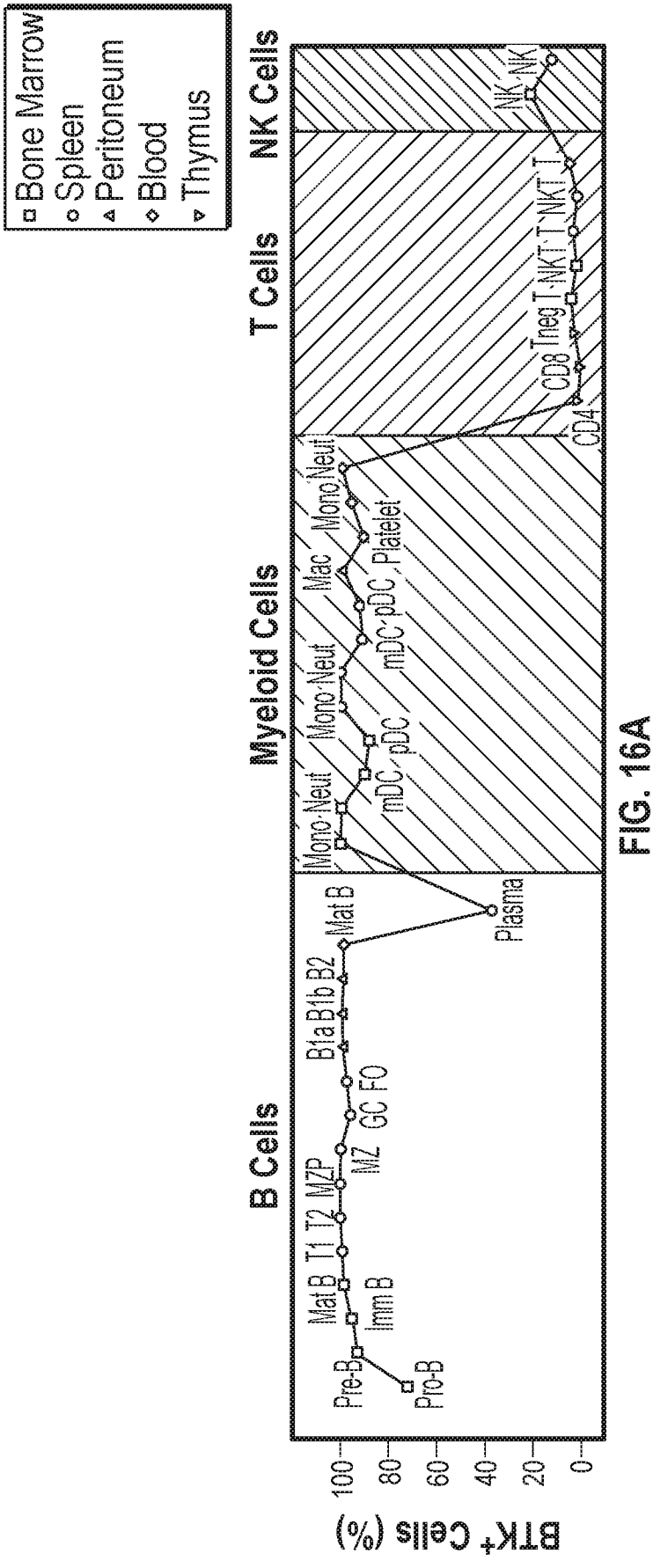


FIG. 16A

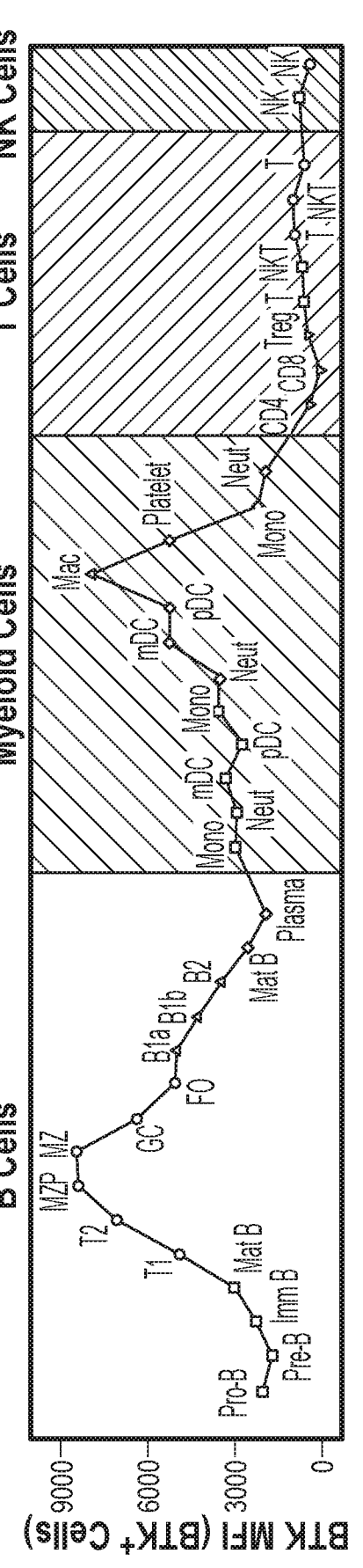


FIG. 16B

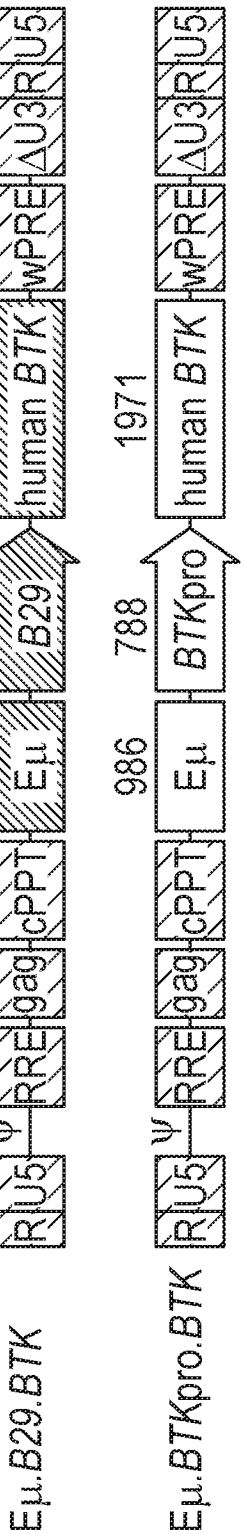


FIG. 16C

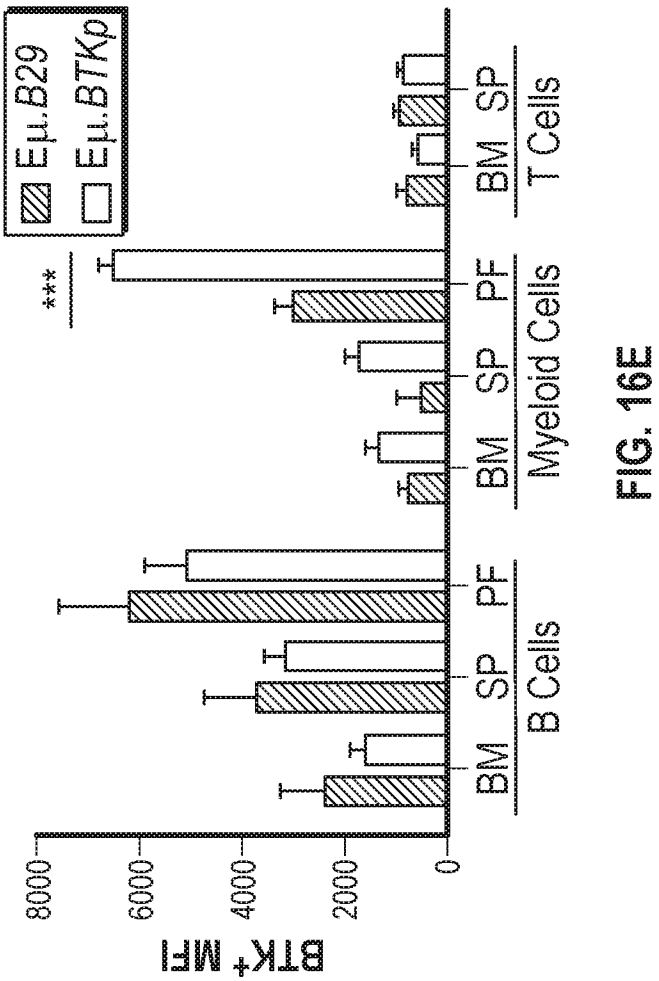


FIG. 16E

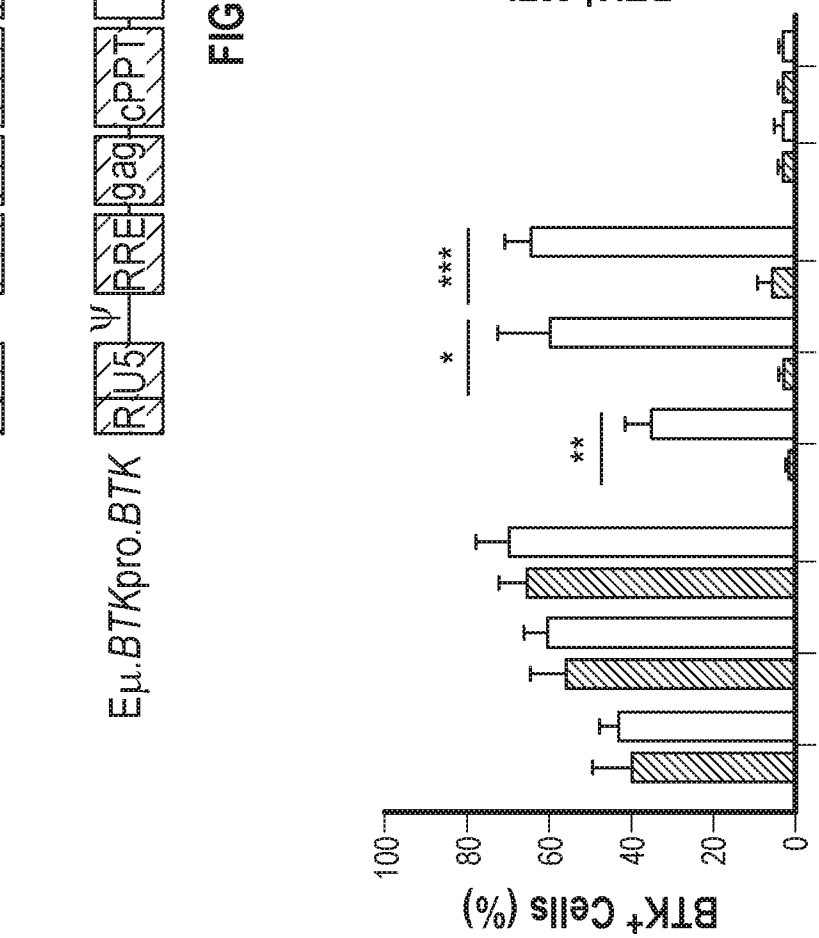


FIG. 16D

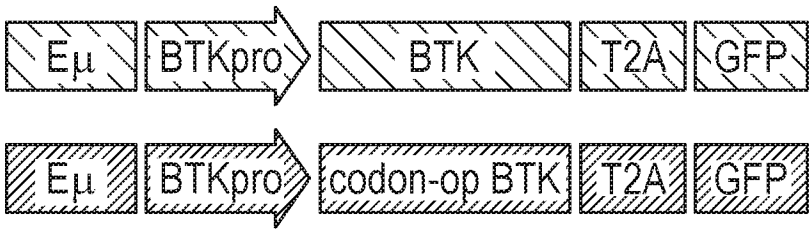


FIG. 17A

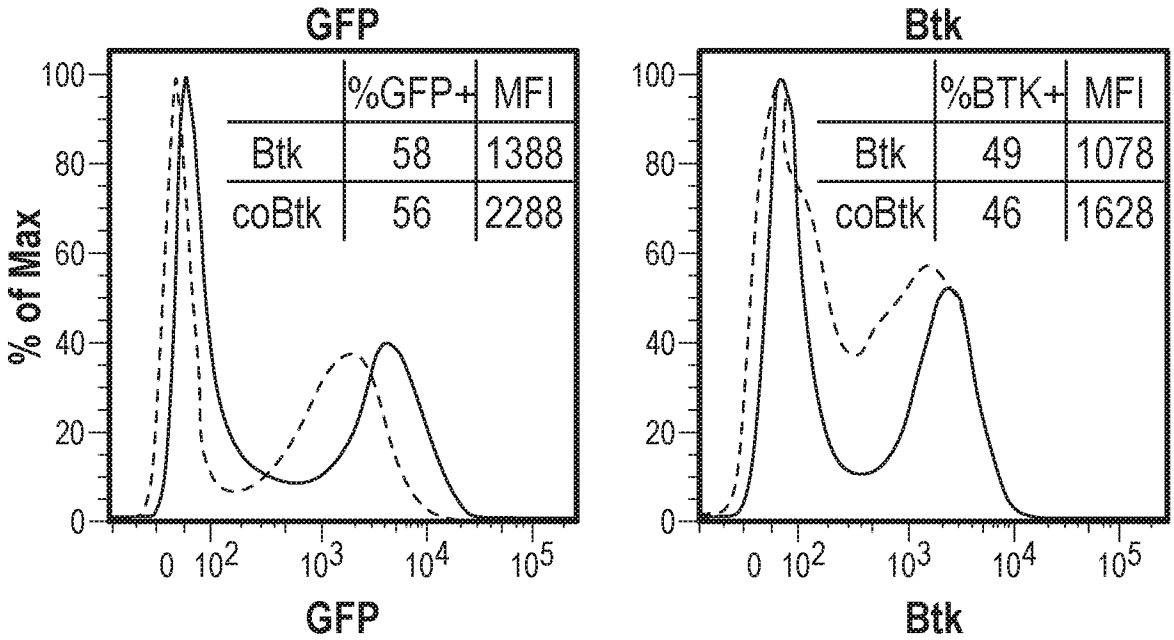


FIG. 17B

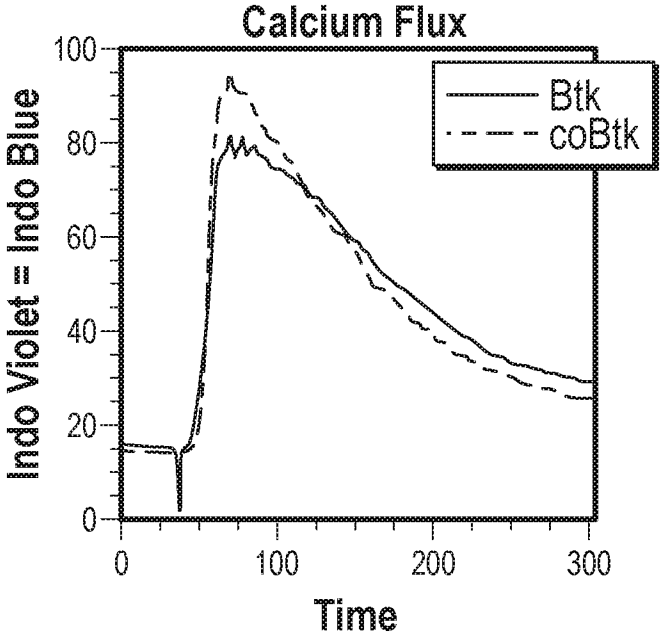


FIG. 17C

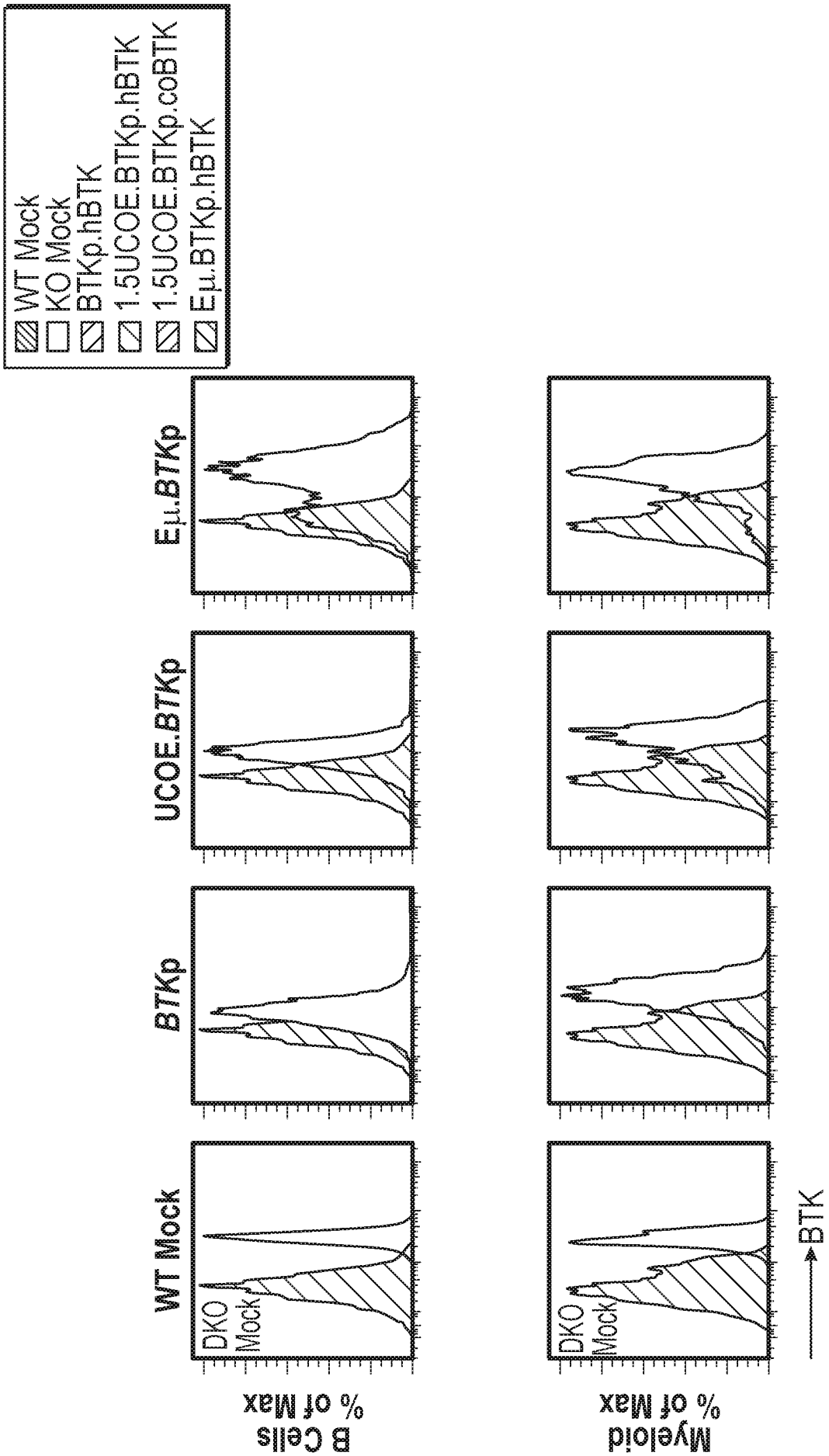

WT Mock
KO Mock
BTKp.hBTK
1.5UCOE.BTKp.hBTK
1.5UCOE.BTKp.coBTK
Eμ.BTKp.hBTK
WT Mock
BTKp
UCOE.BTKp
Eμ.BTKp
DKO
Mock
B Cells
% of Max
Myeloid
% of Max
BTK

FIG. 18A

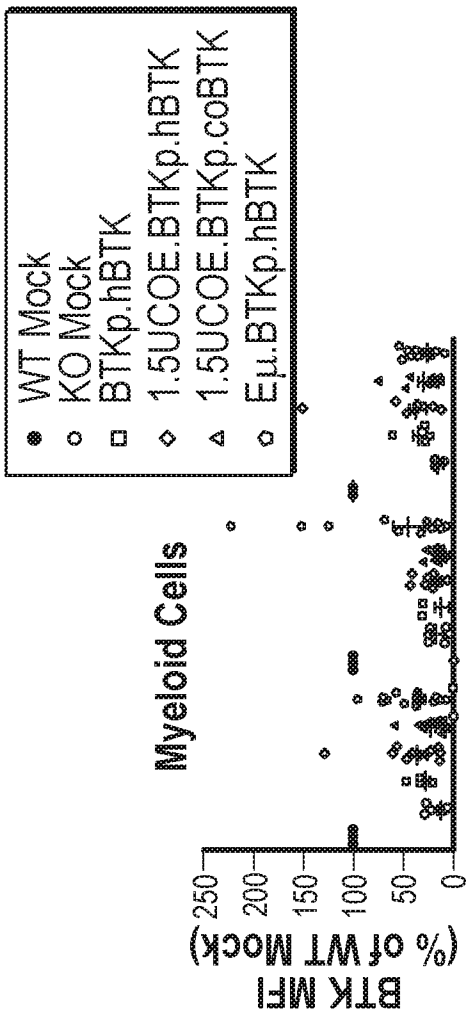


FIG. 18B

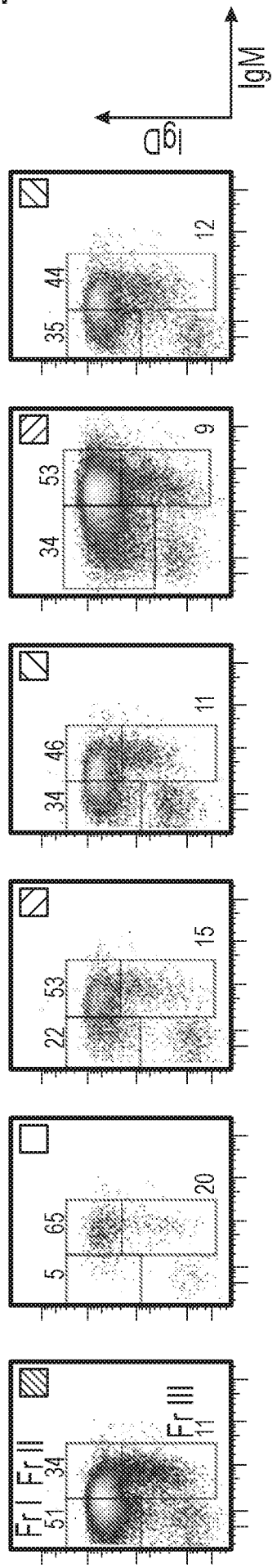


FIG. 18C

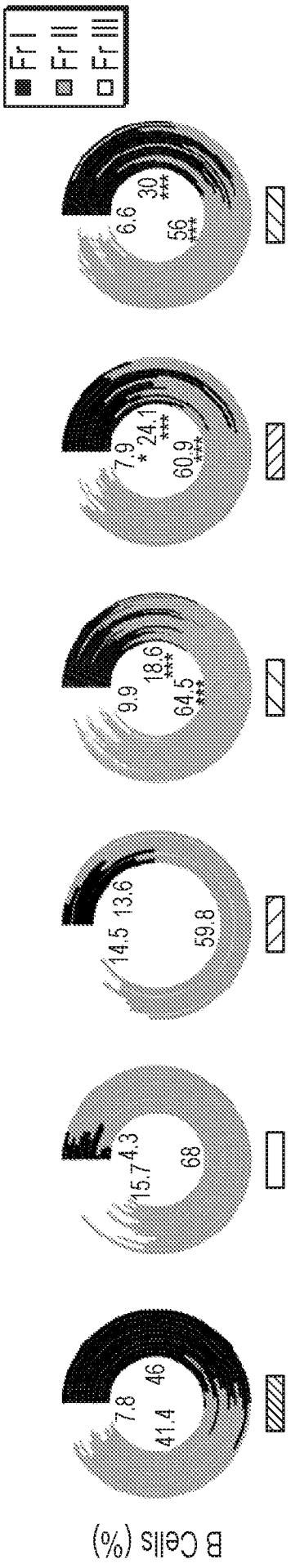


FIG. 18D

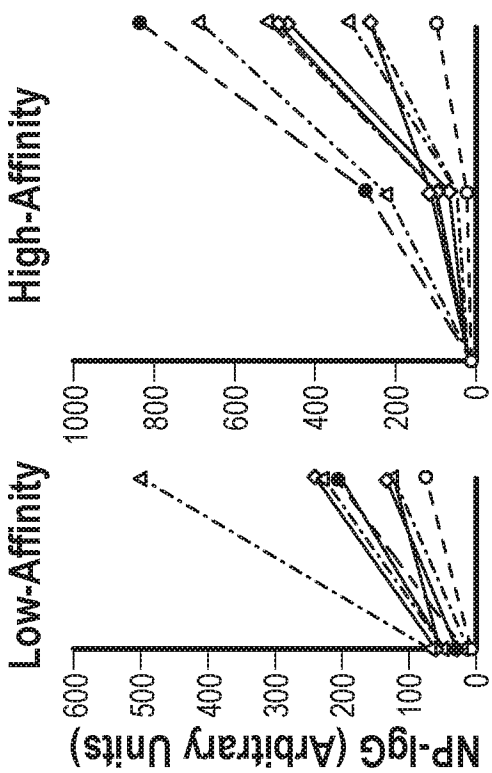


FIG. 18F

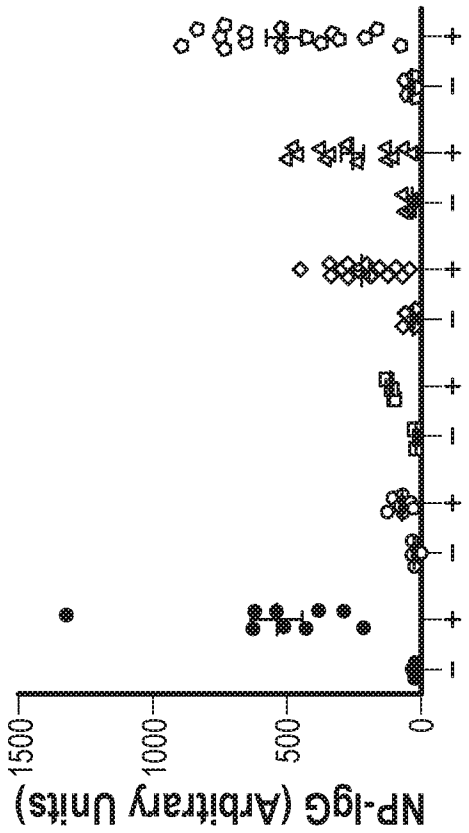


FIG. 18E

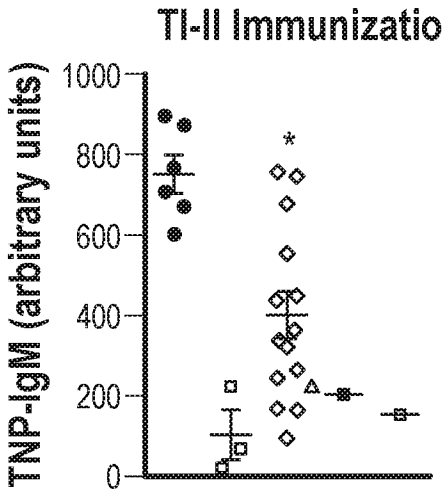


FIG. 18G

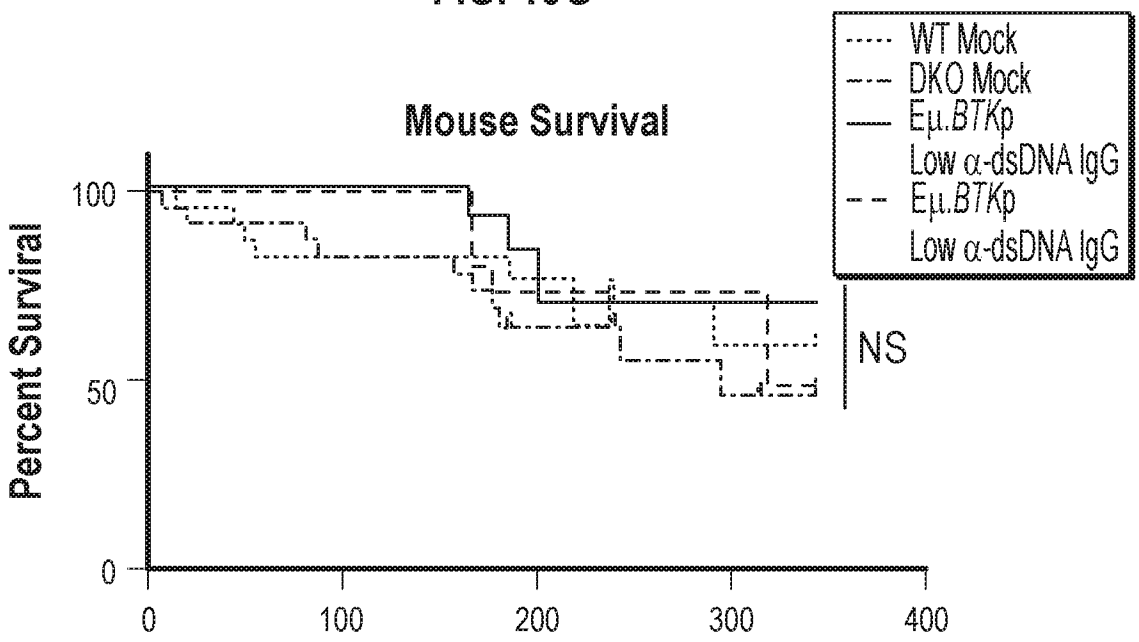


FIG. 19A

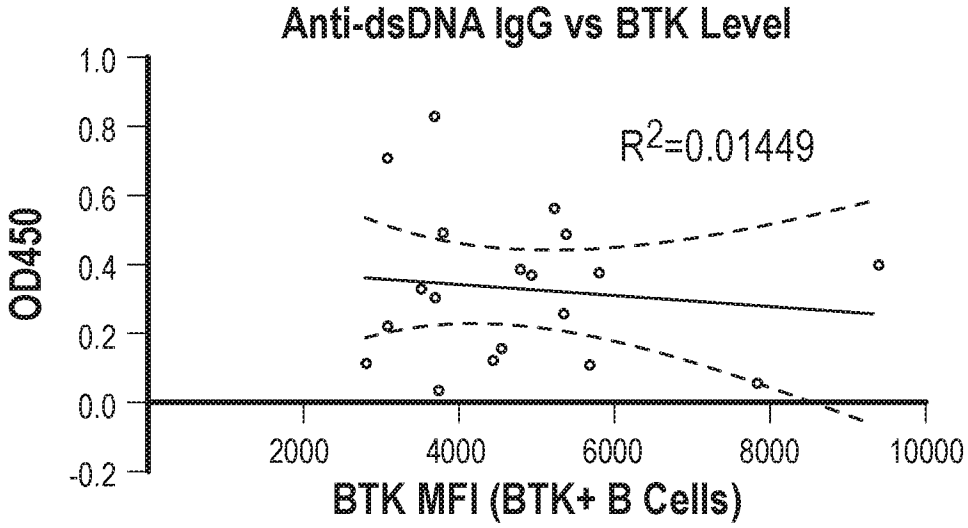


FIG. 19B

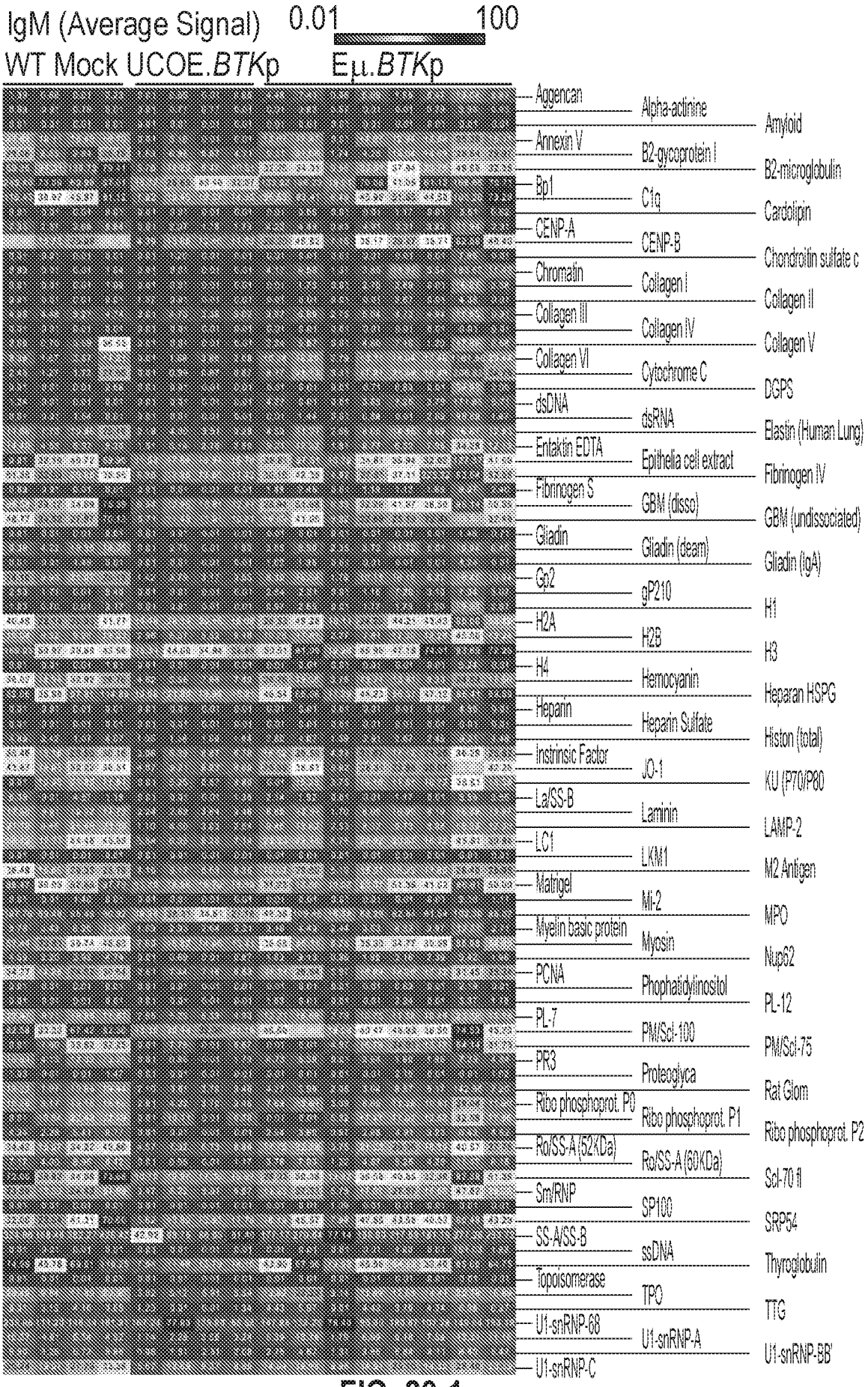

IgM (Average Signal) 0.01 100
WT Mock UCOE.BTKp
Eμ.BTKp
Aggrecan
Annexin V
Bp1
CENP-A
Chromatin
Collagen III
Collagen VI
dsDNA
Entaktin EDTA
Fibrinogen S
Gliadin
Gp2
H2A
H4
Heparin
Instrinsic Factor
La/SS-B
LC1
Matrigel
Myelin basic protein
PCNA
PL-7
PR3
Ribo phosphoprot. P0
Ro/SS-A (52KDa)
Sm/RNP
SS-A/SS-B
Topoisomerase
U1-snRNP-68
U1-snRNP-C
Alpha-actinine
B2-gycoprotein I
C1q
CENP-B
Collagen I
Collagen IV
Cytochrome C
dsRNA
Epithelia cell extract
GBM (disso)
Gliadin (deam)
gP210
H2B
Hemocyanin
Heparin Sulfate
JO-1
Laminin
LKM1
MI-2
Myosin
Phophatidylinositol
PM/Scl-100
Proteoglyca
Ribo phosphoprot. P1
Ro/SS-A (60KDa)
SP100
ssDNA
TPO
U1-snRNP-A
Amyloid
B2-microglobulin
Cardolipin
Chondroitin sulfate c
Collagen II
Collagen V
DGPS
Elastin (Human Lung)
Fibrinogen IV
GBM (undissociated)
Gliadin (IgA)
H1
H3
Heparan HSPG
Histon (total)
KU (P70/P80
LAMP-2
M2 Antigen
MPO
Nup62
PL-12
PM/Scl-75
Rat Glom
Ribo phosphoprot. P2
Scl-70 fl
SRP54
Thyroglobulin
TTG
U1-snRNP-BB'

FIG. 20-1

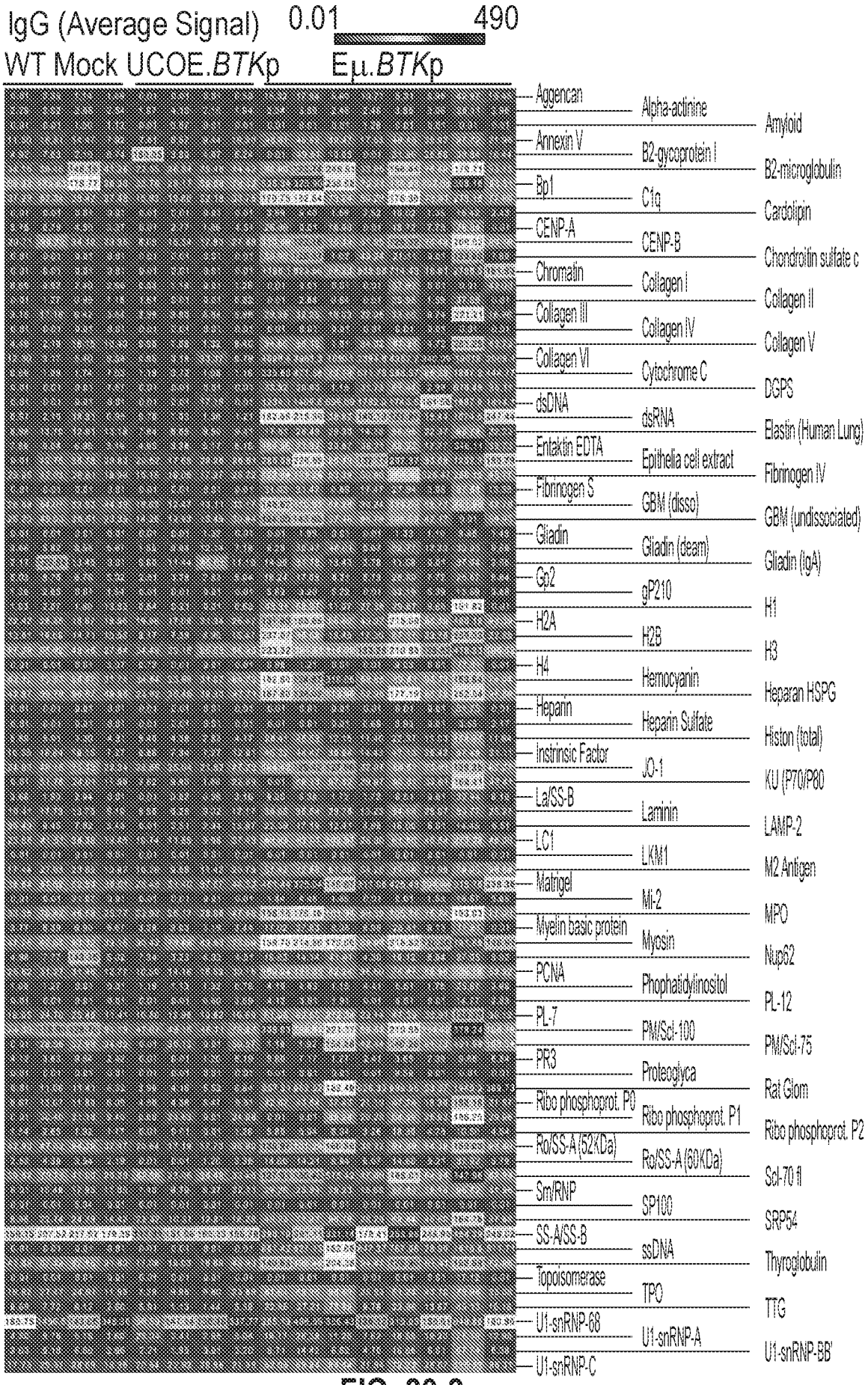

IgG (Average Signal) 0.01 490
WT Mock UCOE.BTKp Eμ.BTKp
Aggrecan
Alpha-actinine
Amyloid
Annexin V
B2-gycoprotein I
B2-microglobulin
Bp1
C1q
Cardiolipin
CENP-A
CENP-B
Chondroitin sulfate c
Chromatin
Collagen I
Collagen II
Collagen III
Collagen IV
Collagen V
Collagen VI
Cytochrome C
DGPS
dsDNA
dsRNA
Elastin (Human Lung)
Entaktin EDTA
Epithelia cell extract
Fibrinogen IV
Fibrinogen S
GBM (disso)
GBM (undissociated)
Gliadin
Gliadin (deam)
Gliadin (IgA)
Gp2
gP210
H1
H2A
H2B
H3
H4
Hemocyanin
Heparan HSPG
Heparin
Heparin Sulfate
Histon (total)
Instrinsic Factor
JO-1
KU (P70/P80
La/SS-B
Laminin
LAMP-2
LC1
LKM1
M2 Antigen
Matrigel
MI-2
MPO
Myelin basic protein
Myosin
Nup62
PCNA
Phophatidylinositol
PL-12
PL-7
PM/Scl-100
PM/Scl-75
PR3
Proteoglyca
Rat Glom
Ribo phosphoprot. P0
Ribo phosphoprot. P1
Ribo phosphoprot. P2
Ro/SS-A (52KDa)
Ro/SS-A (60KDa)
Scl-70 fl
Sm/RNP
SP100
SRP54
SS-A/SS-B
ssDNA
Thyroglobulin
Topoisomerase
TPO
TTG
U1-snRNP-68
U1-snRNP-A
U1-snRNP-BB'
U1-snRNP-C

FIG. 20-2

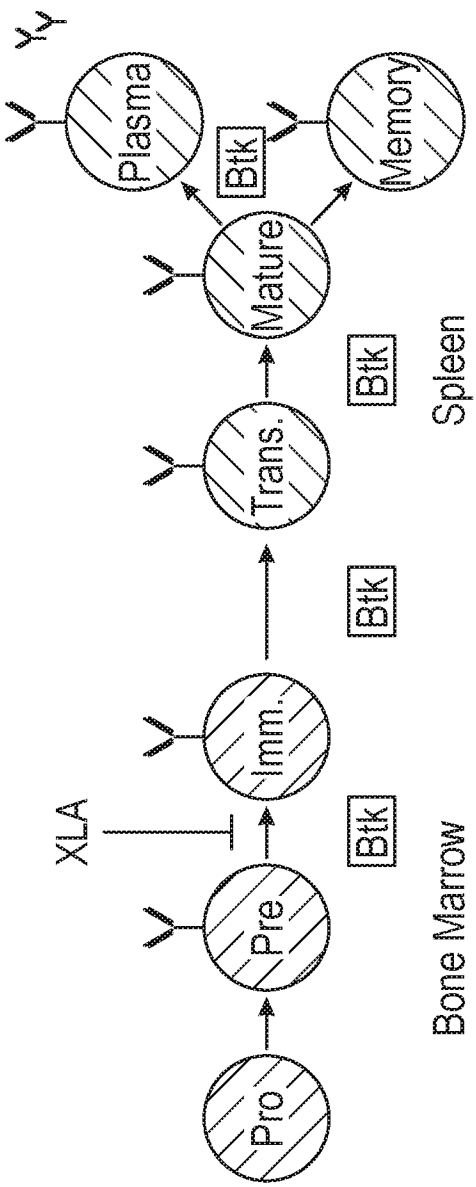

Pro
Pre
Imm.
Trans.
Mature
Plasma
Memory
XLA
Btk
Btk
Btk
Btk
Bone Marrow
Spleen

FIG. 21

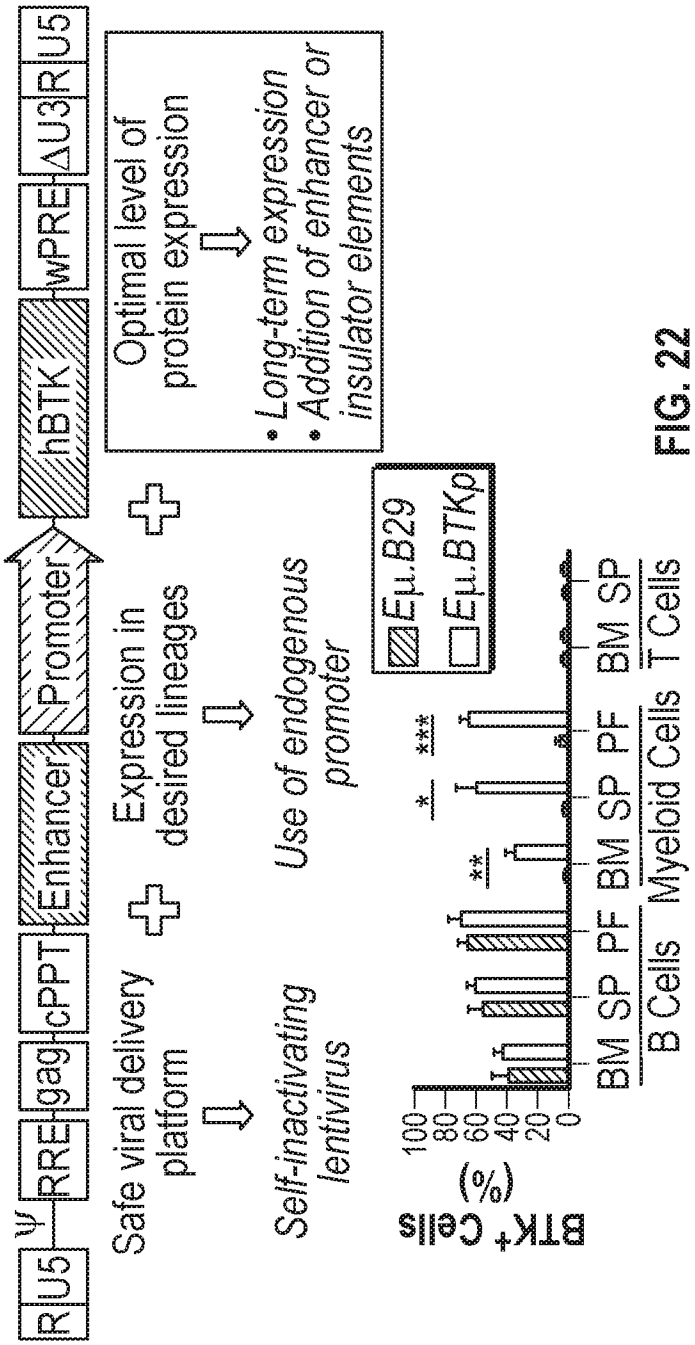

RU5
Ψ
RRE
gag
cPPT
Enhancer
Promoter
hBTK
wPRE
ΔU3
RU5
Safe viral delivery platform
Self-inactivating lentivirus
Expression in desired lineages
Use of endogenous promoter
Optimal level of protein expression
• Long-term expression
• Addition of enhancer or insulator elements
Eμ.B29
Eμ.BTKp
BTK+ Cells (%)
100
80
60
40
20
0
*
**
***
BM SP PF BM SP PF BM SP
B Cells Myeloid Cells T Cells

FIG. 22

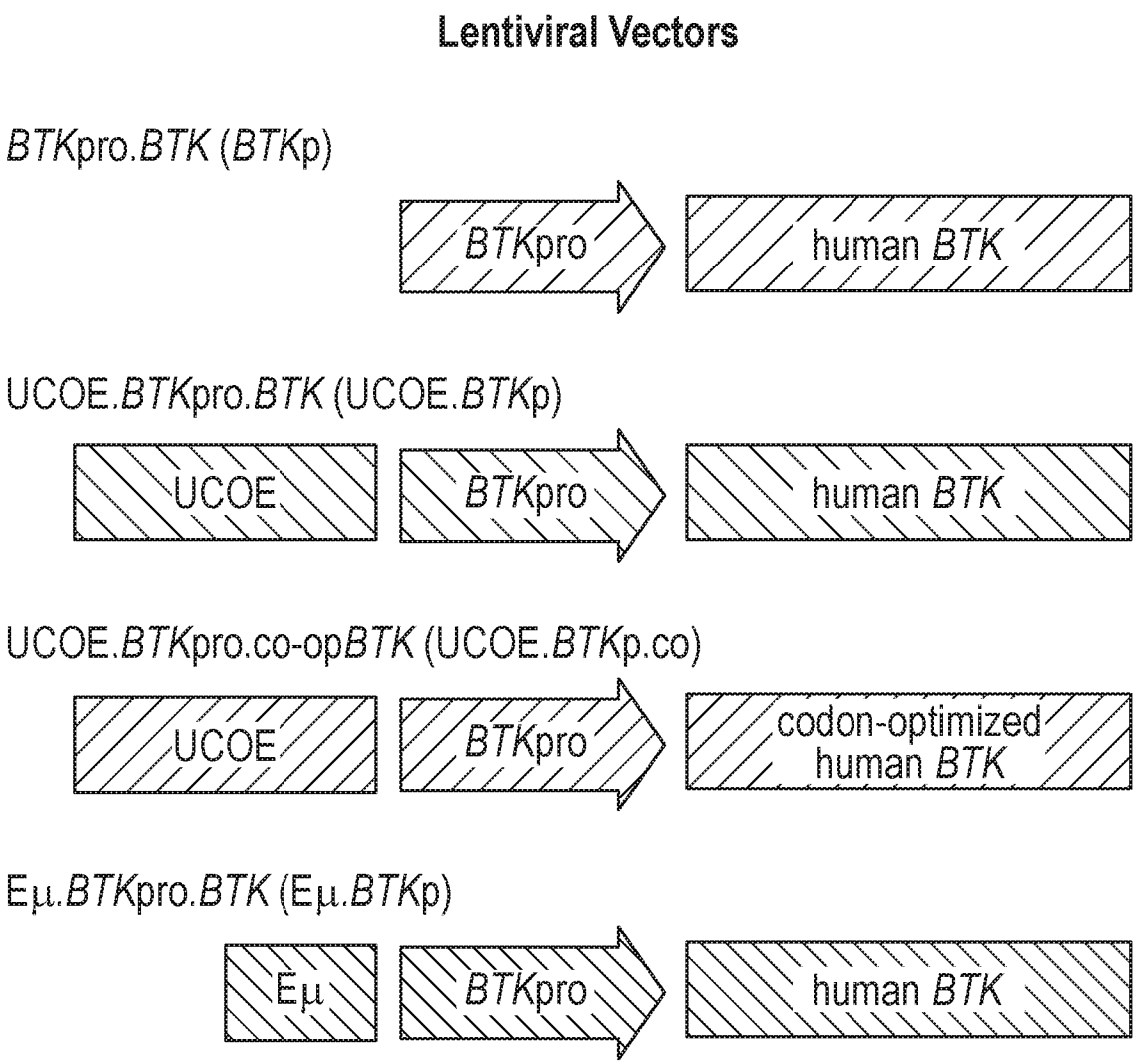

Lentiviral Vectors
BTKpro.BTK (BTKp)
BTKpro
human BTK
UCOE.BTKpro.BTK (UCOE.BTKp)
UCOE
BTKpro
human BTK
UCOE.BTKpro.co-opBTK (UCOE.BTKp.co)
UCOE
BTKpro
codon-optimized human BTK
Eμ.BTKpro.BTK (Eμ.BTKp)
Eμ
BTKpro
human BTK

FIG. 23

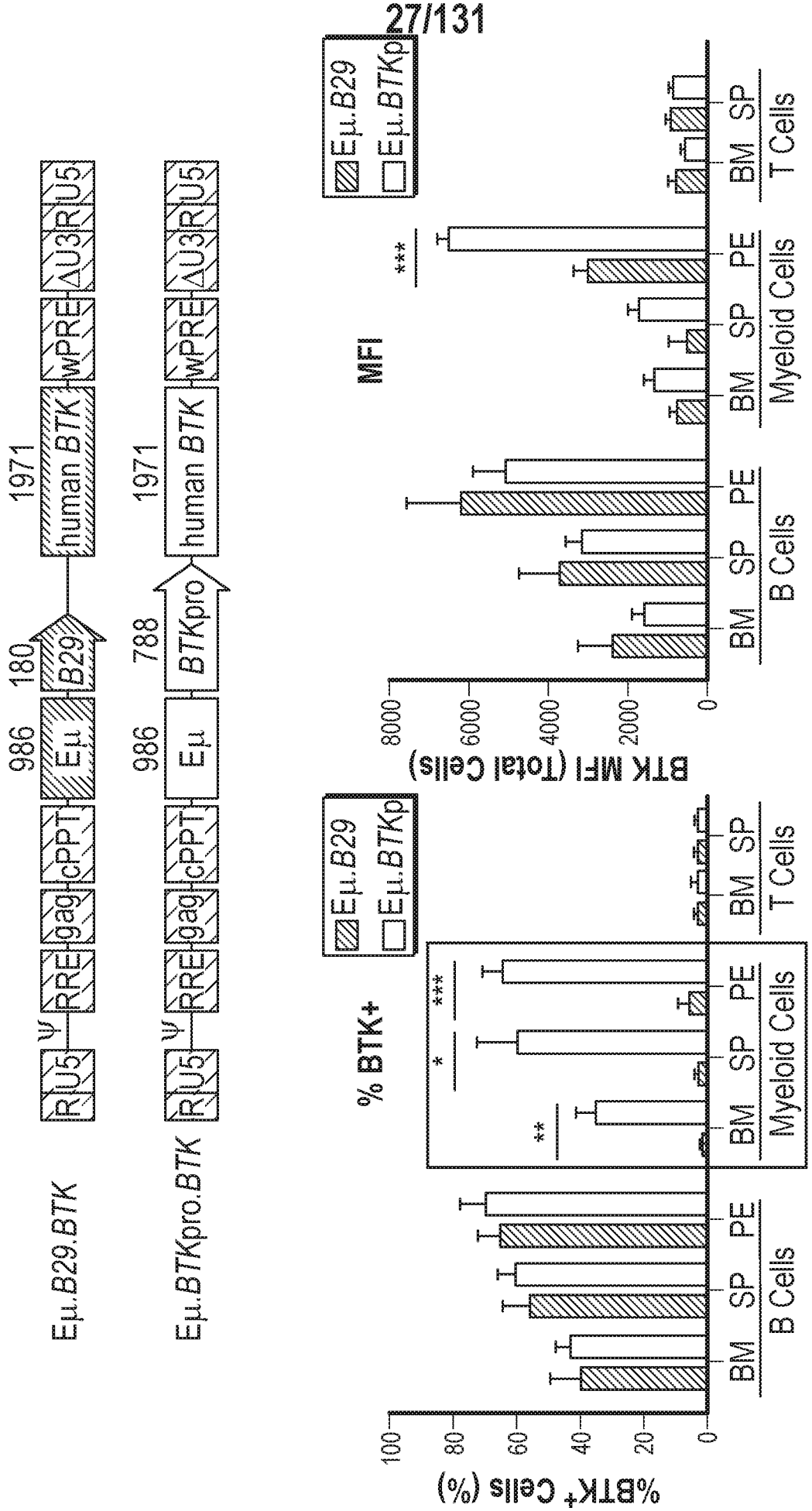

Eμ.B29.BTK
R U5 Ψ RRE gag cPPT 986 Eμ 180 B29 1971 human BTK wPRE ΔU3R U5
Eμ.BTKpro.BTK
R U5 Ψ RRE gag cPPT 986 Eμ 788 BTKpro 1971 human BTK wPRE ΔU3R U5
Eμ.B29
Eμ.BTKp
% BTK+
%BTK+ Cells (%)
100 80 60 40 20 0
BM SP PE BM SP PE BM SP BM SP
B Cells Myeloid Cells T Cells
* ** ***
MFI
BTK MFI (Total Cells)
8000 6000 4000 2000 0
***

FIG. 24

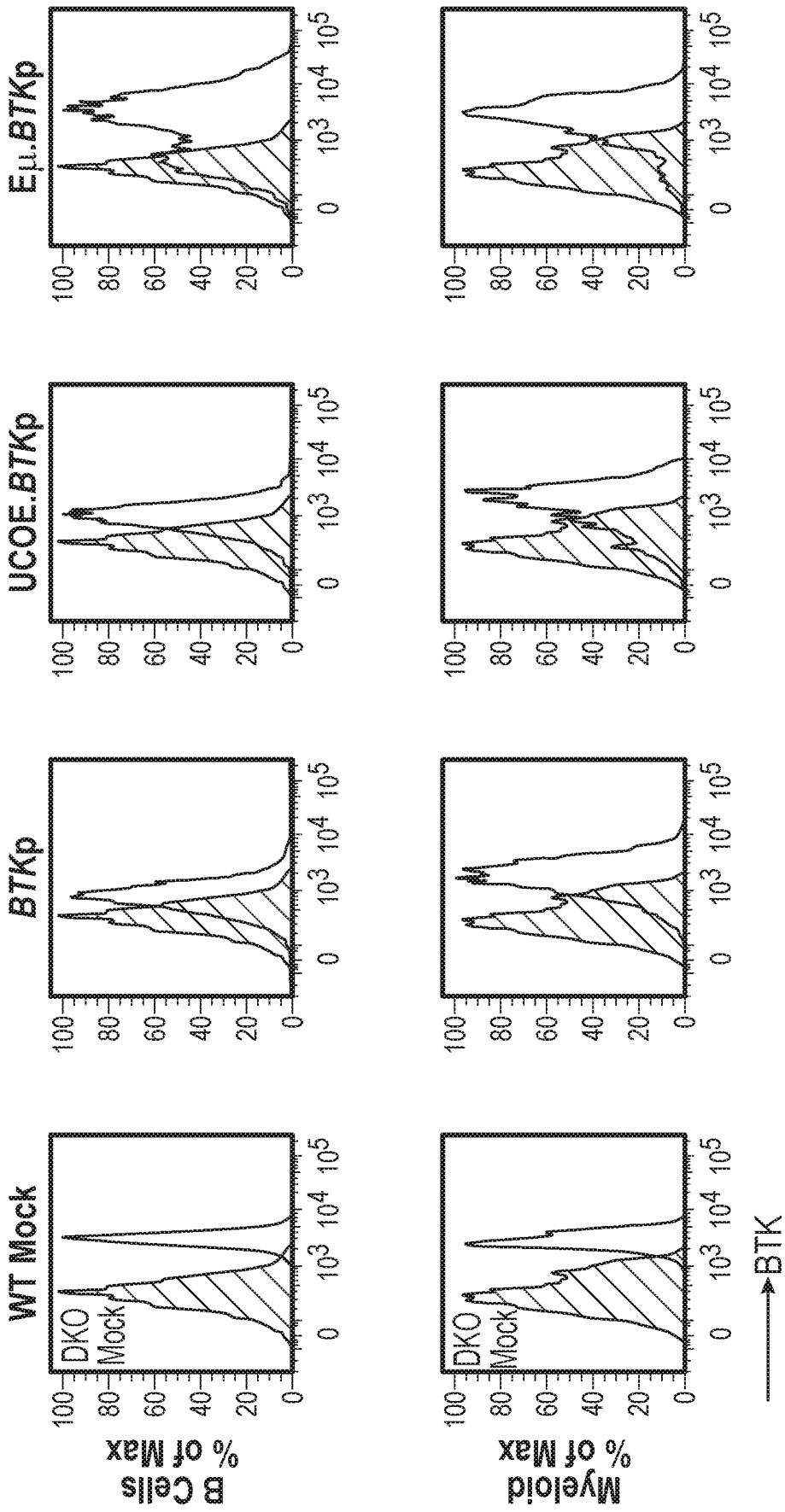

WT Mock
BTKp
UCOE.BTKp
Eμ.BTKp
DKO
Mock
B Cells
% of Max
Myeloid
% of Max
BTK
0
20
40
60
80
100
0
10^3
10^4
10^5

FIG. 25

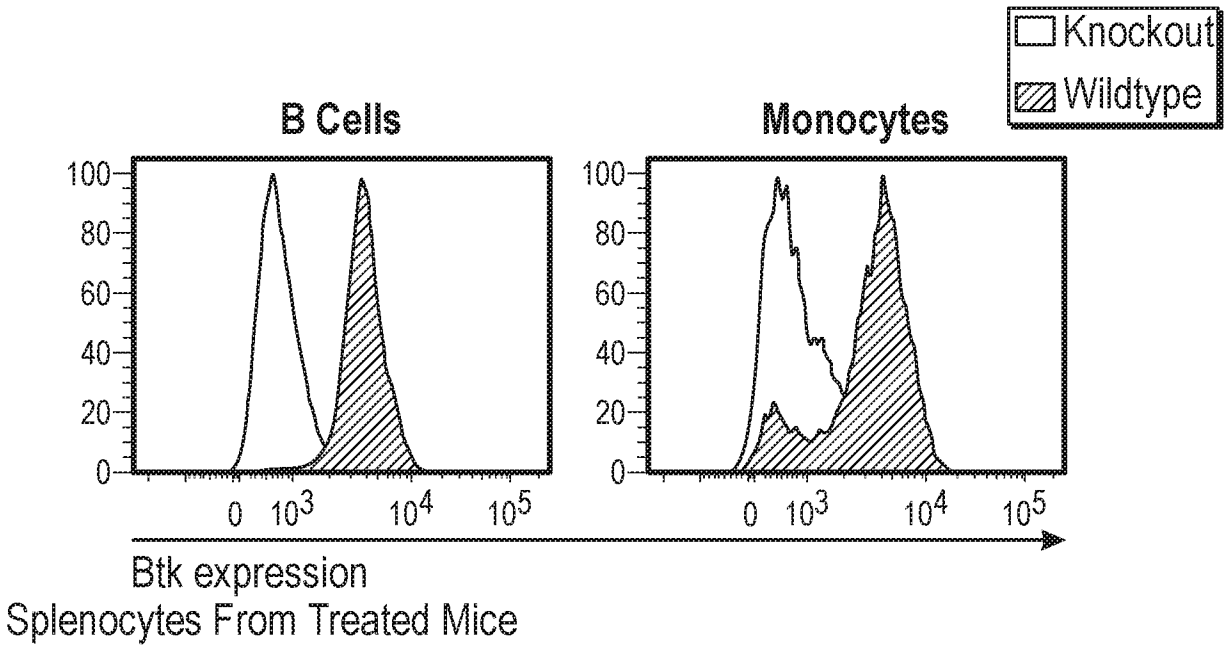

Knockout
Wildtype
B Cells
Monocytes
100
80
60
40
20
0
0
10^3
10^4
10^5
Btk expression
Splenocytes From Treated Mice

FIG. 26

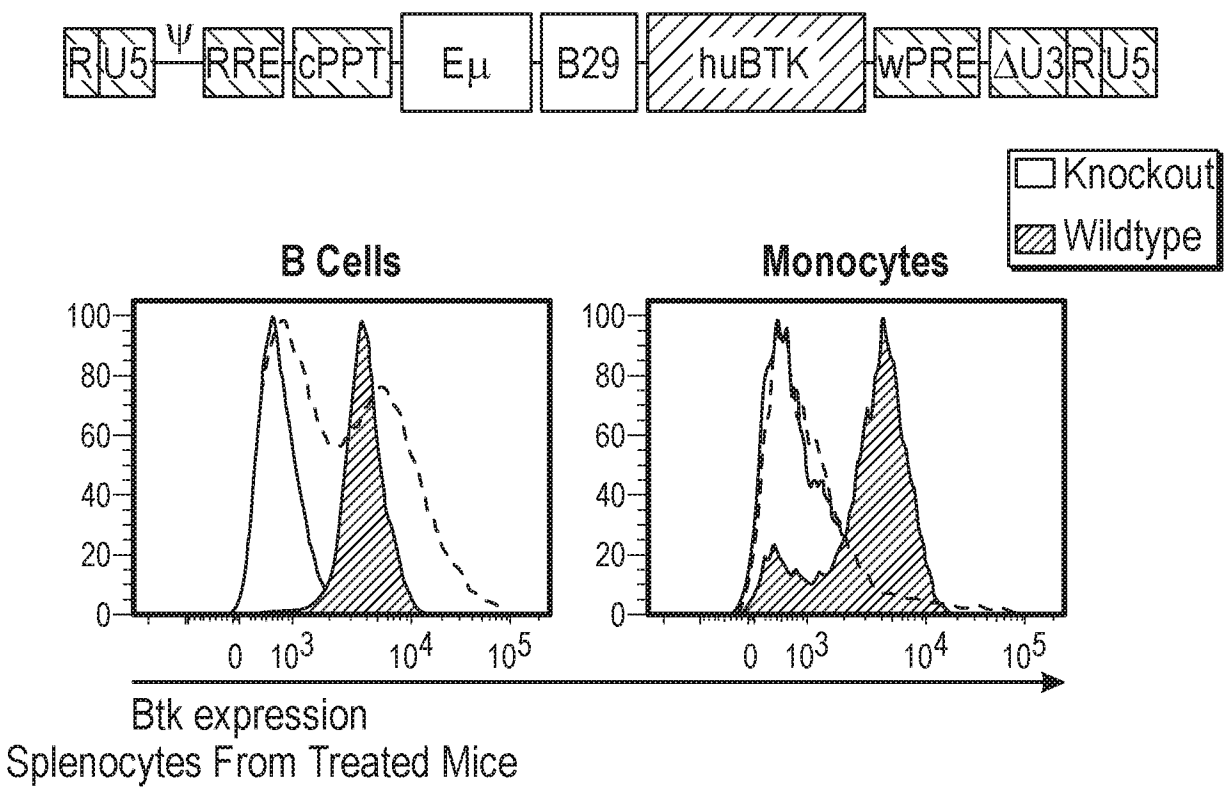

R
U5
Ψ
RRE
cPPT
Eμ
B29
huBTK
wPRE
ΔU3
R
U5
Knockout
Wildtype
B Cells
Monocytes
100
80
60
40
20
0
0
10^3
10^4
10^5
Btk expression
Splenocytes From Treated Mice

FIG. 27

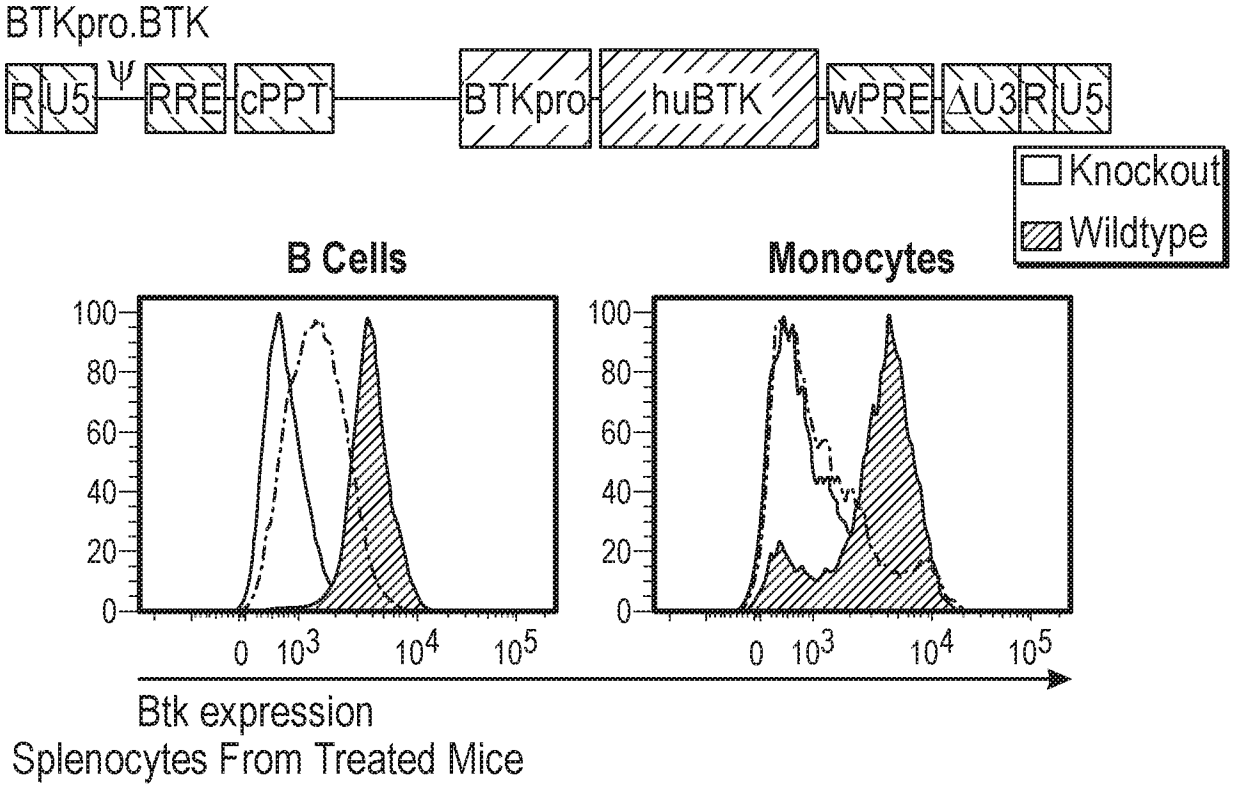

BTKpro.BTK
R
U5
Ψ
RRE
cPPT
BTKpro
huBTK
wPRE
ΔU3
R
U5
Knockout
Wildtype
B Cells
Monocytes
100
80
60
40
20
0
0
10^3
10^4
10^5
Btk expression
Splenocytes From Treated Mice

FIG. 28

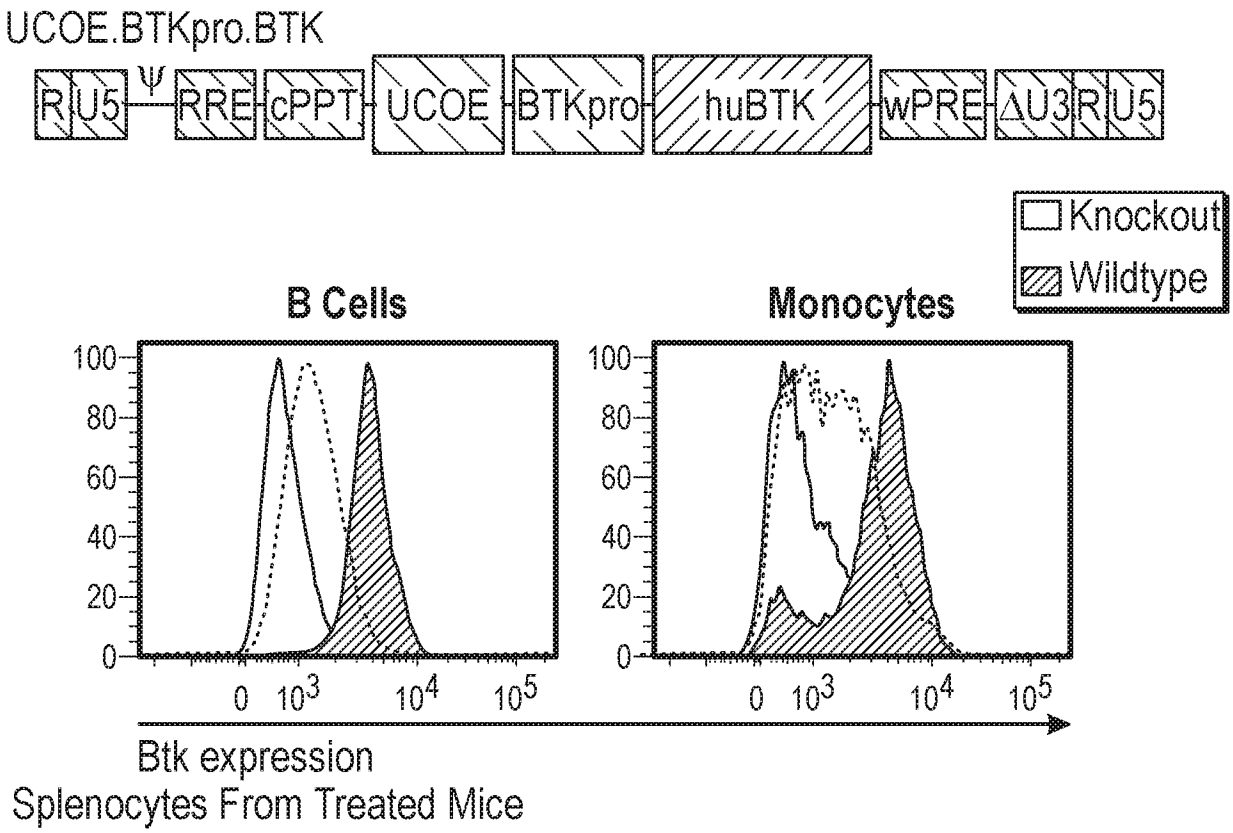

UCOE.BTKpro.BTK
R
U5
Ψ
RRE
cPPT
UCOE
BTKpro
huBTK
wPRE
ΔU3
R
U5
Knockout
Wildtype
B Cells
Monocytes
100
80
60
40
20
0
0
10^3
10^4
10^5
Btk expression
Splenocytes From Treated Mice

FIG. 29

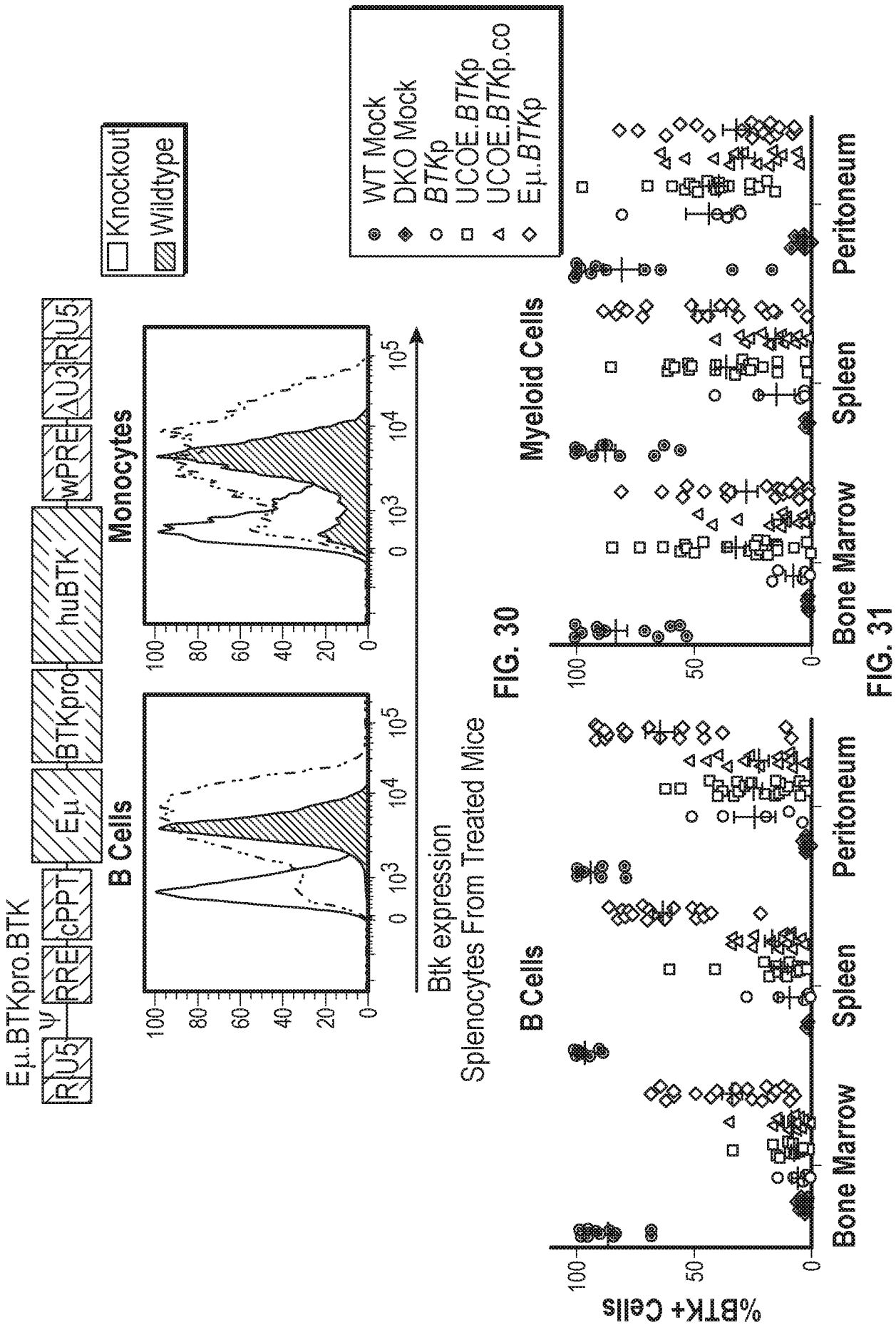

Eμ.BTKpro.BTK
RU5
Ψ
RRE
cPPT
Eμ
BTKpro
huBTK
wPRE
ΔU3RU5
Knockout
Wildtype
B Cells
Monocytes
Btk expression
Splenocytes From Treated Mice
WT Mock
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
Myeloid Cells
B Cells
%BTK+ Cells
Bone Marrow
Spleen
Peritoneum

FIG. 30

FIG. 31

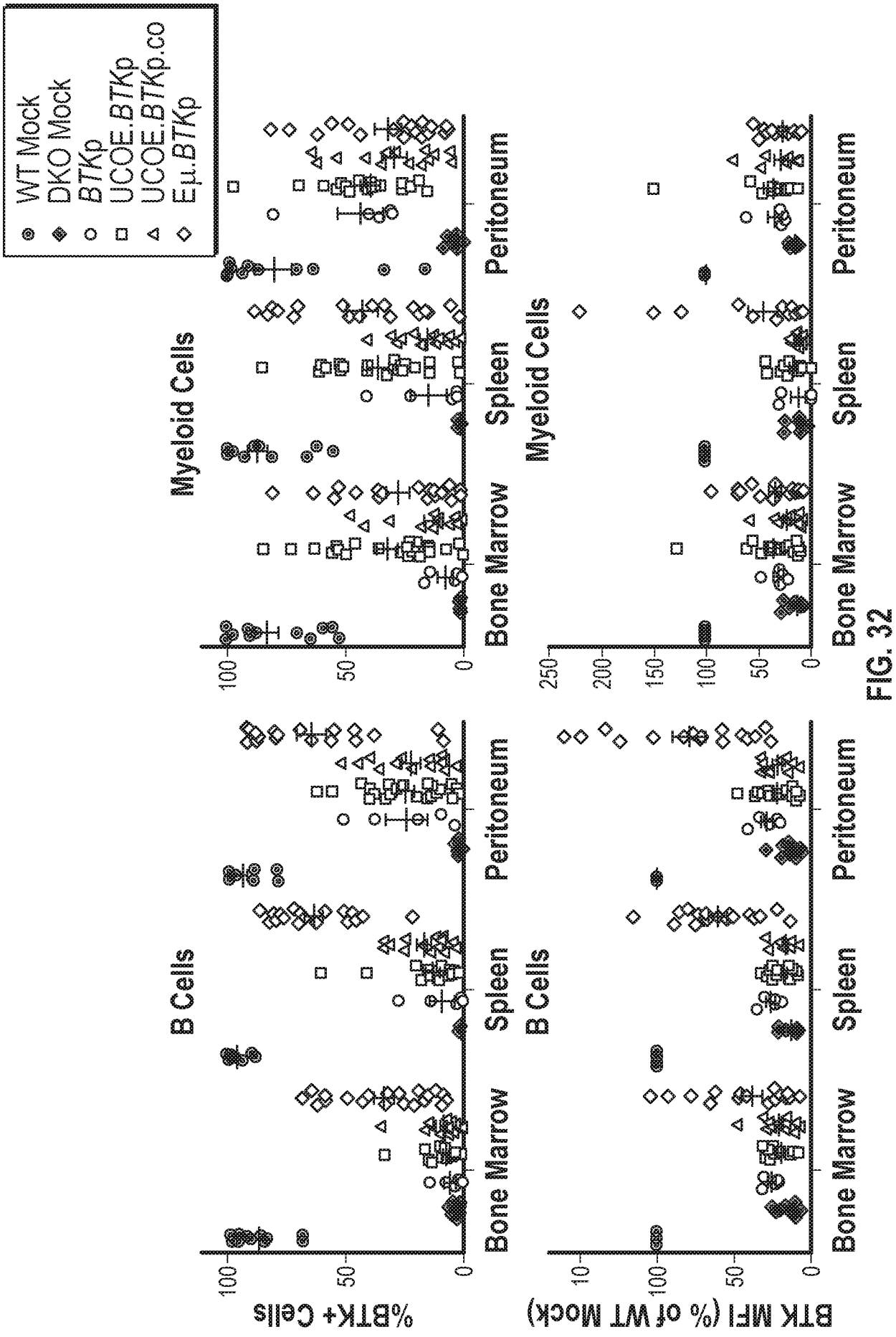

WT Mock
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
Myeloid Cells
B Cells
%BTK+ Cells
BTK MFI (% of WT Mock)
Bone Marrow
Spleen
Peritoneum
100
50
0
250
200
150
10

FIG. 32

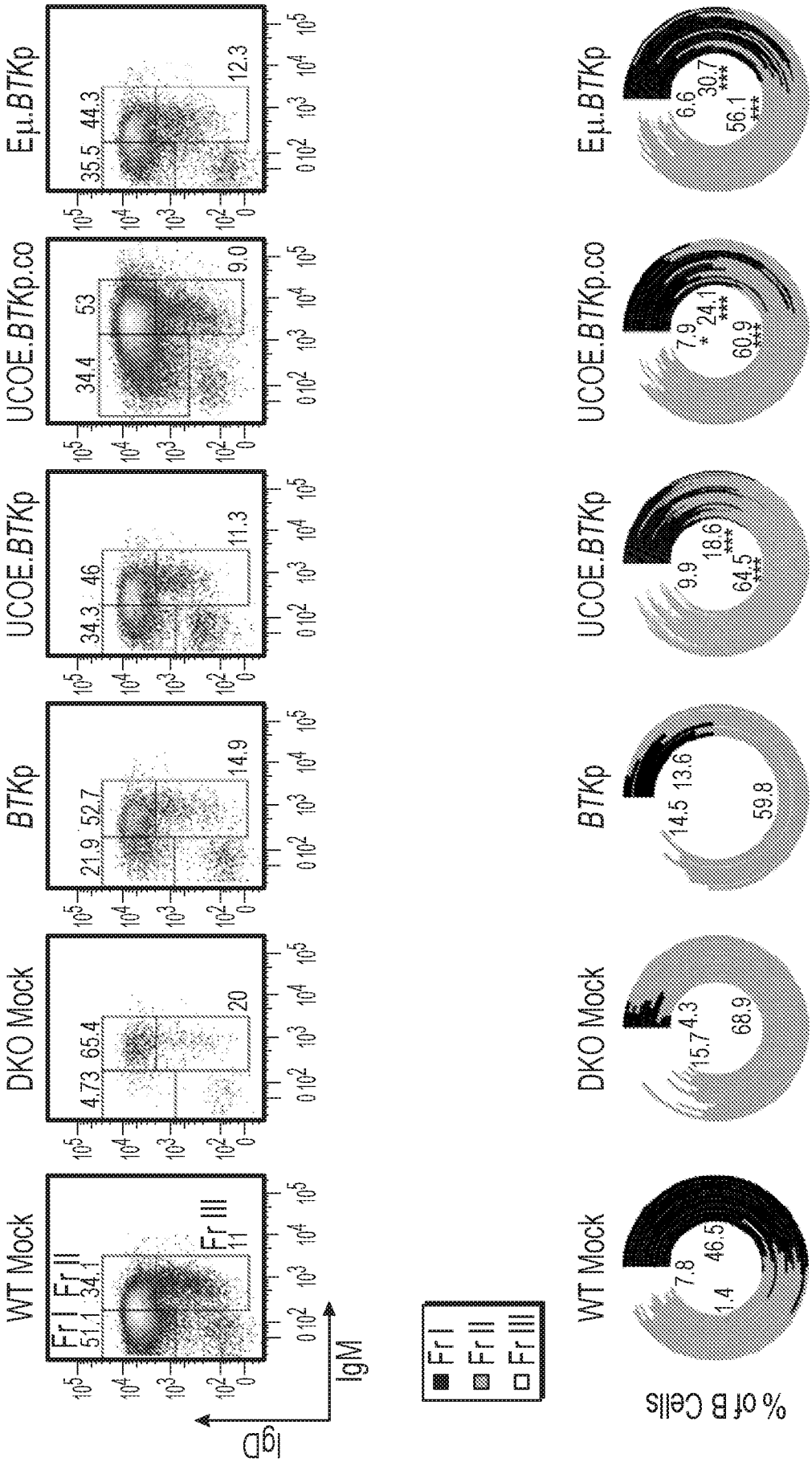
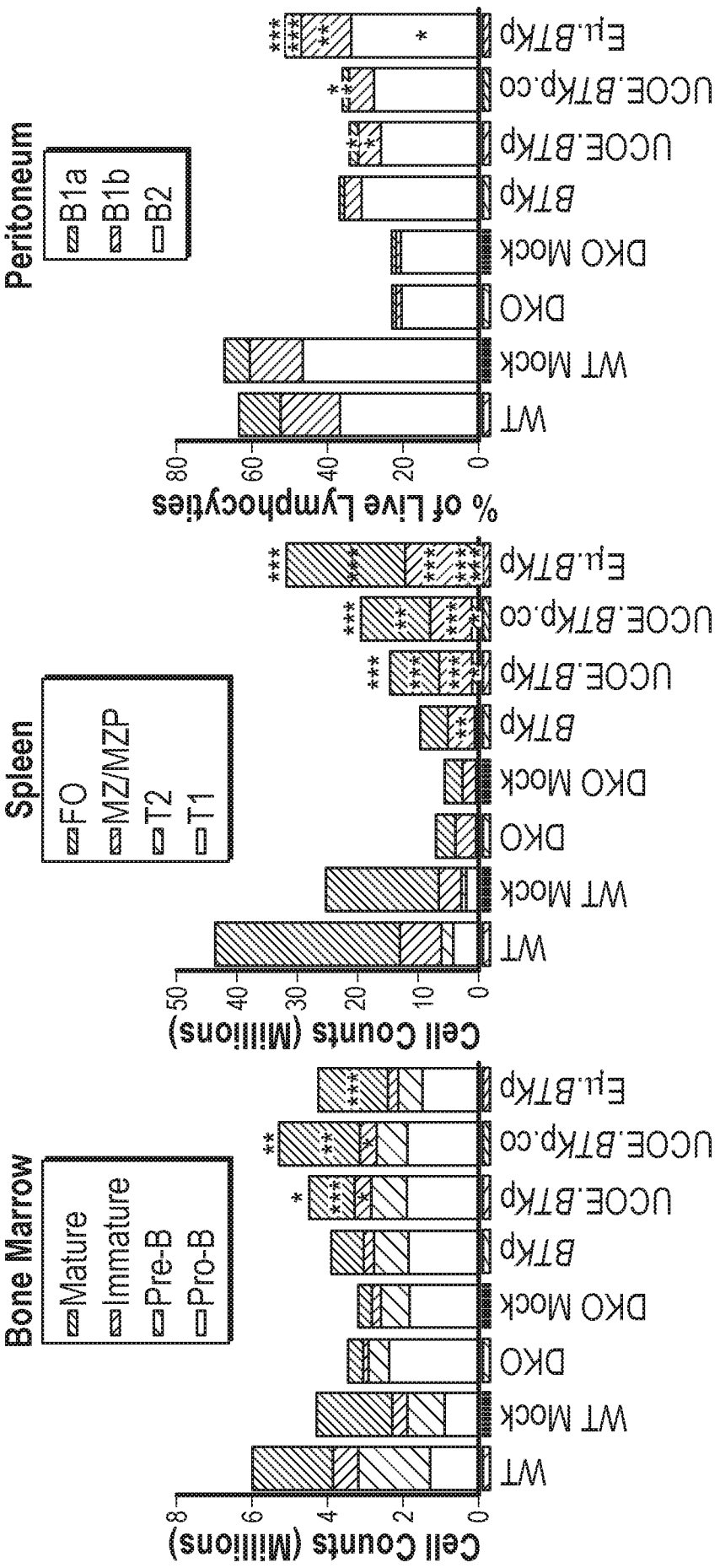

WT Mock
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
IgD
IgM
Fr I
Fr II
Fr III
% of B Cells

FIG. 33



N= ~20-30 WT or KO mock controls each, 30-40 recipients for each LV construct, > 10 independet experimental cohorts

FIG. 34

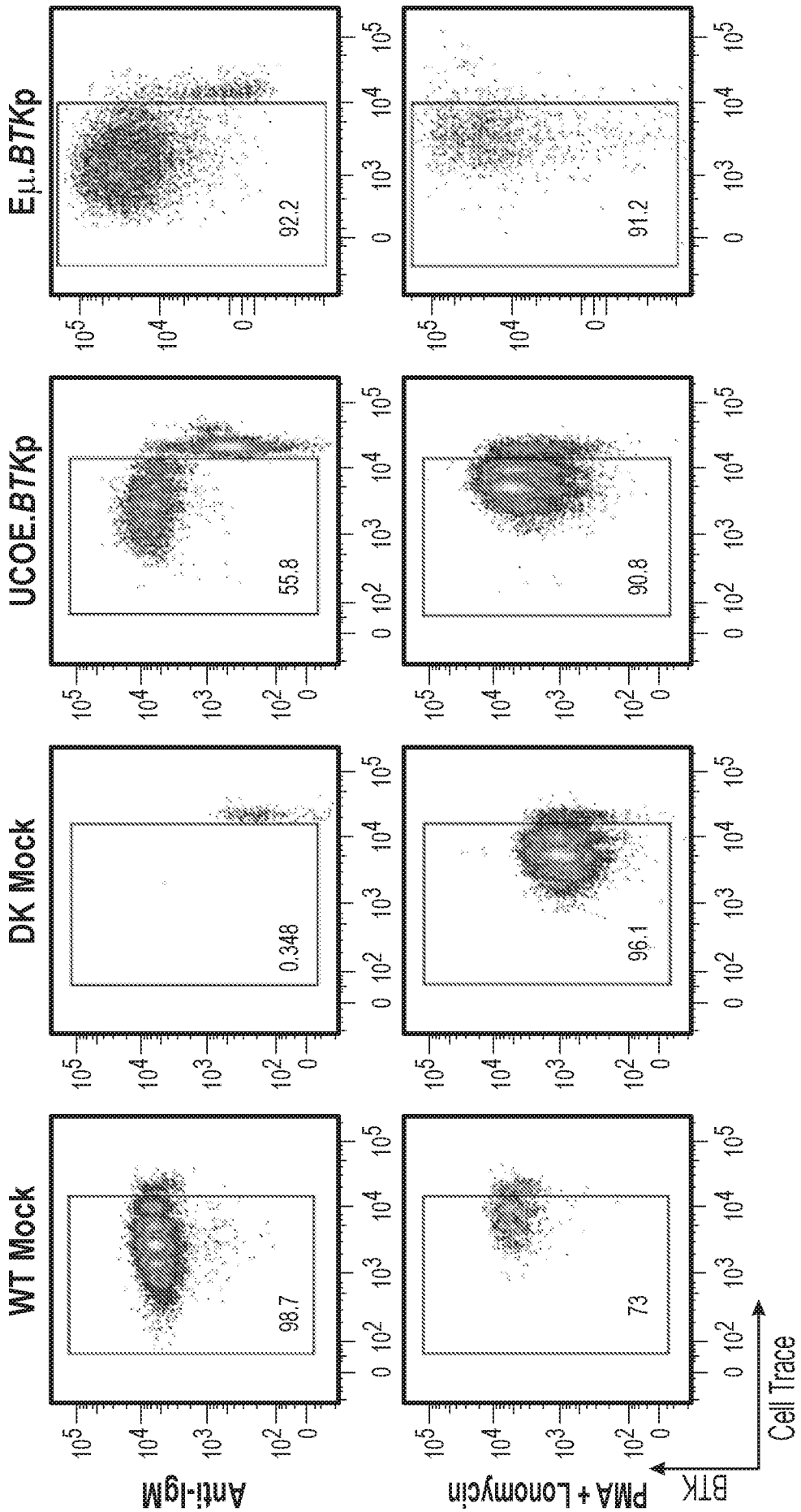

WT Mock
DK Mock
UCOE.BTKp
Eμ.BTKp
Anti-IgM
PMA + Lonomycin
BTK
Cell Trace
98.7
0.348
55.8
92.2
73
96.1
90.8
91.2

FIG. 35

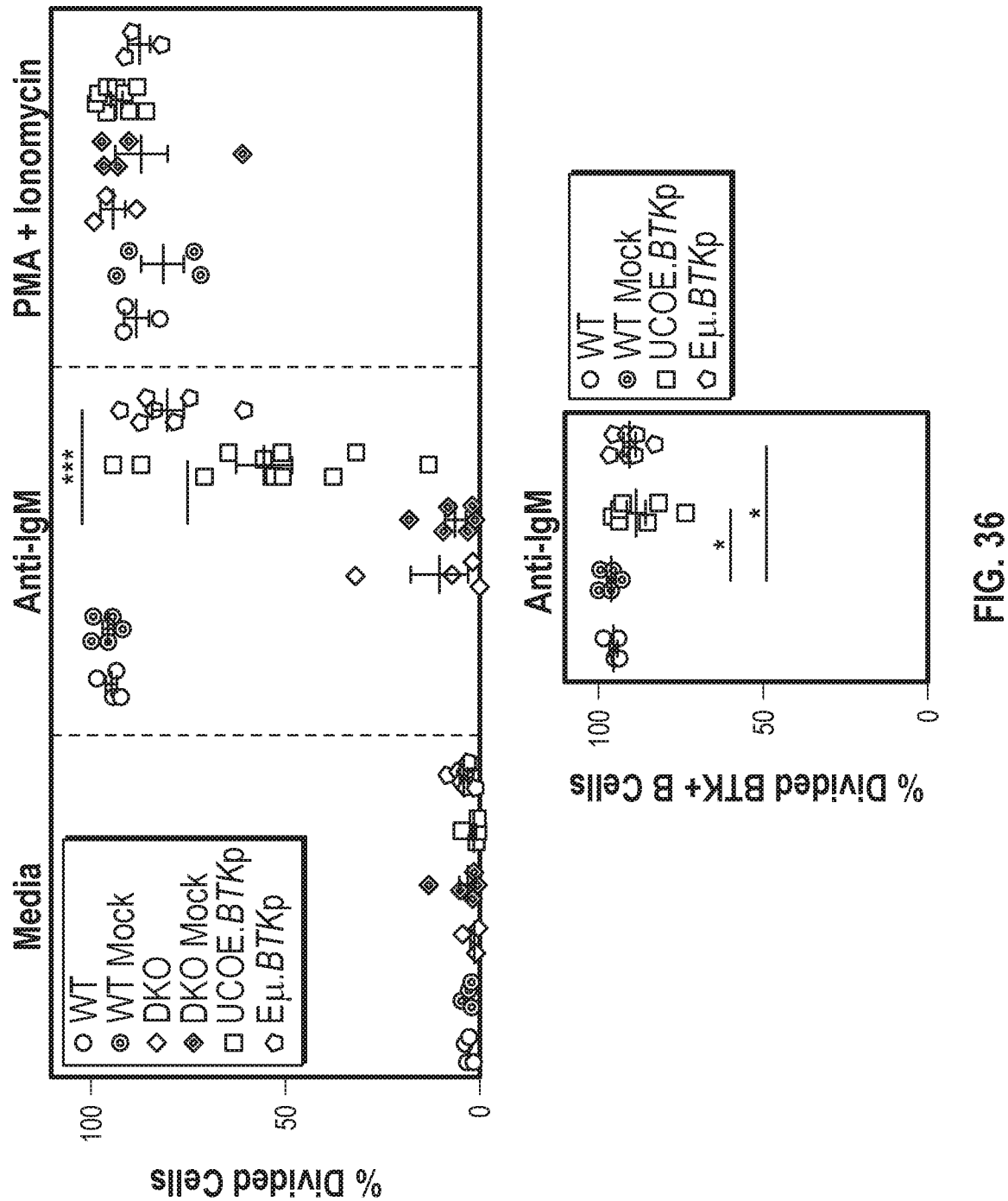
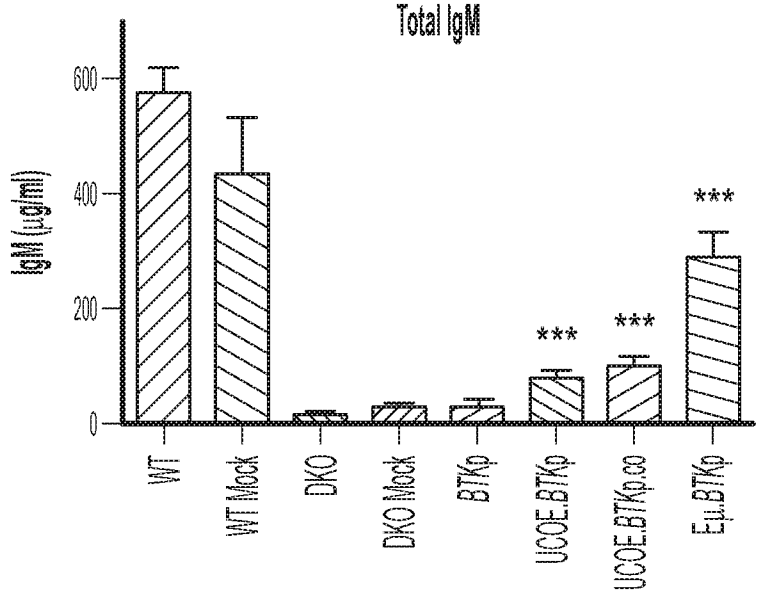
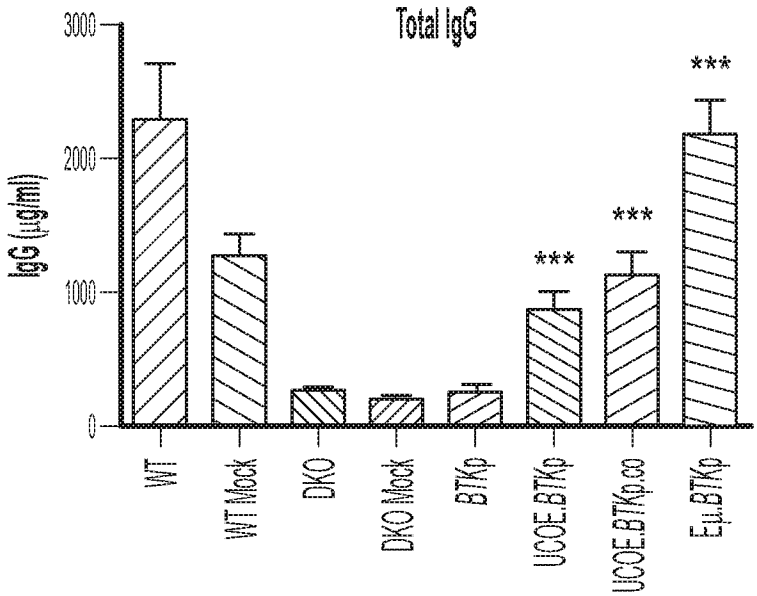

Media
Anti-IgM
PMA + Ionomycin
WT
WT Mock
DKO
DKO Mock
UCOE.BTKp
Eμ.BTKp
***
% Divided Cells
100
50
0
Anti-IgM
*
*
% Divided BTK+ B Cells

FIG. 36


Total IgM
IgM (µg/ml)
600
400
200
0
***
***
***
WT
WT Mock
DKO
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp


Total IgG
IgG (µg/ml)
3000
2000
1000
0
***
***
***
WT
WT Mock
DKO
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp

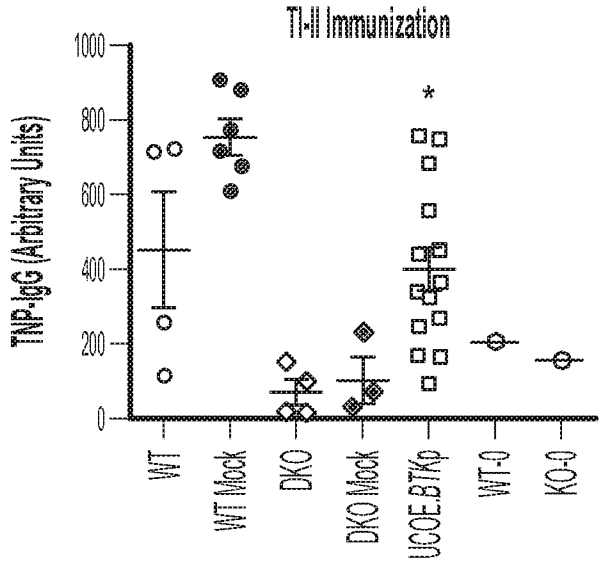

TI-II Immunization
TNP-IgG (Arbitrary Units)
1000
800
600
400
200
0
*
WT
WT Mock
DKO
DKO Mock
UCOE.BTKp
WT-0
KO-0

FIG. 37

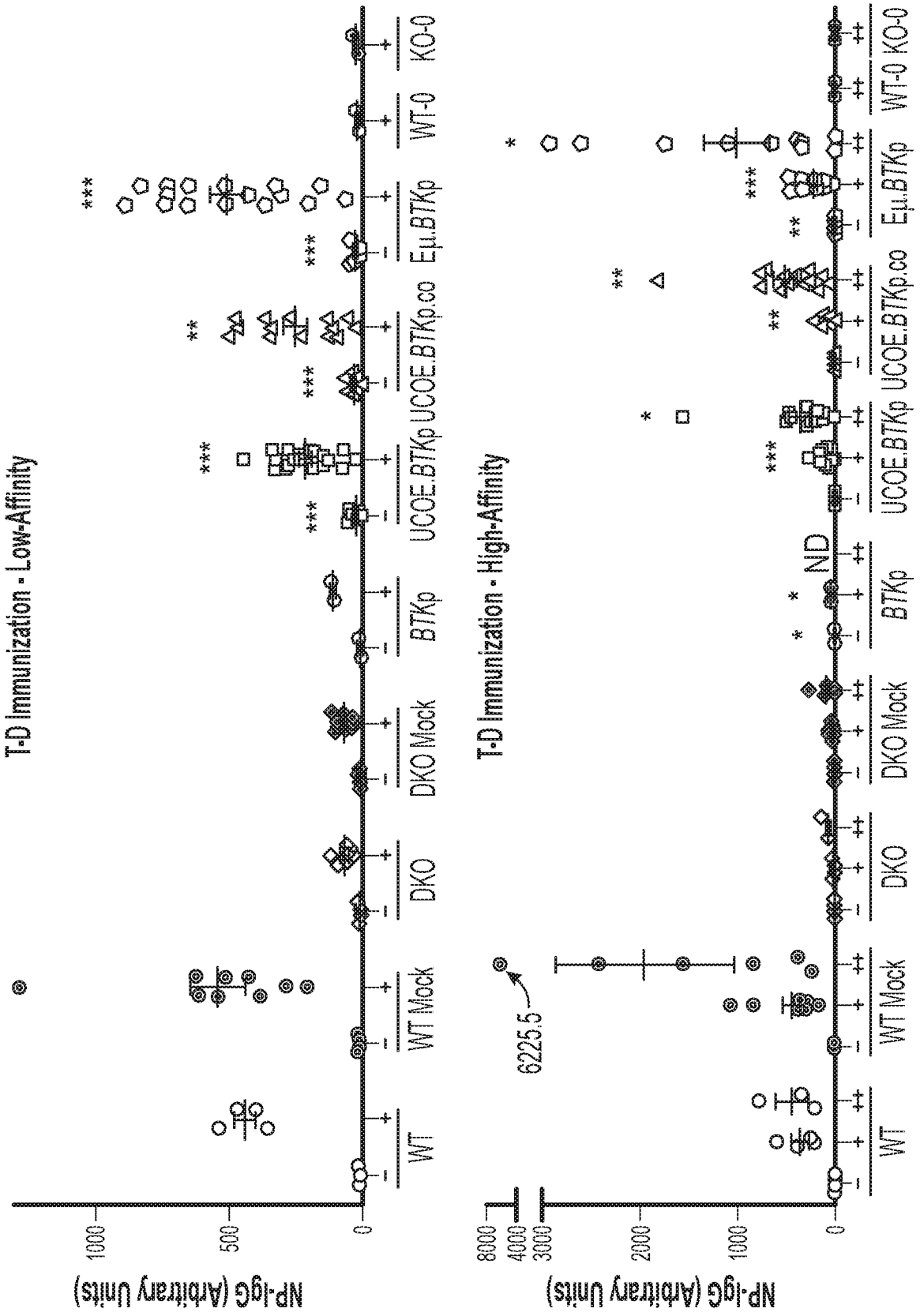

T-D Immunization - Low-Affinity
NP-IgG (Arbitrary Units)
0
500
1000
WT
WT Mock
DKO
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
WT-0
KO-0
T-D Immunization - High-Affinity
NP-IgG (Arbitrary Units)
0
1000
2000
3000
4000
8000
6225.5
ND
WT
WT Mock
DKO
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
WT-0
KO-0

FIG. 38

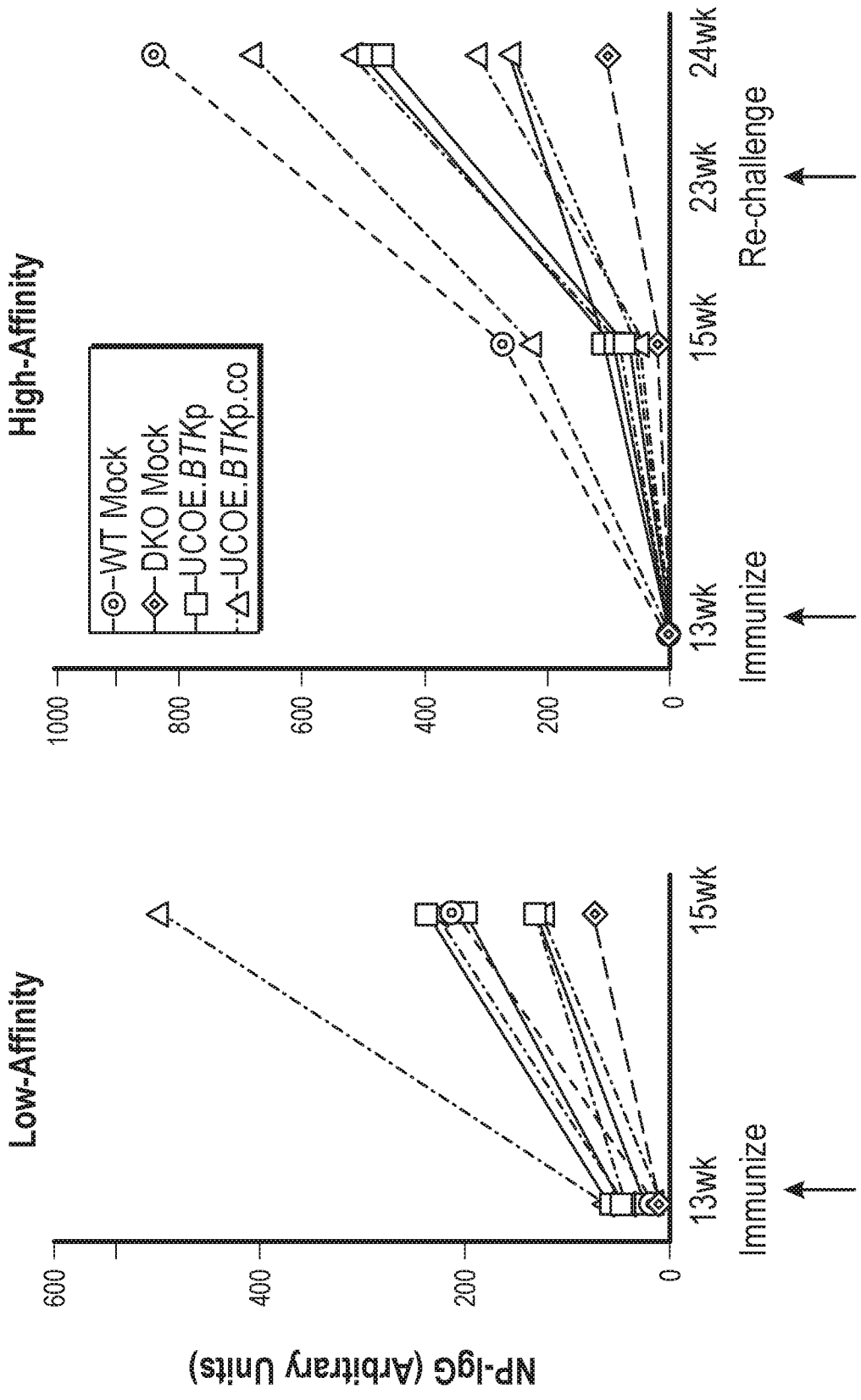

NP-IgG (Arbitrary Units)
Low-Affinity
High-Affinity
WT Mock
DKO Mock
UCOE.BTKp
UCOE.BTKp.co
Immunize
Re-challenge
13wk
15wk
23wk
24wk
0
200
400
600
800
1000

FIG. 39

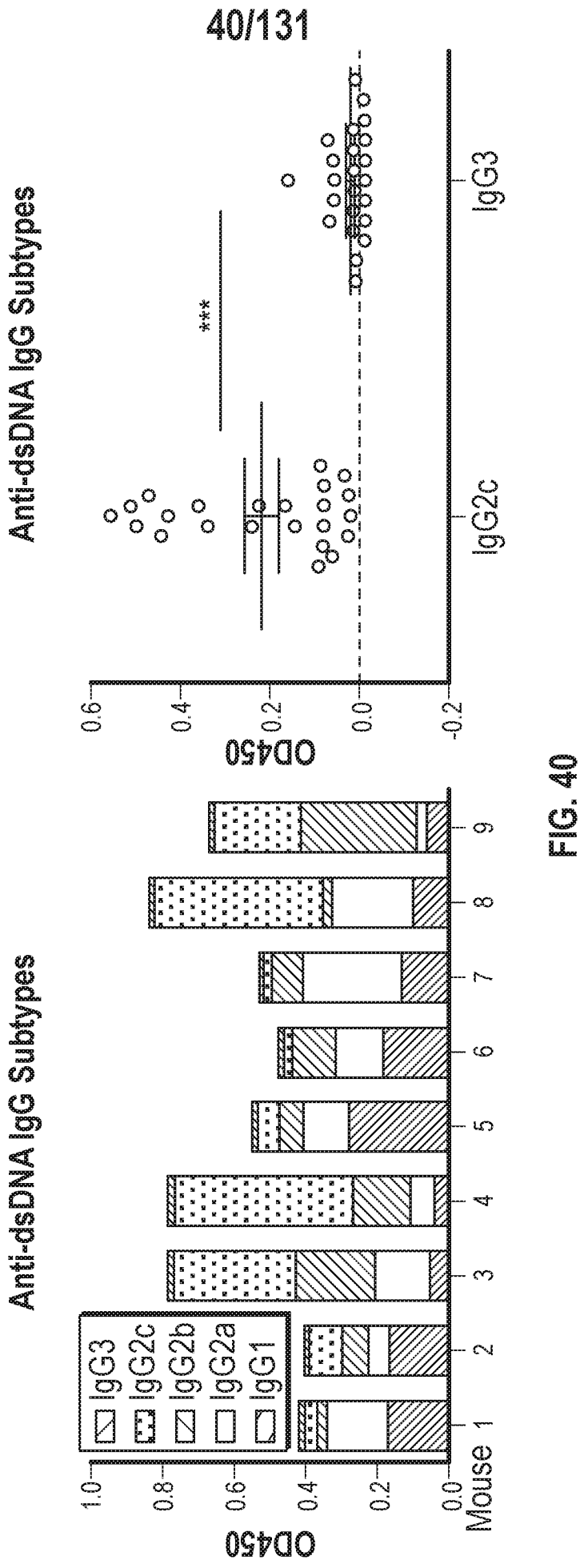

40/131
Anti-dsDNA IgG Subtypes
***
IgG3
IgG2c
OD450
0.6
0.4
0.2
0.0
-0.2
Anti-dsDNA IgG Subtypes
IgG3
IgG2c
IgG2b
IgG2a
IgG1
1.0
0.8
0.6
0.4
0.2
0.0
OD450
Mouse 1
2
3
4
5
6
7
8
9

FIG. 40

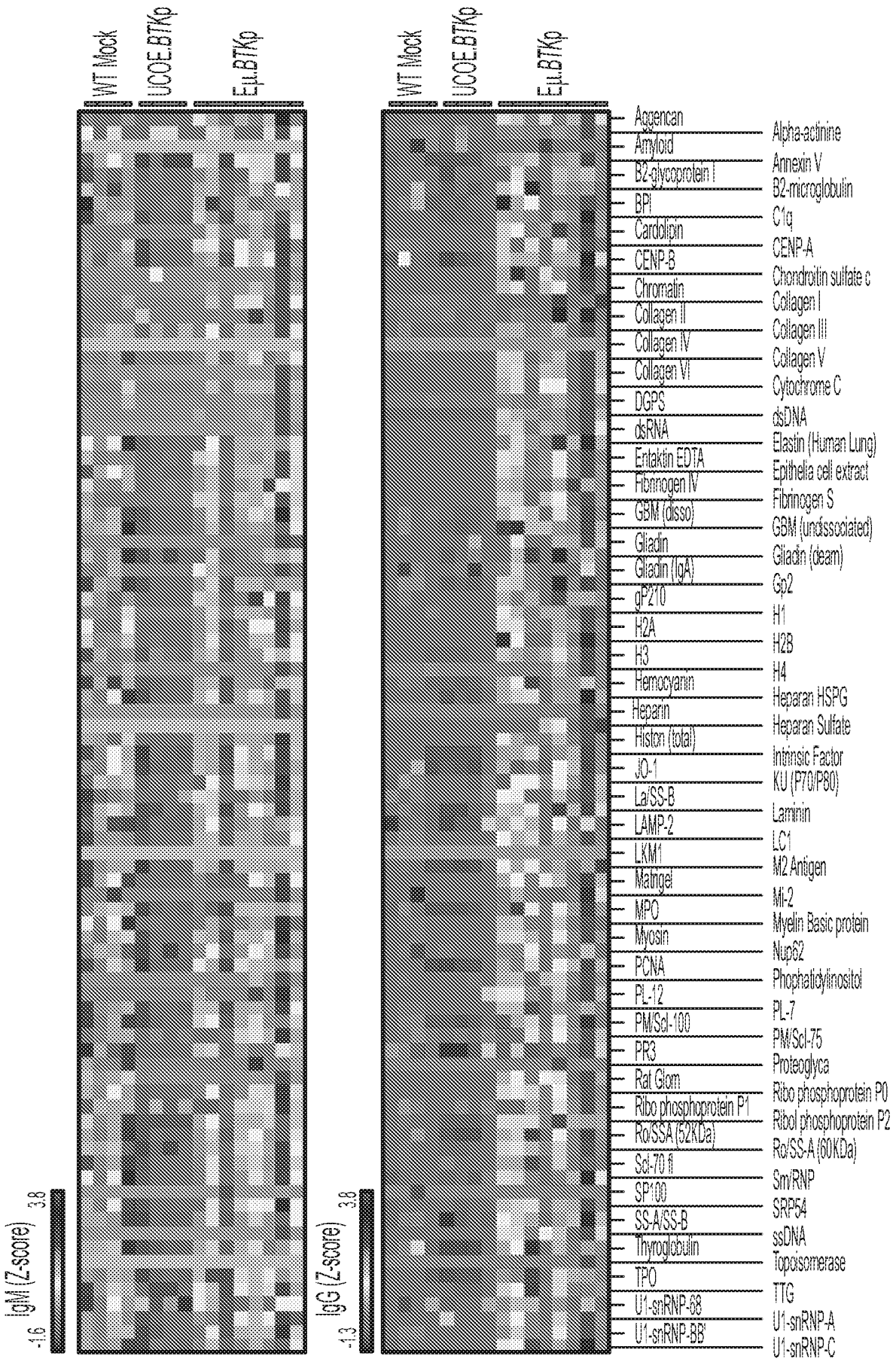

WT Mock
UCOE.BTKp
E.μ.BTKp
WT Mock
UCOE.BTKp
E.μ.BTKp
IgM (Z-score)
3.8
-1.6
IgG (Z-score)
3.8
-1.3
Aggrecan
Amyloid
B2-glycoprotein I
BPI
Cardiolipin
CENP-B
Chromatin
Collagen II
Collagen IV
Collagen VI
DGPS
dsRNA
Entaktin EDTA
Fibrinogen IV
GBM (disso)
Gliadin
Gliadin (IgA)
gP210
H2A
H3
Hemocyanin
Heparin
Histon (total)
JO-1
La/SS-B
LAMP-2
LKM1
Matrigel
MPO
Myosin
PCNA
PL-12
PM/Scl-100
PR3
Rat Glom
Ribo phosphoprotein P1
Ro/SSA (52KDa)
Scl-70 fl
SP100
SS-A/SS-B
Thyroglobulin
TPO
U1-snRNP-68
U1-snRNP-BB'
Alpha-actinine
Annexin V
B2-microglobulin
C1q
CENP-A
Chondroitin sulfate c
Collagen I
Collagen III
Collagen V
Cytochrome C
dsDNA
Elastin (Human Lung)
Epithelia cell extract
Fibrinogen S
GBM (undissociated)
Gliadin (deam)
Gp2
H1
H2B
H4
Heparan HSPG
Heparan Sulfate
Intrinsic Factor
KU (P70/P80)
Laminin
LC1
M2 Antigen
Mi-2
Myelin Basic protein
Nup62
Phosphatidylinositol
PL-7
PM/Scl-75
Proteoglyca
Ribo phosphoprotein P0
Ribol phosphoprotein P2
Ro/SS-A (60KDa)
Sm/RNP
SRP54
ssDNA
Topoisomerase
TTG
U1-snRNP-A
U1-snRNP-C

FIG. 41

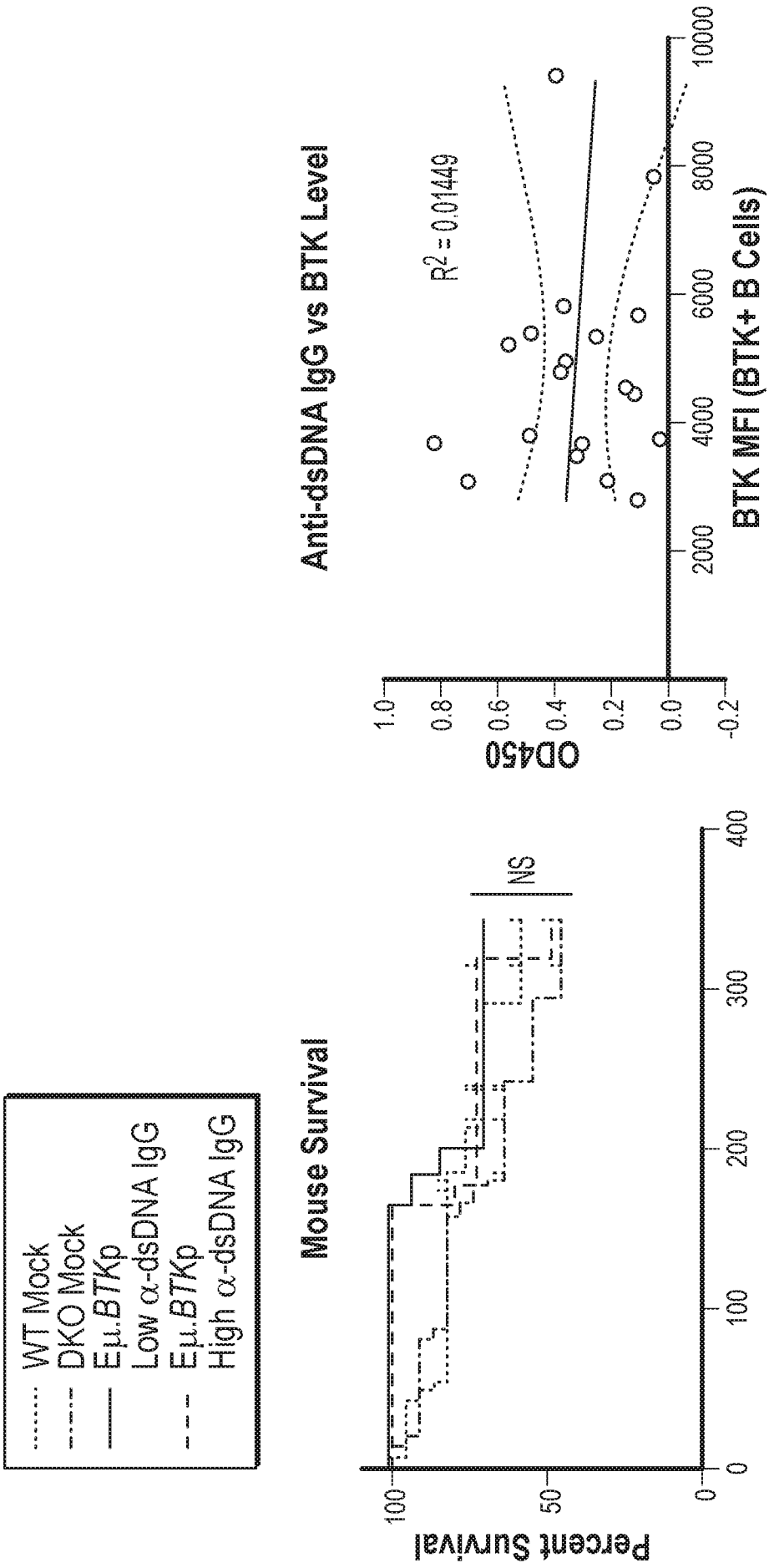

WT Mock
DKO Mock
Eμ.BTKp
Low α-dsDNA IgG
Eμ.BTKp
High α-dsDNA IgG
Mouse Survival
Percent Survival
100
50
0
0
100
200
300
400
NS
Anti-dsDNA IgG vs BTK Level
OD450
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
R2 = 0.01449
2000
4000
6000
8000
10000
BTK MFI (BTK+ B Cells)

FIG. 42

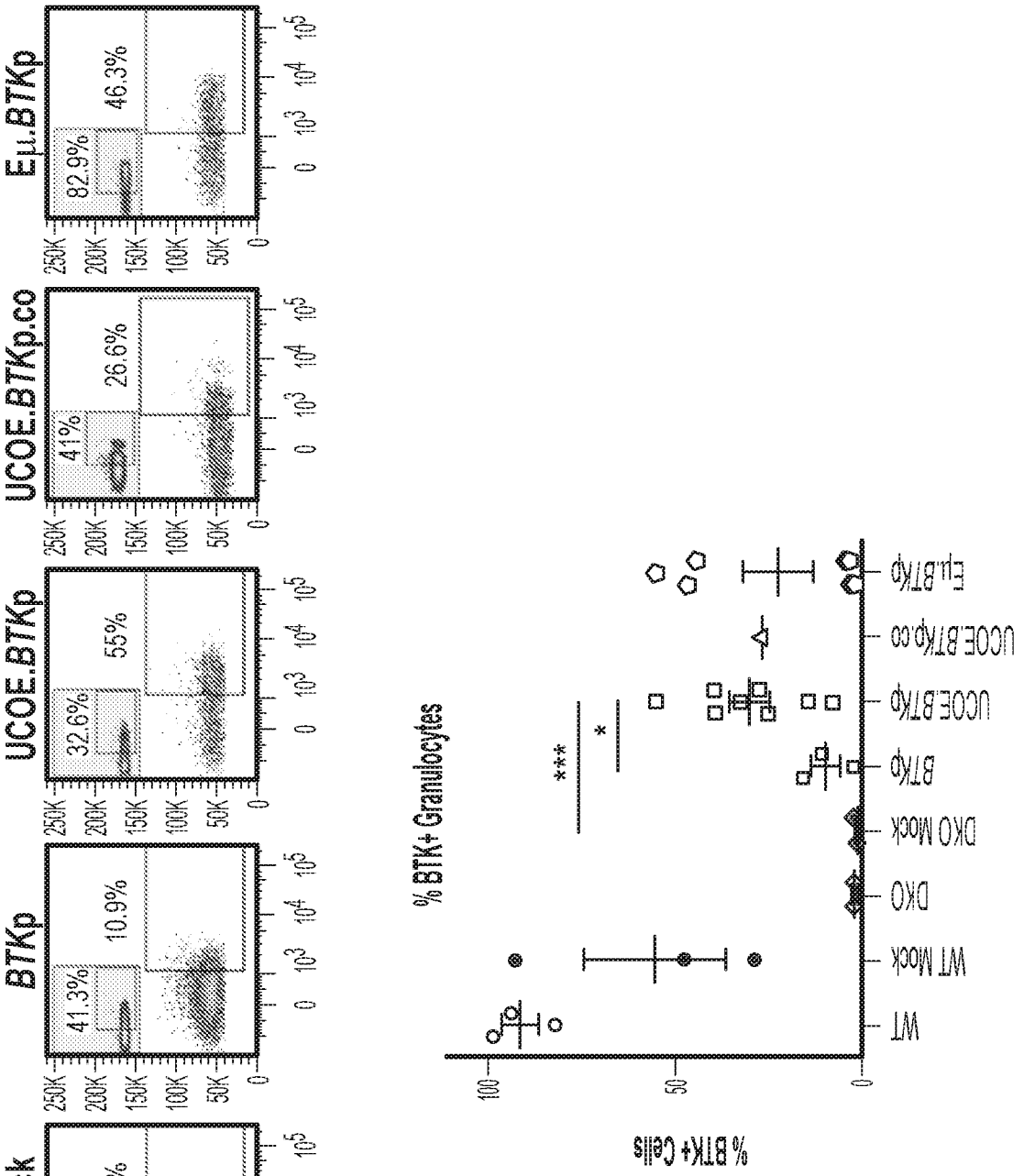

WT Mock
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
88.3%
92%
1.92%
1.6%
41.3%
10.9%
32.6%
55%
41%
26.6%
82.9%
46.3%
FSC
BTK
% BTK+ Granulocytes
% BTK+ Cells
***
*
WT
WT Mock
DKO
DKO Mock
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp

FIG. 43

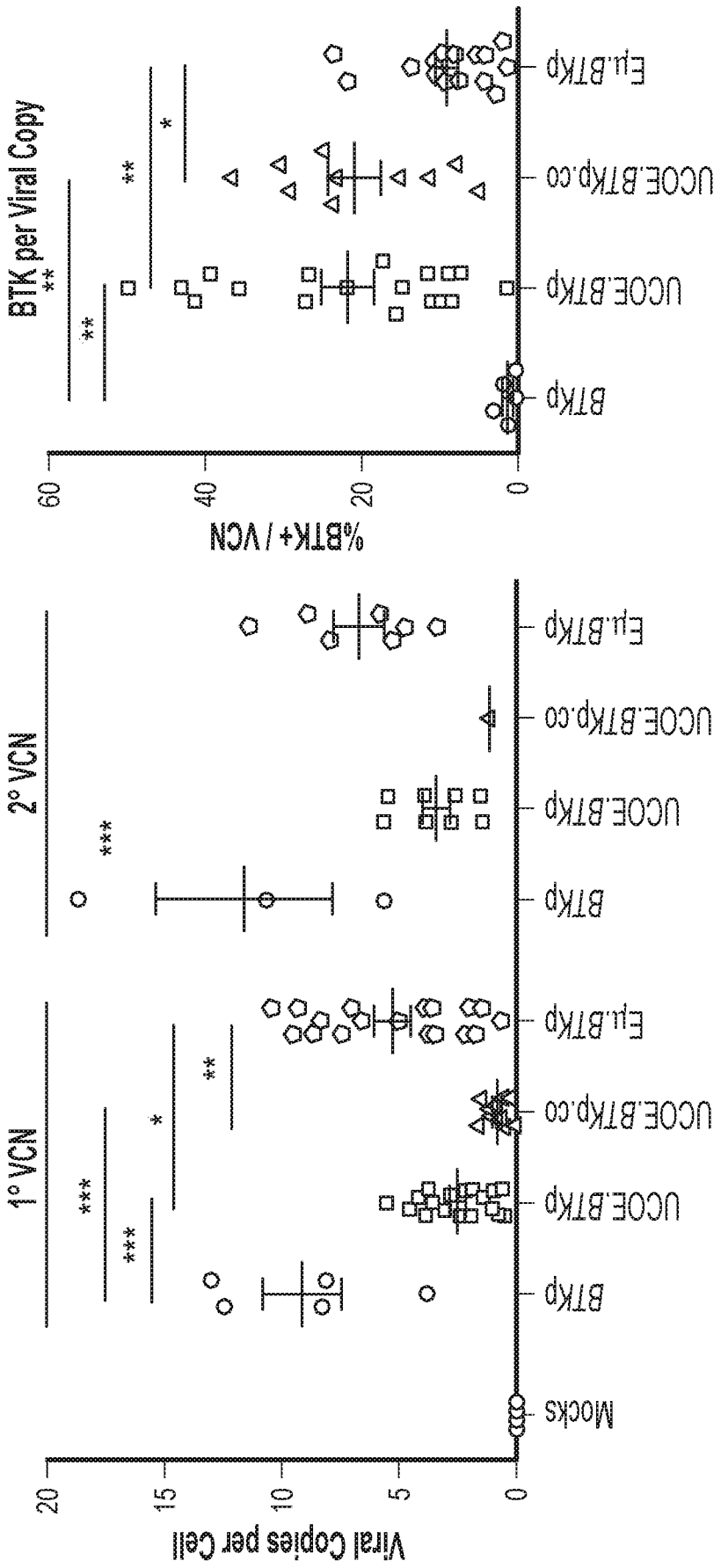

BTK per Viral Copy
%BTK+ / VCN
0
20
40
60
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
**
**
**
*
1° VCN
2° VCN
Viral Copies per cell
0
5
10
15
20
Mocks
BTKp
UCOE.BTKp
UCOE.BTKp.co
Eμ.BTKp
***
***
*
**
***

FIG. 44

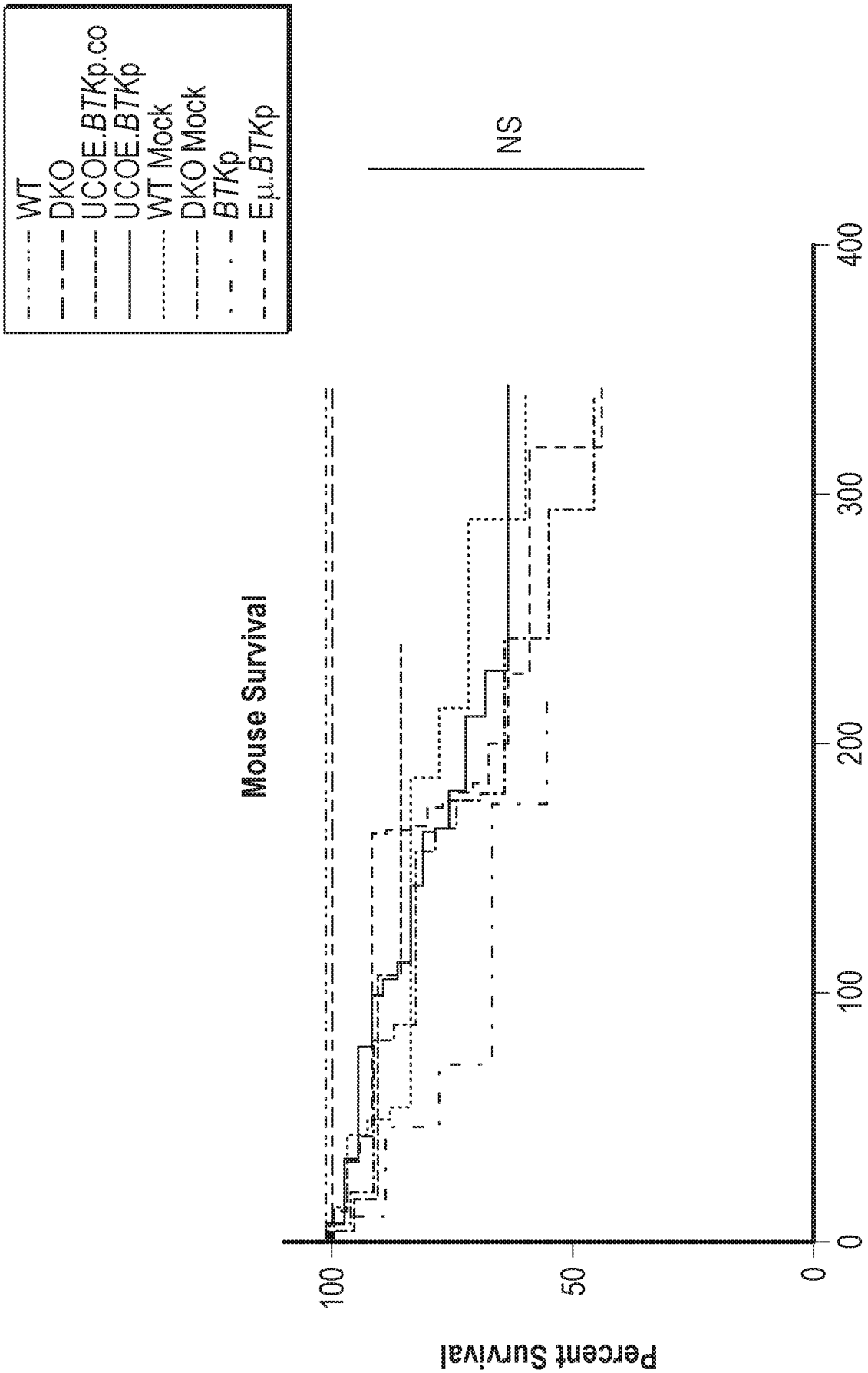

WT
DKO
UCOE.BTKp.co
UCOE.BTKp
WT Mock
DKO Mock
BTKp
Eμ.BTKp
NS
Mouse Survival
Percent Survival
100
50
0
0
100
200
300
400

FIG. 45

BTKpro.BTK (5.4kb)
BTKpro
human BTK
1.5 kb.UCOE.BTKpro.BTK (6.9kb)
1.5 UCOE
BTKpro
human BTK
1.5 kb.UCOE.BTKpro.co-opBTk (6.4kb)
1.5 UCOE
BTKpro
human BTK
Eμ.BTKpro.BTK (6.4kb)
Eμ
BTKpro
human BTK
WT Mock
KO Mock
B Cells
BTK+ Cells(%)
Bone Marrow
Spleen
Peritoneum
Viral Copies per Cell
Methylation (%)
Anti-dsDNA IgG
OD450
1.5UCOE provides marked improvement over Btkpro only LV. However this LV construct still needs additional improvement:
• Large vector size
• Low titer
• Would like to increase BTK expression

FIG. 46

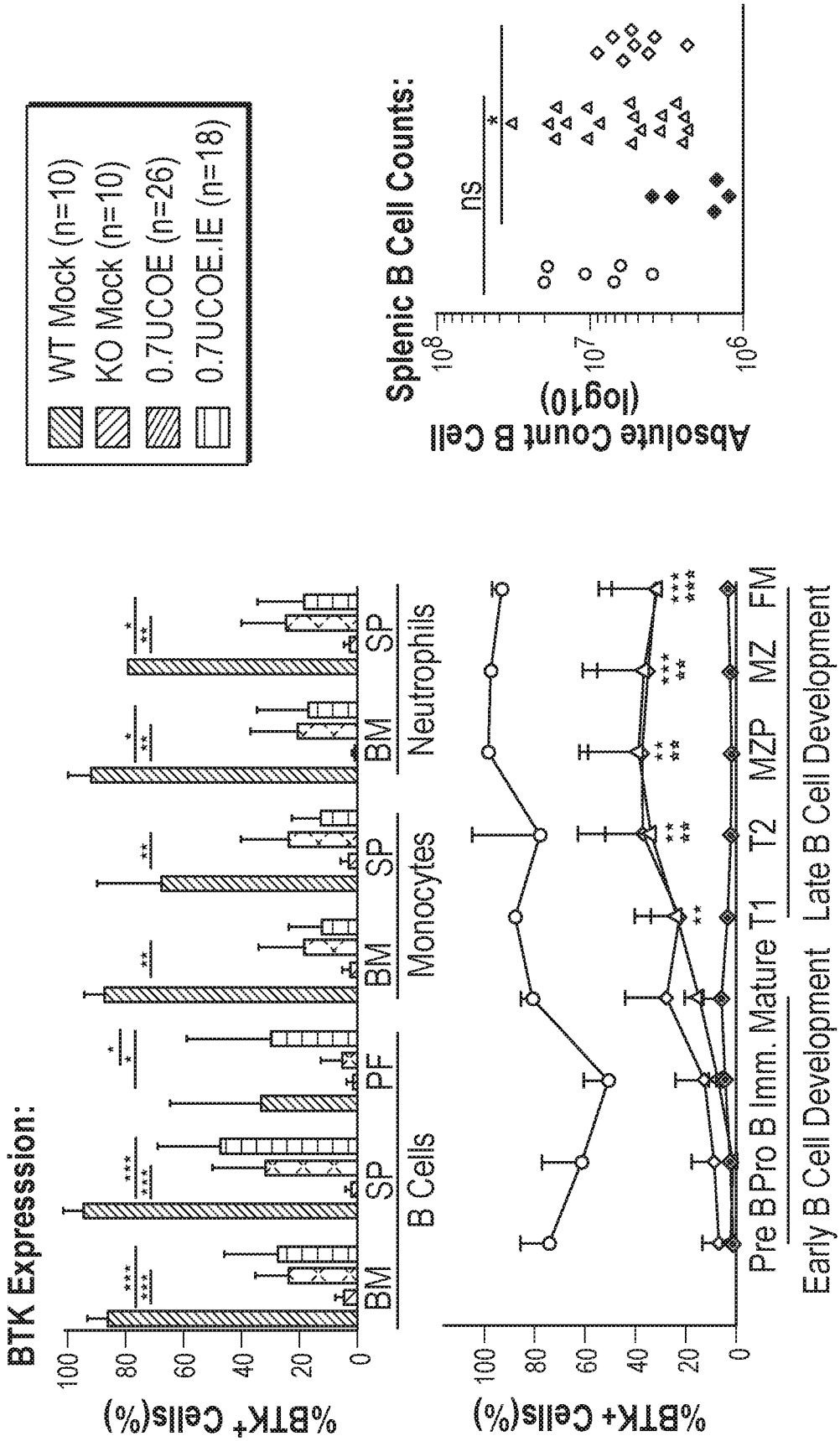

0.7UCOE.BTKp and 0.7UCOE.IE.BTKp rescue BTK expression and splenic B Cell counts
WT Mock (n=10)
KO Mock (n=10)
0.7UCOE (n=26)
0.7UCOE.IE (n=18)
Splenic B Cell Counts:
Absolute Count B Cell (log10)
ns
BTK Expression:
%BTK+ Cells(%)
BM
SP
PF
B Cells
Monocytes
Neutrophils
Pre B
Pro B
Imm.
Mature
T1
T2
MZP
MZ
FM
Early B Cell Development
Late B Cell Development

FIG. 47

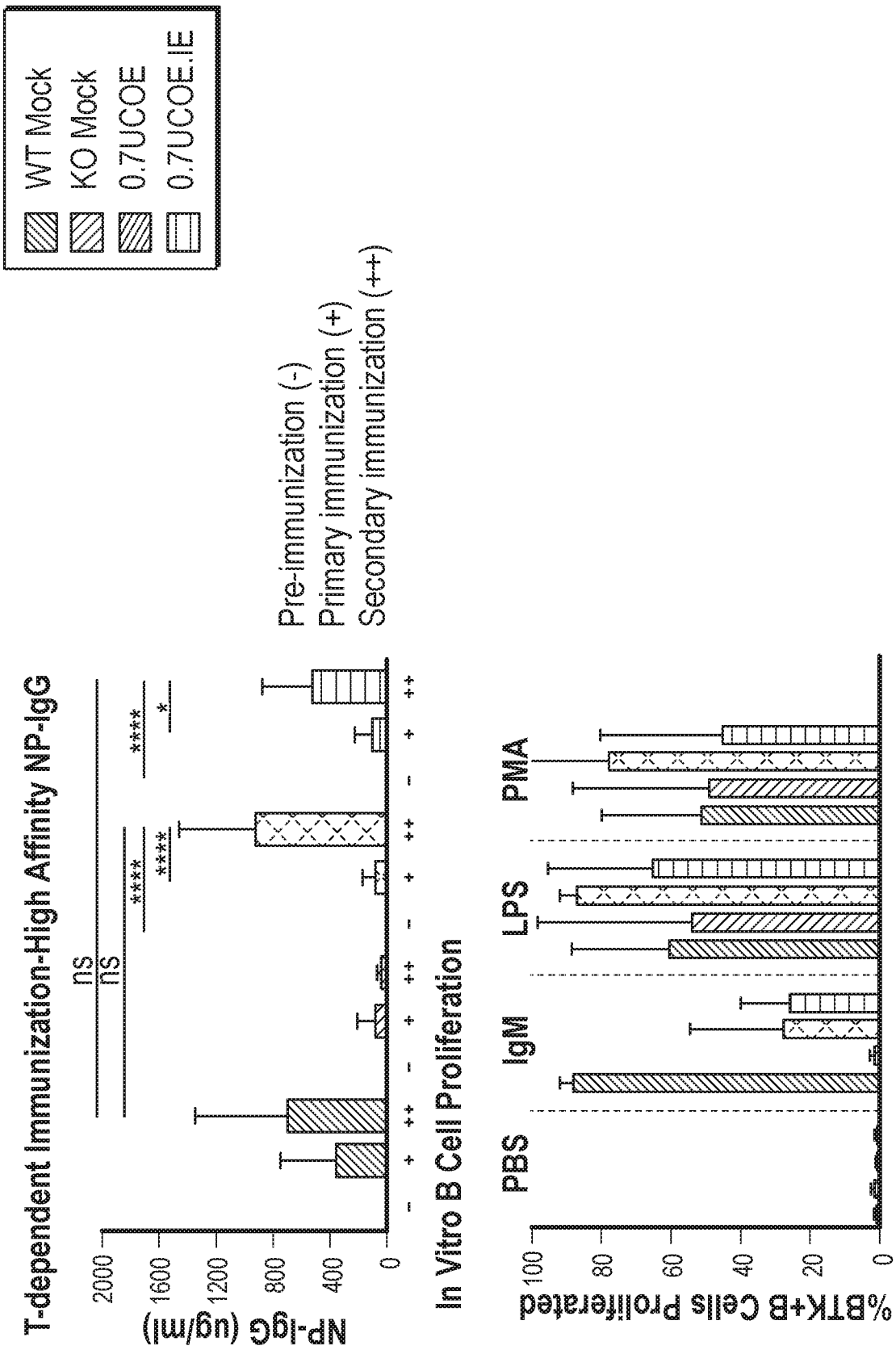

WT Mock
KO Mock
0.7UCOE
0.7UCOE.IE
T-dependent Immunization-High Affinity NP-IgG
NP-IgG (ug/ml)
2000
1600
1200
800
400
0
ns
ns
****
****
****
*
Pre-immunization (-)
Primary immunization (+)
Secondary immunization (++)
In Vitro B Cell Proliferation
PBS
IgM
LPS
PMA
%BTK+B Cells Proliferated
100
80
60
40
20
0

FIG. 48

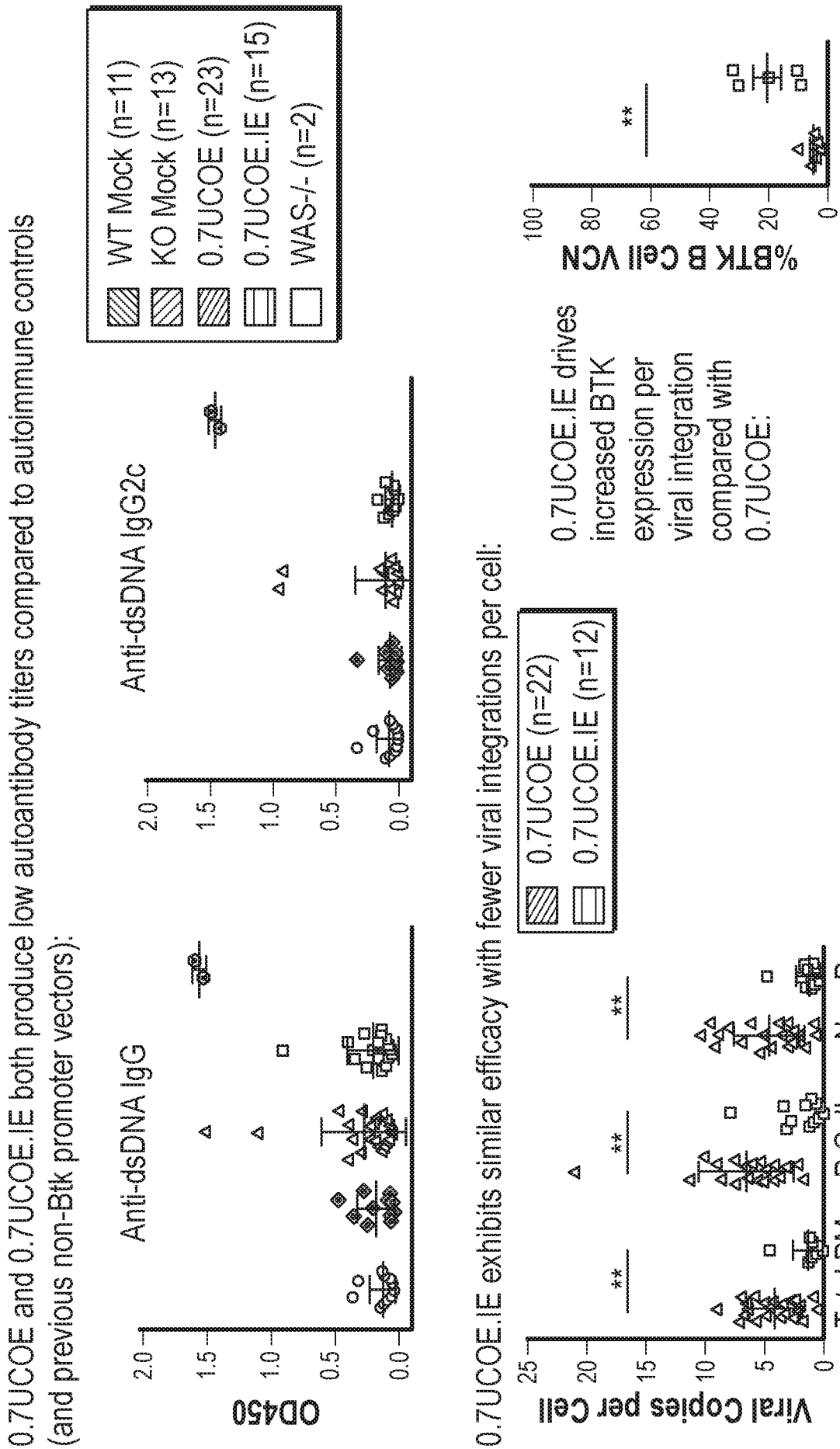

0.7UCOE and 0.7UCOE.IE both produce low autoantibody titers compared to autoimmune controls
(and previous non-Btk promoter vectors):
Anti-dsDNA IgG
Anti-dsDNA IgG2c
OD450
2.0
1.5
1.0
0.5
0.0
WT Mock (n=11)
KO Mock (n=13)
0.7UCOE (n=23)
0.7UCOE.IE (n=15)
WAS-/- (n=2)
0.7UCOE.IE exhibits similar efficacy with fewer viral integrations per cell:
0.7UCOE (n=22)
0.7UCOE.IE (n=12)
Viral Copies per Cell
25
20
15
10
5
0
**
Total BM
B Cells
Non B
Spleen
0.7UCOE.IE drives increased BTK expression per viral integration compared with 0.7UCOE:
%BTK B cell VCN
100
80
60
40
20
0

FIG. 49

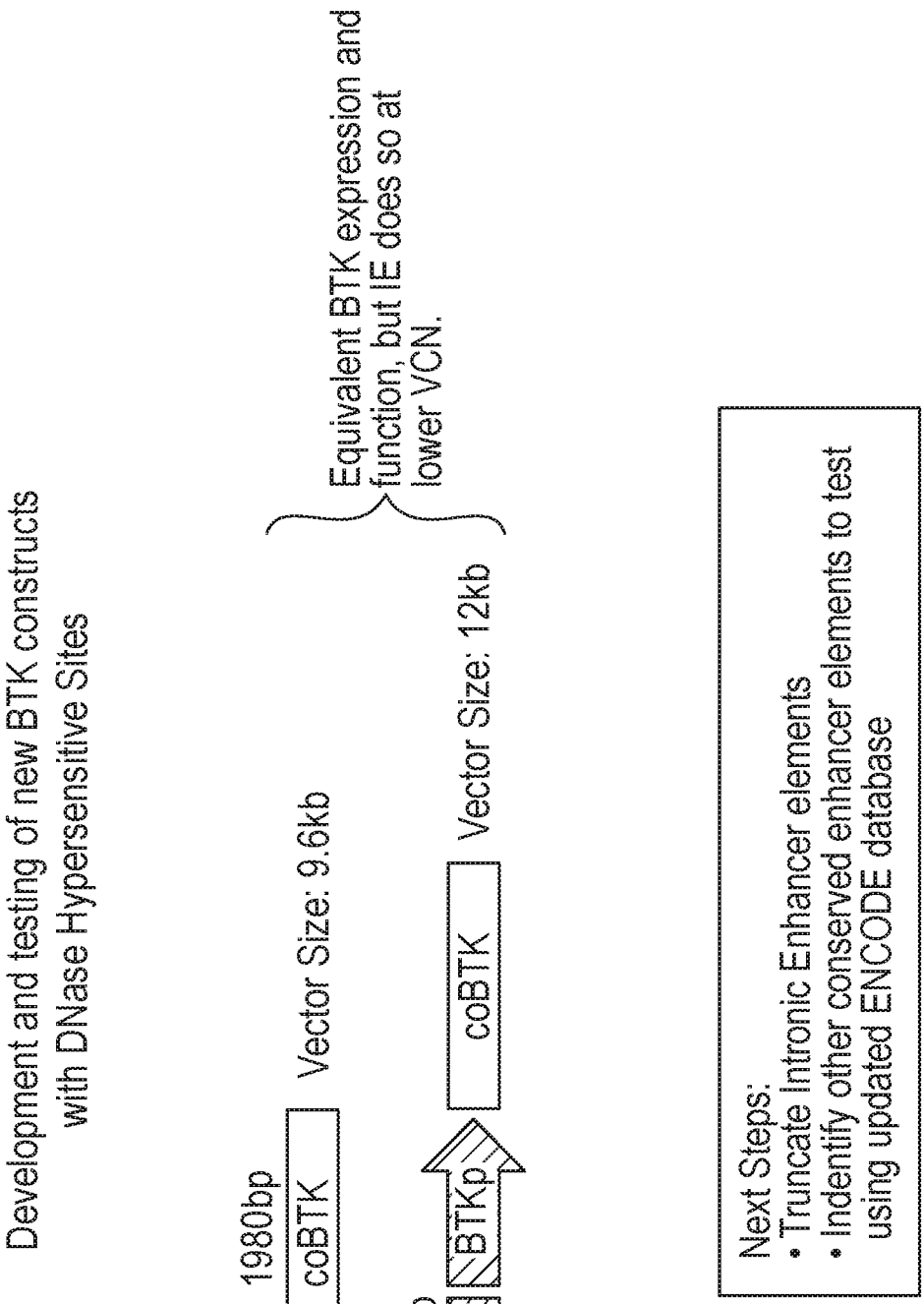

Development and testing of new BTK constructs
with DNase Hypersensitive Sites
673bp
0.7UCOE
796bp
BTKp
1980bp
coBTK
Vector Size: 9.6kb
1178bp
INT5
1226bp
INT4
BTKp
coBTK
Vector Size: 12kb
Equivalent BTK expression and function, but IE does so at lower VCN.
Next Steps:
• Truncate Intronic Enhancer elements
• Indentify other conserved enhancer elements to test using updated ENCODE database

FIG. 50


Identification of DNase Hypersensitive Sites:
Exon:
BTK
BTKp
Basic Gene Annotation Set from GENCODE Version 19
BTK
BTK
Transcription Levels Assayed by RNA-seq on 9 Cell Lines from ENCODE
ln(x+1) 50
0
Transcription
H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE
200
0
Layered H3K27Ac
DNase Hyper-sensitive Sites:
DNase I Hypersensitive Site Master List (125 cell types) from Encode/Analysis
B Cell Line:
GM12878 DNaseI HS Uniform Peaks from ENCODE/Analysis
h1-hESC DNaseI HS Uniform Peaks from Encode Analysis
K562 DNaseI HS Uniform Peaks from Encode Analysis
HUVEC DNaseI HS Uniform Peaks from Encode Analysis
HeLa-S3 DNaseI HS Uniform Peaks from Encode Analysis
HepG2 DNaseI HS Uniform Peaks from Encode Analysis
A549 DNaseI HS Uniform Peaks from Encode Analysis
CD20+ Cell:
CD20+ B cell DNaseI HS Uniform Peaks from ENCODE/Analysis
MCF-7 DNaseI HS Uniform Peaks from ENCODE/Analysis
Monocytes-CD14+ DNaseI HS Uniform Peaks from ENCODE/Analysis
Mobilized CD34+:
CD34_Mobilized DNaseI HS Uniform Peaks from ENCODE/Analysis
NHEK DNaseI HS Uniform Peaks from ENCODE/Analysis

FIG. 51-1

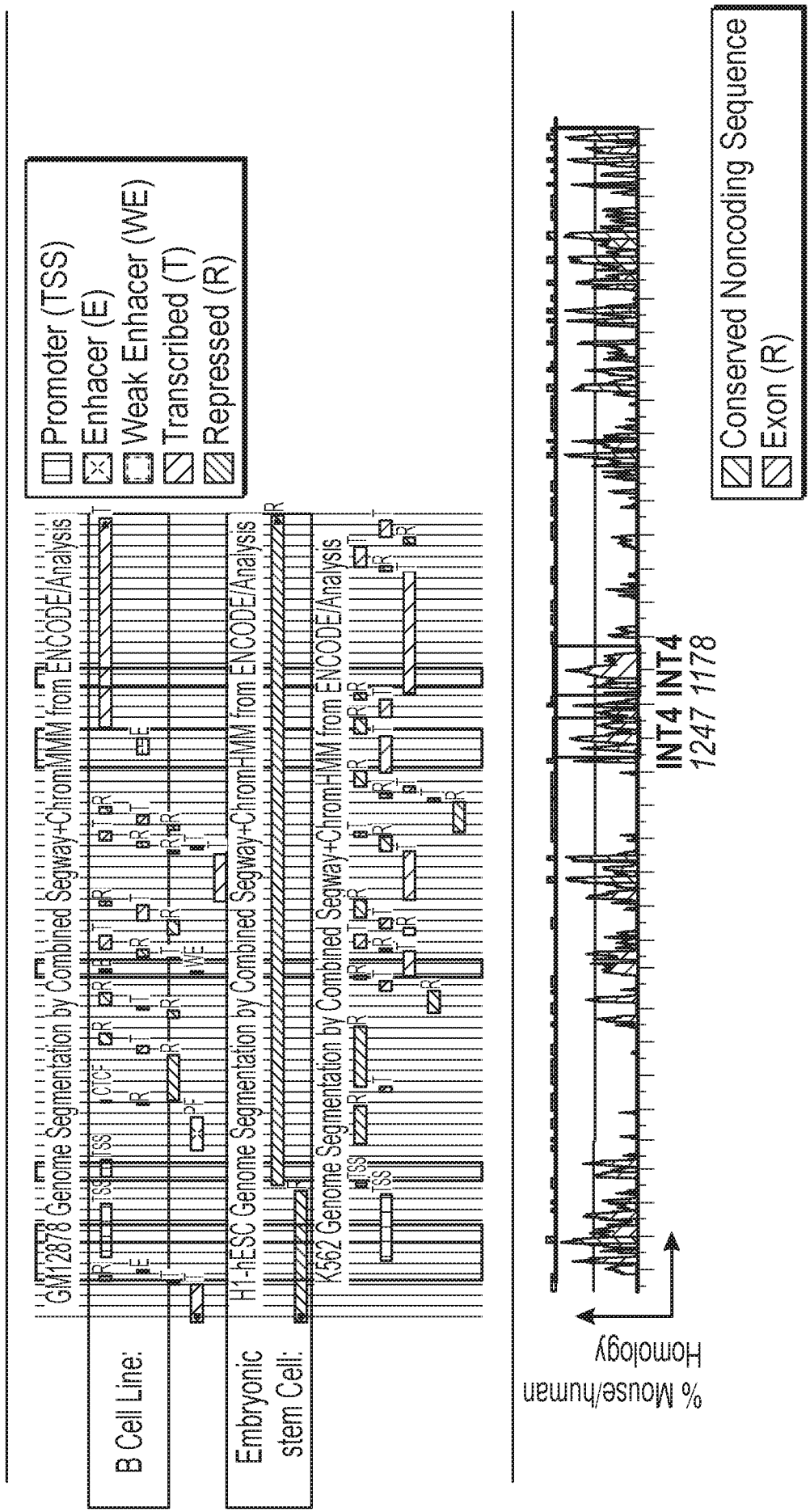

Promoter (TSS)
Enhacer (E)
Weak Enhacer (WE)
Transcribed (T)
Repressed (R)
Conserved Noncoding Sequence
Exon (R)
B Cell Line:
GM12878 Genome Segmentation by Combined Segway+ChromHMM from ENCODE/Analysis
Embryonic stem Cell:
H1-hESC Genome Segmentation by Combined Segway+ChromHMM from ENCODE/Analysis
K562 Genome Segmentation by Combined Segway+ChromHMM from ENCODE/Analysis
INT4 INT4
1247 1178
% Mouse/human Homology

FIG. 51-2

Constructs Evaluated:
0.7UCOE.BTKp.coBTK
673bp
796bp
1980bp
0.7UCOE
BTKp
coBTK
Vector Size: 9.6kb
0.7UCOE.IE.BTKp.coBTK
1178bp
1226bp
0.7UCOE
INT5
INT4
BTKp
coBTK
Vector Size: 12kb
New Constructs with Candidate DNase Hypersensitive Sites:
0.7UCOE.DHS4.BTKp.coBTK
453bp
0.7UCOE
DHS4
BTKp
coBTK
Vector Size: 10kb
0.7UCOE.DHS1,2.BTKp.coBTK
334bp 409bp
0.7UCOE
DHS1
DHS2
BTKp
coBTK
Vector Size: 10.4kb
0.7UCOE.DHS1,2,4.BTKp.coBTK
334bp 409bp 453bp
0.7UCOE
DHS1
DHS2
DHS4
BTKp
coBTK
Vector Size: 10.8kb
0.7UCOE.DHS1-5.BTKp.coBTK
334bp 409bp 353bp 453bp 149bp
0.7UCOE
DHS1
DHS2
DHS3
DHS4
DHS5
BTKp
coBTK
Vector Size: 11.3kb

FIG. 52

In Vivio Comparison of DHS constructs to 0.7UCOE and 0.7UCOE.IE

- Experiment #10 setup: 40ul virus per 1x10e6 cells (hope for matched VCN), overnight transduction
- RO Injection of 1x10e6 cells/condition into TBKBP mice (900 rads irradiation prior to transplant)

LV Vector	Volumen Added	Titer	# of Mice
0.7UCOE.BTKp.coBTK	40ul per 1x10e6 cells	1.31E+08	4
0.7UCOE.IE.BTKp.coBTK	40ul per 1x10e6 cells	1.14E+08	4
0.7UCOE.DHS4.BTKp.coBTK	40ul per 1x10e6 cells	4.11E+07	4
0.7UCOE.DHS1,2.BTKp.coBTK	40ul per 1x10e6 cells	1.18E+08	4
0.7UCOE.DHS1,2,4.BTKp.coBTK	40ul per 1x10e6 cells	4.29E+07	3
0.7UCOE.DHS1-5.BTKp.coBTK	40ul per 1x10e6 cells	9.86E+07	3
KO Mock/WT Mock			2 each

FIG. 53

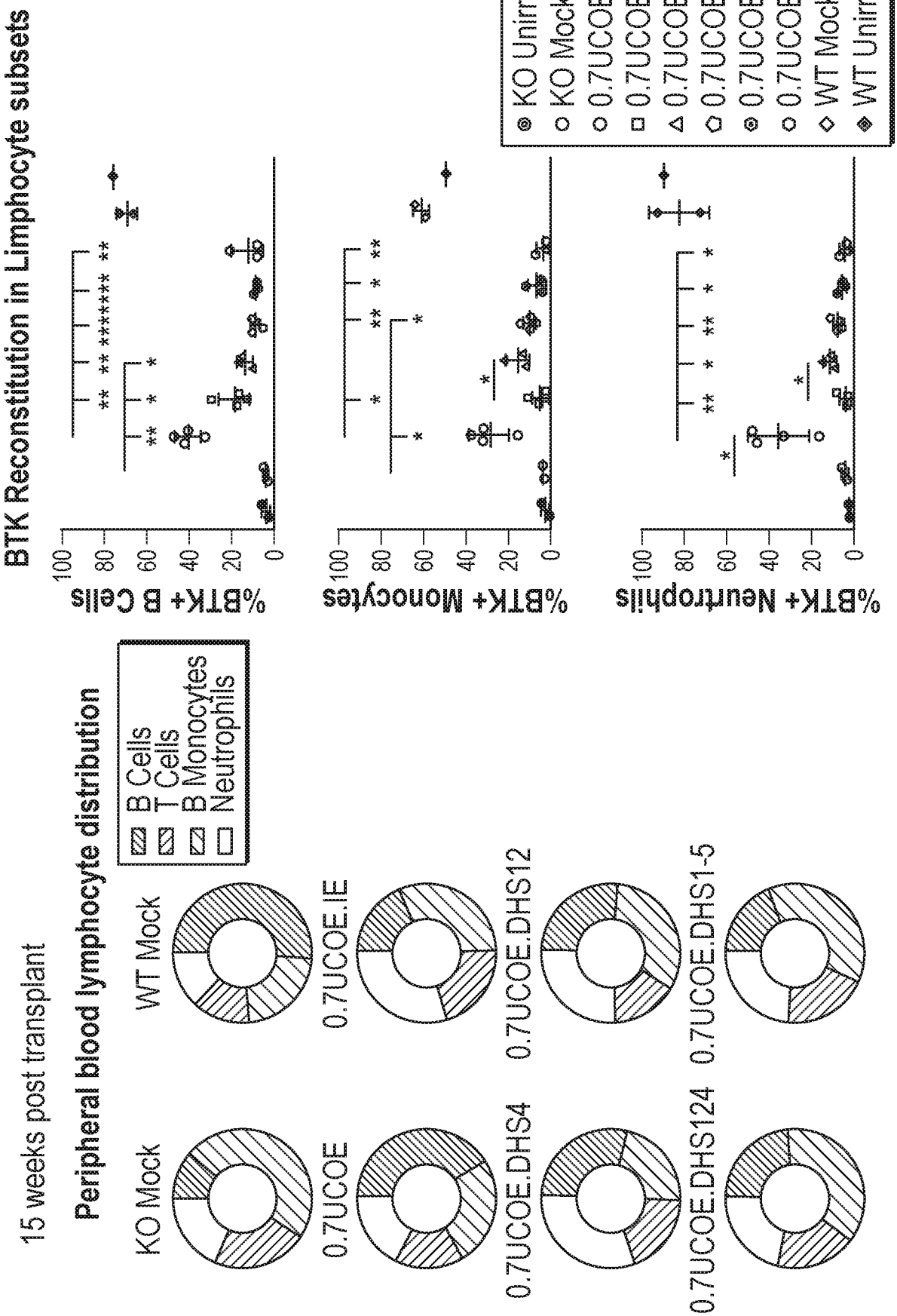
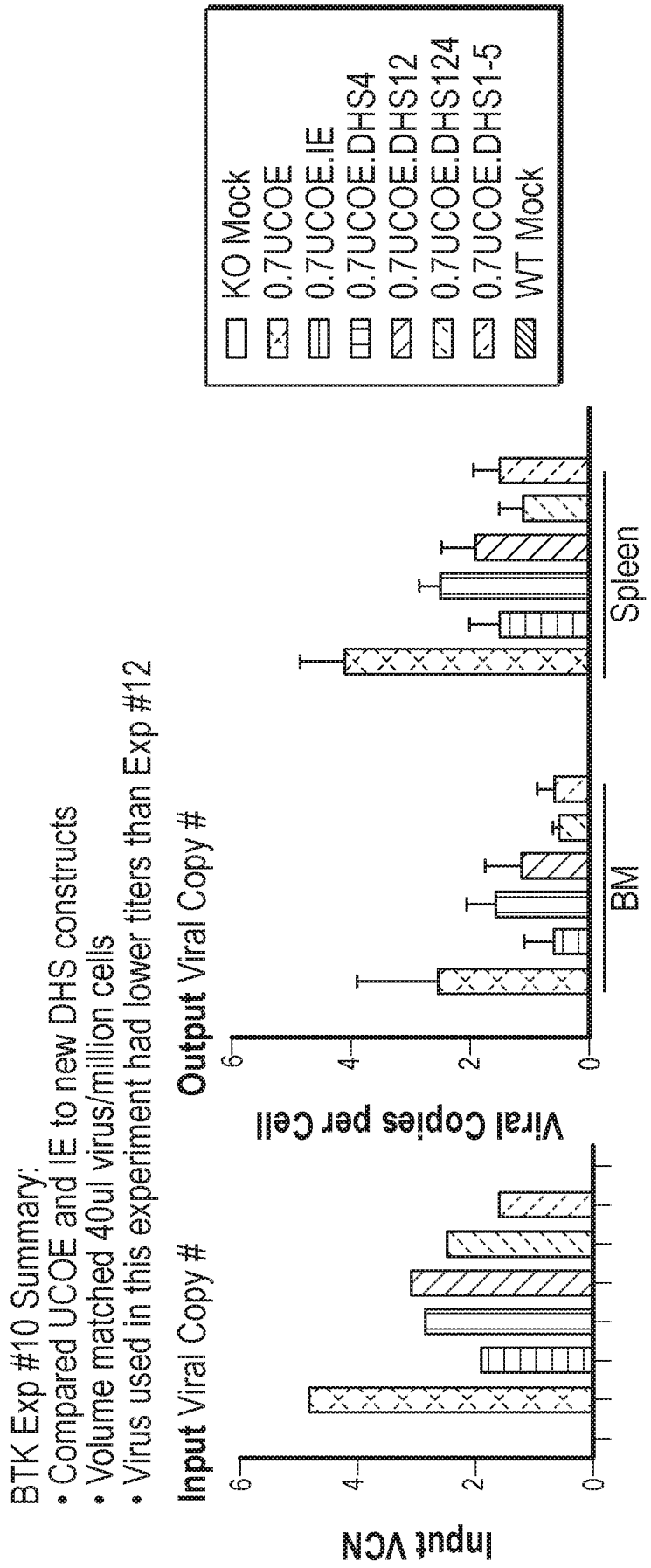

BTK Reconstitution in Limphocyte subsets
%BTK+ B Cells
%BTK+ Monocytes
%BTK+ Neutrophils
KO Unirradiated
KO Mock
0.7UCOE
0.7UCOE.IE
0.7UCOE.DHS4
0.7UCOE.DHS12
0.7UCOE.DHS124
0.7UCOE.DHS1-5
WT Mock
WT Unirradiated
15 weeks post transplant
Peripheral blood lymphocyte distribution
B Cells
T Cells
B Monocytes
Neutrophils
KO Mock
WT Mock
0.7UCOE
0.7UCOE.IE
0.7UCOE.DHS4
0.7UCOE.DHS12
0.7UCOE.DHS124
0.7UCOE.DHS1-5

FIG. 54



LV Vector	Titer
0.7UCOE.BTKp	1.31E+08
0.7UCOE.IE.BTKp	1.14E+08
0.7UCOE.DHS4.BTKp	4.11E+07
0.7UCOE.DHS1,2.BTKp	1.18E+08
0.7UCOE.DHS1,2,4.BTK	4.29E+07
0.7UCOE.DHS1-5.BTKp	9.86E+07

FIG. 55

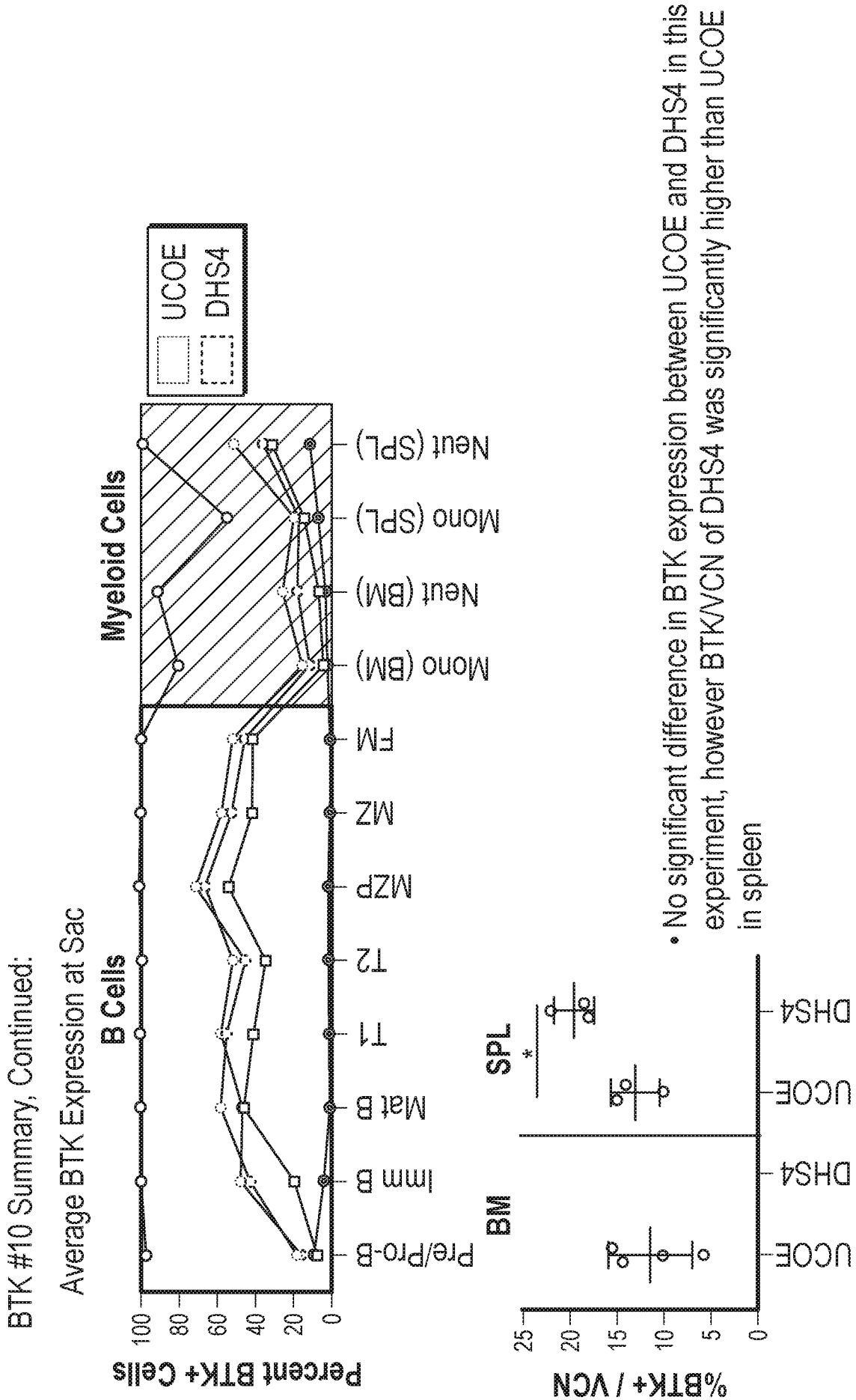

BTK #10 Summary, Continued:
Average BTK Expression at Sac
B Cells
Myeloid Cells
UCOE
DHS4
Percent BTK+ Cells
100
80
60
40
20
0
Pre/Pro-B
Imm B
Mat B
T1
T2
MZP
MZ
FM
Mono (BM)
Neut (BM)
Mono (SPL)
Neut (SPL)
BM
SPL
%BTK+ / VCN
25
20
15
10
5
0
UCOE
DHS4
UCOE
DHS4
• No significant difference in BTK expression between UCOE and DHS4 in this experiment, however BTK/VCN of DHS4 was significantly higher than UCOE in spleen

FIG. 56

Experiment set-up:

- Harvested Lin-cells from TBK donor mice
- Transduction:
  - **Matched volume: 10ul virus/million cells** (target: matched input VCN of ~3, as predicted by *in vitro* test)
  - 16hr transduction, 4x10e6 cells/ml in SCGM transduction media (mSCF, mTPO) + polybrene
- Transplanted 1.5x10e6 cells/mouse (recipients: TBK, 900 rads irradiation)

FIG. 57-1

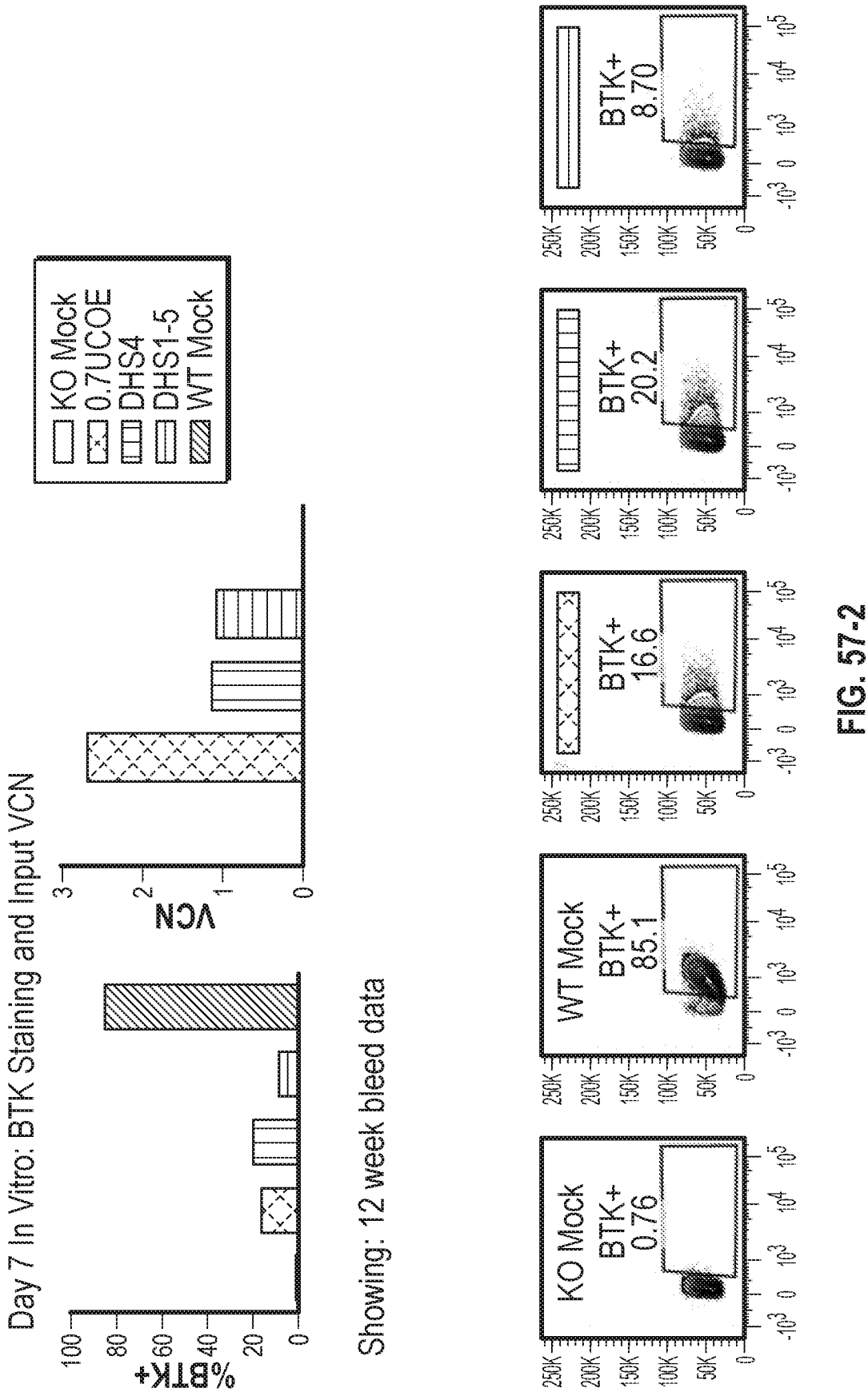

Day 7 In Vitro: BTK Staining and Input VCN
%BTK+
VCN
KO Mock
0.7UCOE
DHS4
DHS1-5
WT Mock
Showing: 12 week bleed data
KO Mock
BTK+
0.76
WT Mock
BTK+
85.1
BTK+
16.6
BTK+
20.2
BTK+
8.70

FIG. 57-2

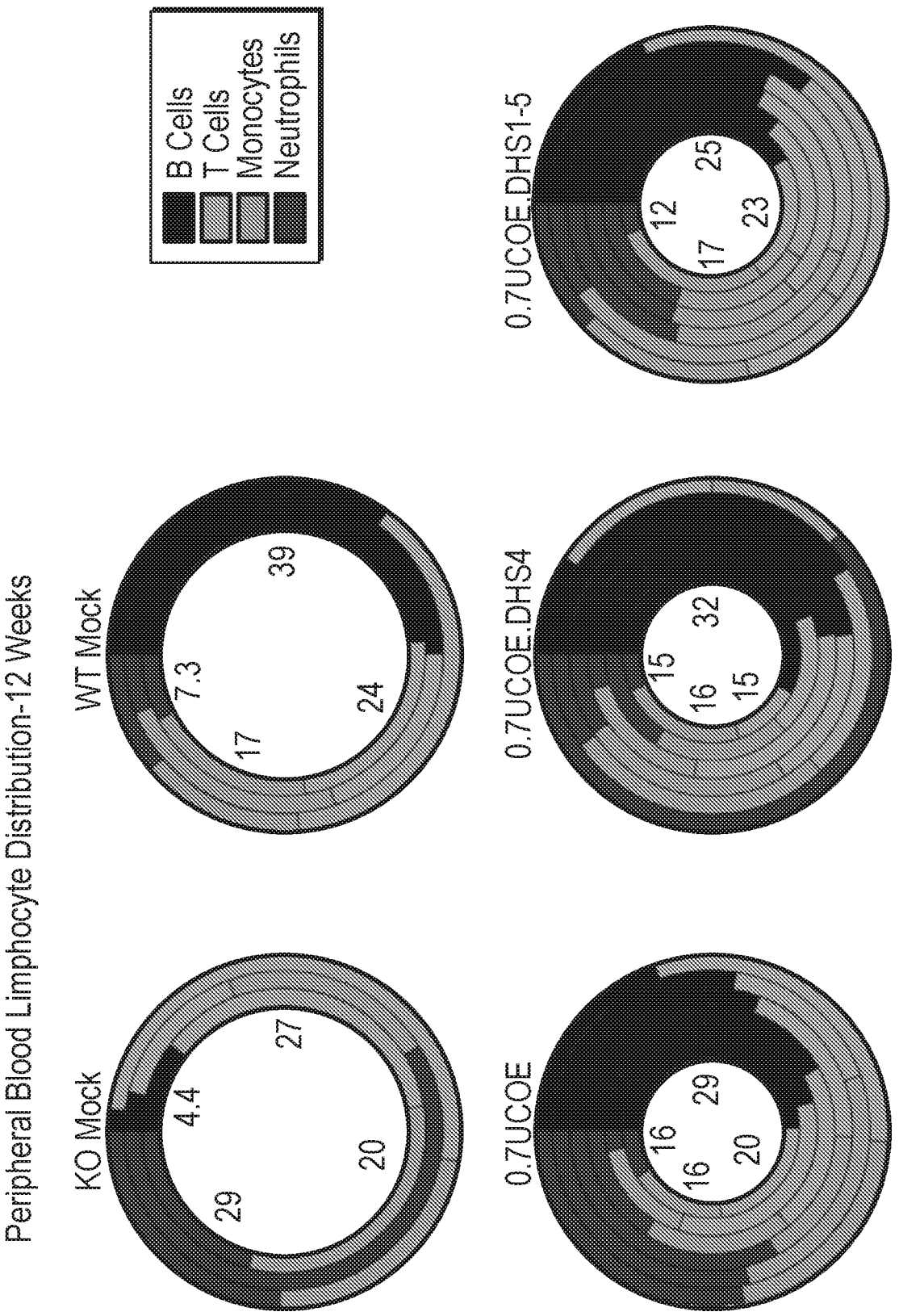

Peripheral Blood Limphocyte Distribution-12 Weeks
B Cells
T Cells
Monocytes
Neutrophils
KO Mock
4.4
27
29
20
WT Mock
7.3
39
17
24
0.7UCOE.DHS1-5
12
25
17
23
0.7UCOE
16
29
16
20
0.7UCOE.DHS4
15
32
16
15

FIG. 58

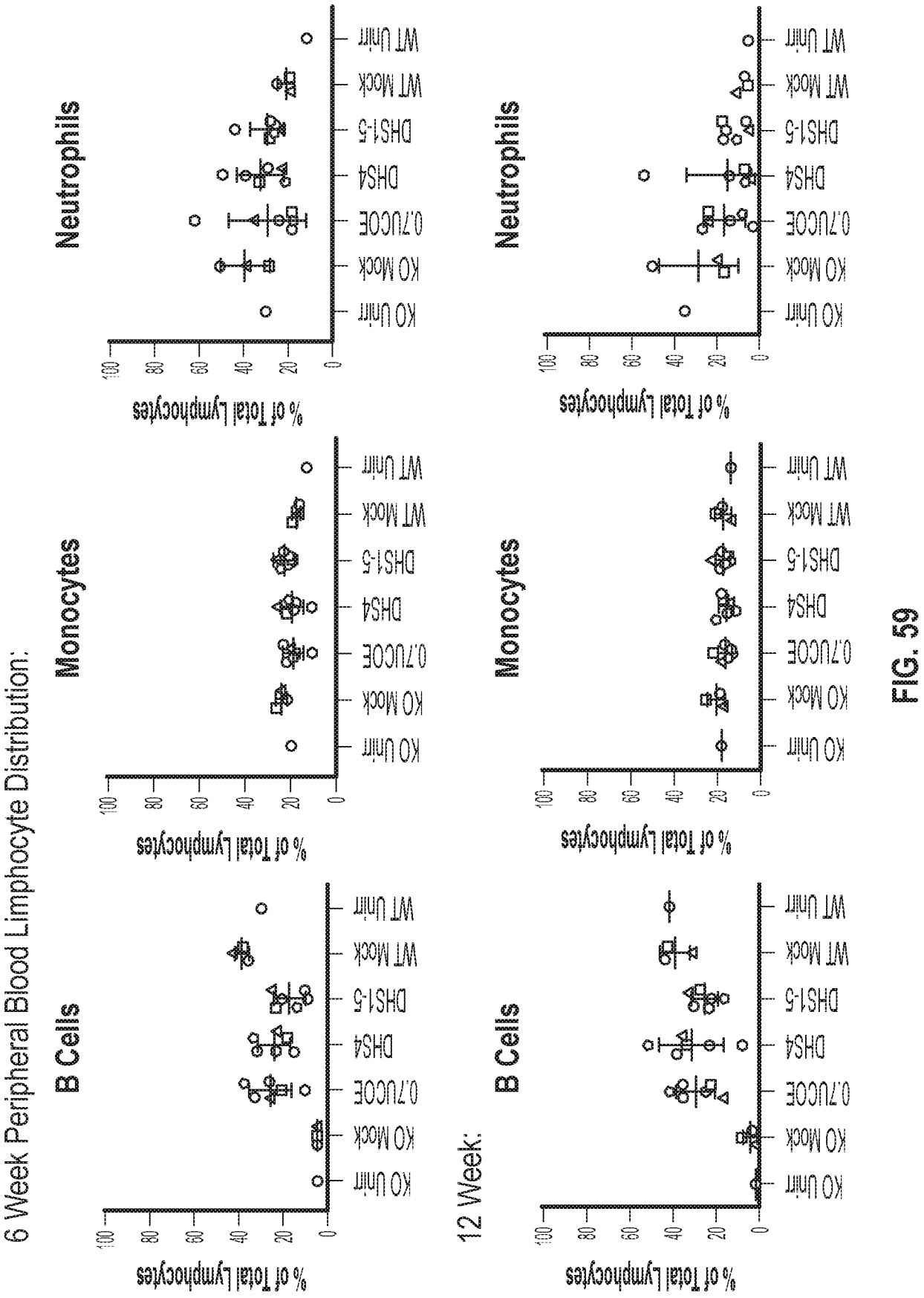

6 Week Peripheral Blood Limphocyte Distribution:
12 Week:
B Cells
Monocytes
Neutrophils
% of Total Lymphocytes
0
20
40
60
80
100
KO Unitr
KO Mock
0.7UCOE
DHS4
DHS1-5
WT Mock
WT Unitr

FIG. 59

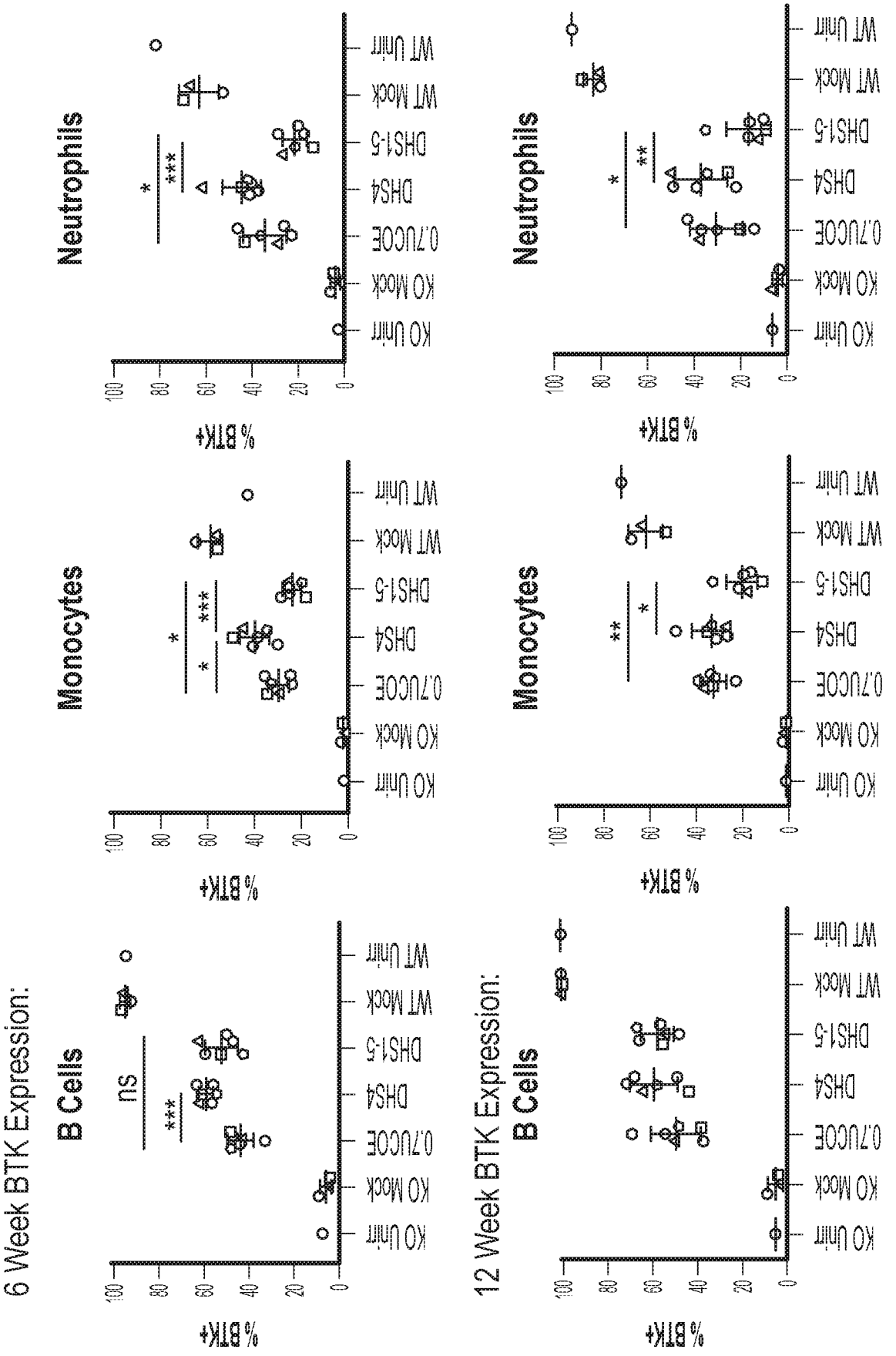

6 Week BTK Expression:
12 Week BTK Expression:
B Cells
Monocytes
Neutrophils
% BTK+
KO Unitr
KO Mock
0.7UCOE
DHS4
DHS1-5
WT Mock
WT Unitr
ns
***
**
*

FIG. 60

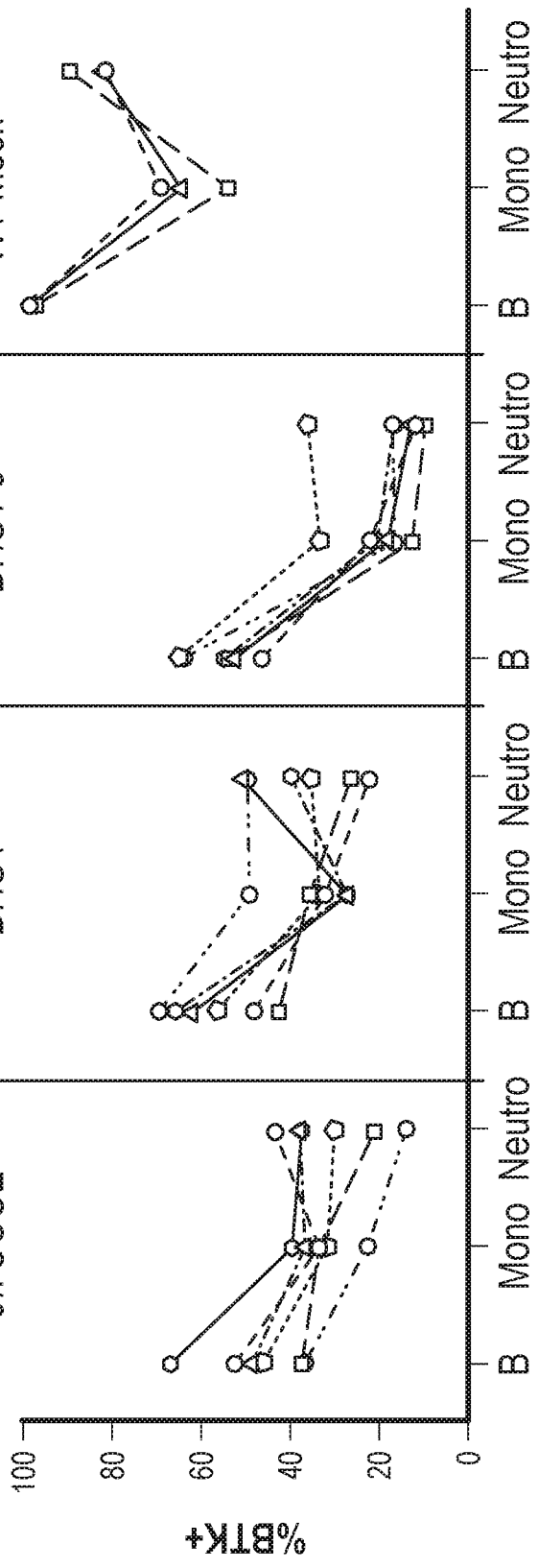

%BTK+
100
80
60
40
20
0
0.7UCOE
DHS4
DHS1-5
WT Mock
B
Mono
Neutro
12 week bleed: BTK expression across cell subsets

FIG. 61

In vitro comparison of original coBTK vs new coBTK

Objective: compare the BTK expression/staining of two different versions of codon optimized BTK

Set-up:
Isolated Lin-cells from TBK mice
Transduction media: complete SCGM + mSCF + mTPO + polybrene
Added 5, 10 or 20ul virus to 1x10e6 cells (4x10e6 cells/ml)
7-day in vitro culture, then BTK stain and VCN at Day 7

Lentiviral constructs:
0.7UCOE.BTKp.**coBTK** (Titer: 1.17E+09)
0.7UCOE.DHS4.BTKp.**coBTK** (Titer: 1.09E+09)

0.7UCOE.BTKp.**newcoBTK** (Titer: 1.81E+08)
0.7UCOE.DHS4.BTKp.**newcoBTK** (Titer: 1.13E+08)

FIG. 62

In Vitro Comparison - TKB Lineage Negative Cells,
Volume Matched Virus (Day 7 BTK Stain)

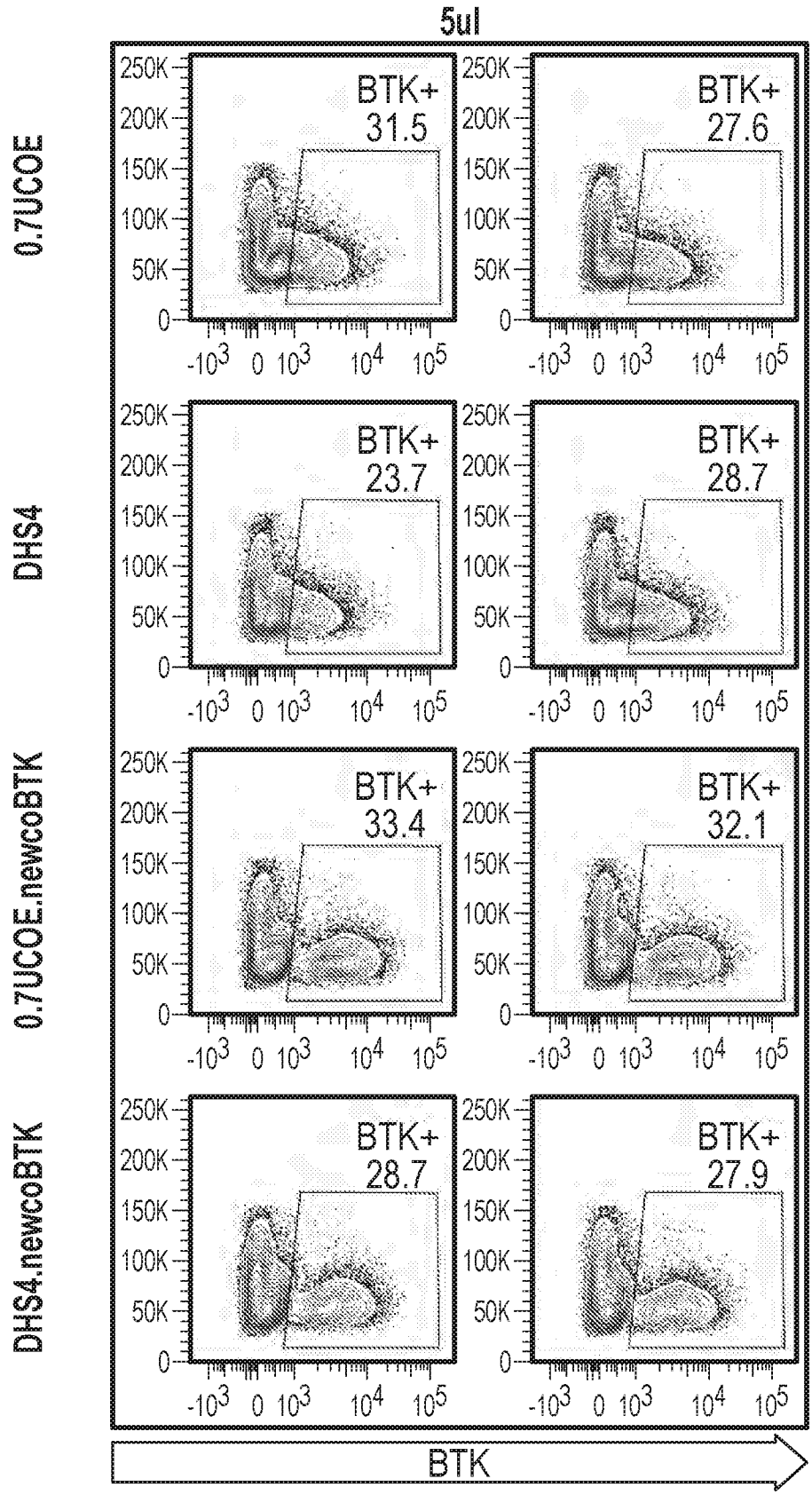


FIG. 63-1

66/131

In Vitro Comparison - TKB Lineage Negative Cells,
Volume Matched Virus (Day 7 BTK Stain)

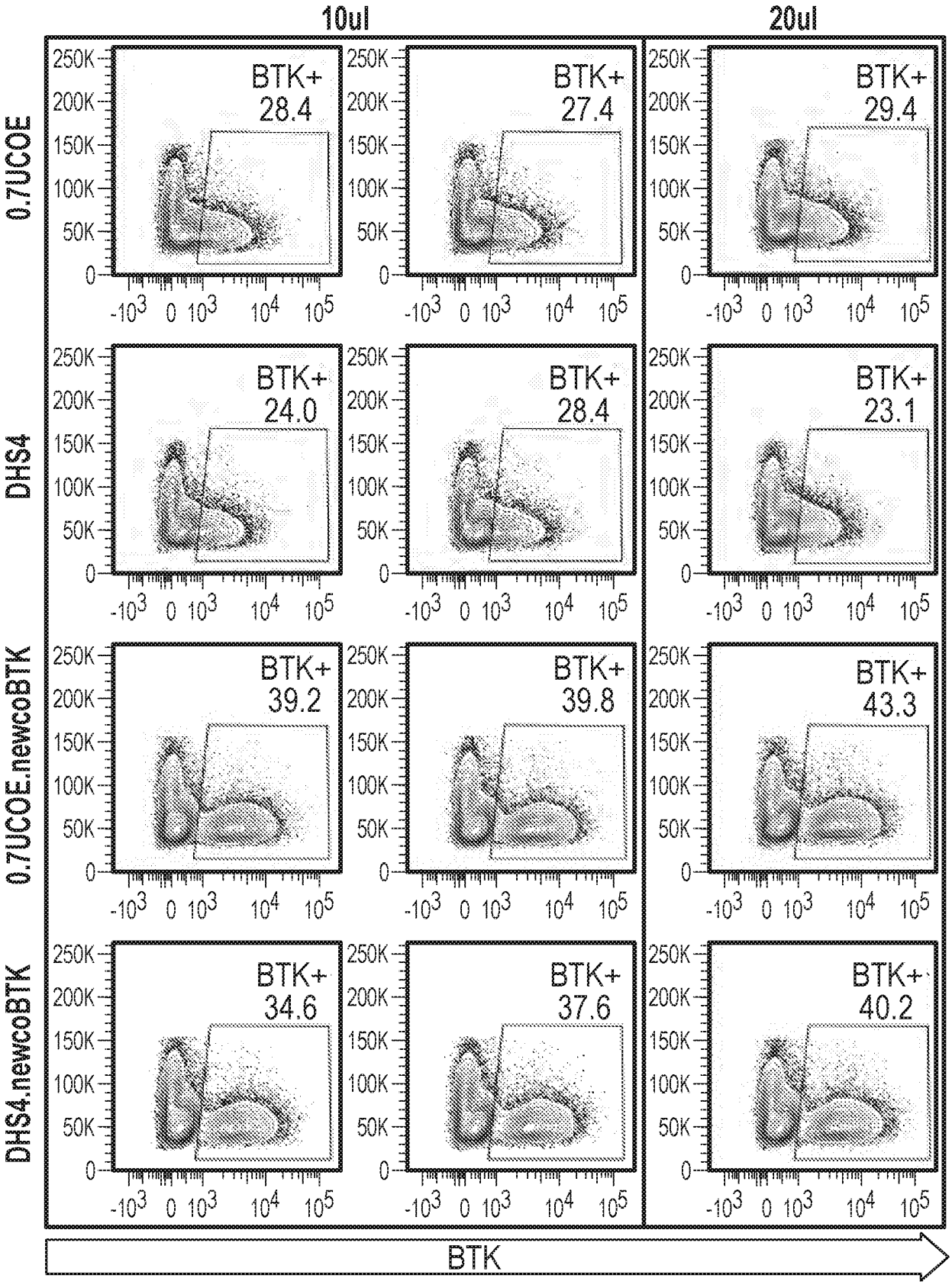


FIG. 63-2

In Vitro Comparison - TKB Lineage Negative Cells,
Volume Matched Virus (Day 7 Stain)

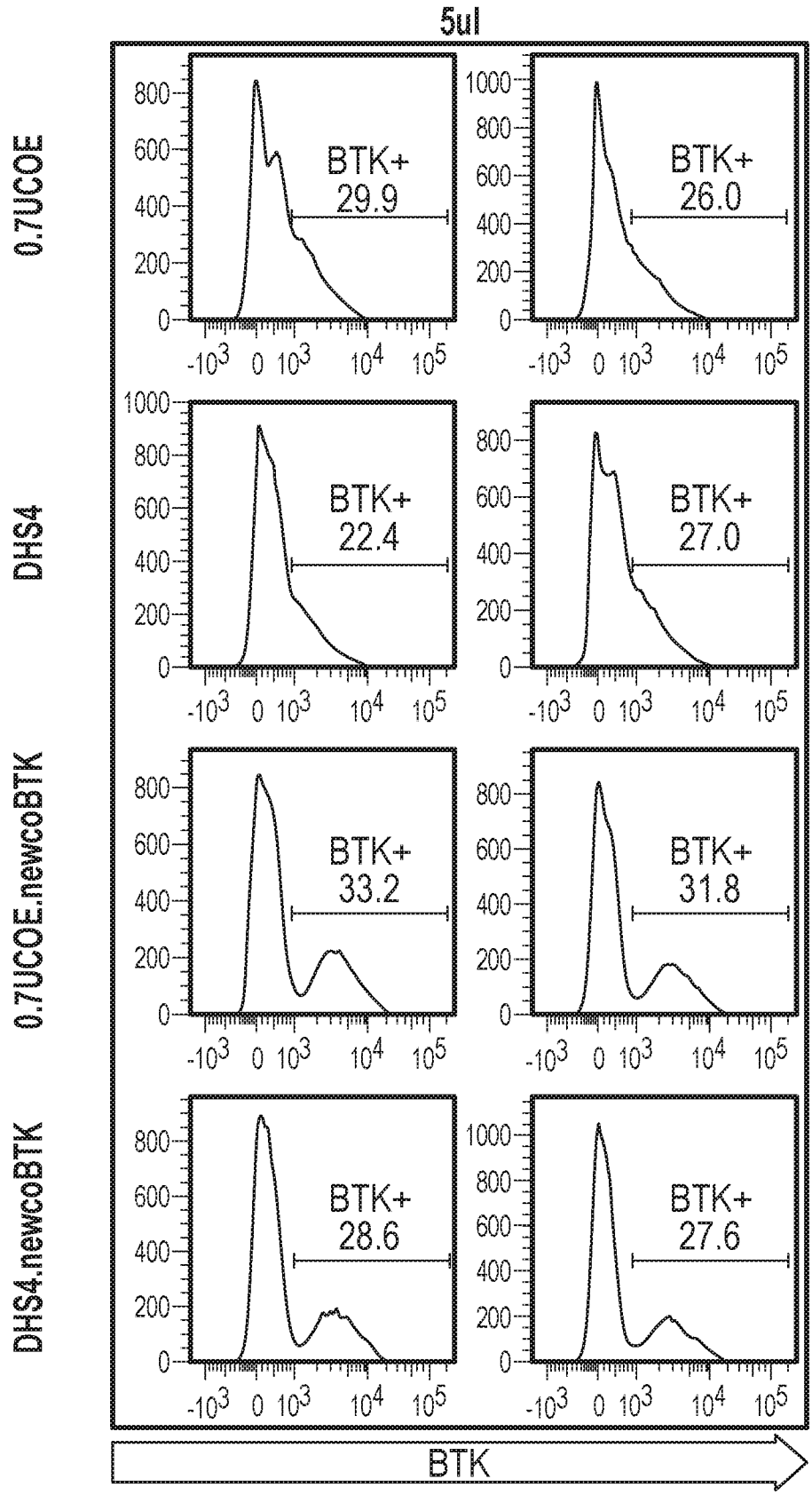


FIG. 63-3

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In Vitro Comparison - TKB Lineage Negative Cells,
Volume Matched Virus (Day 7 Stain)

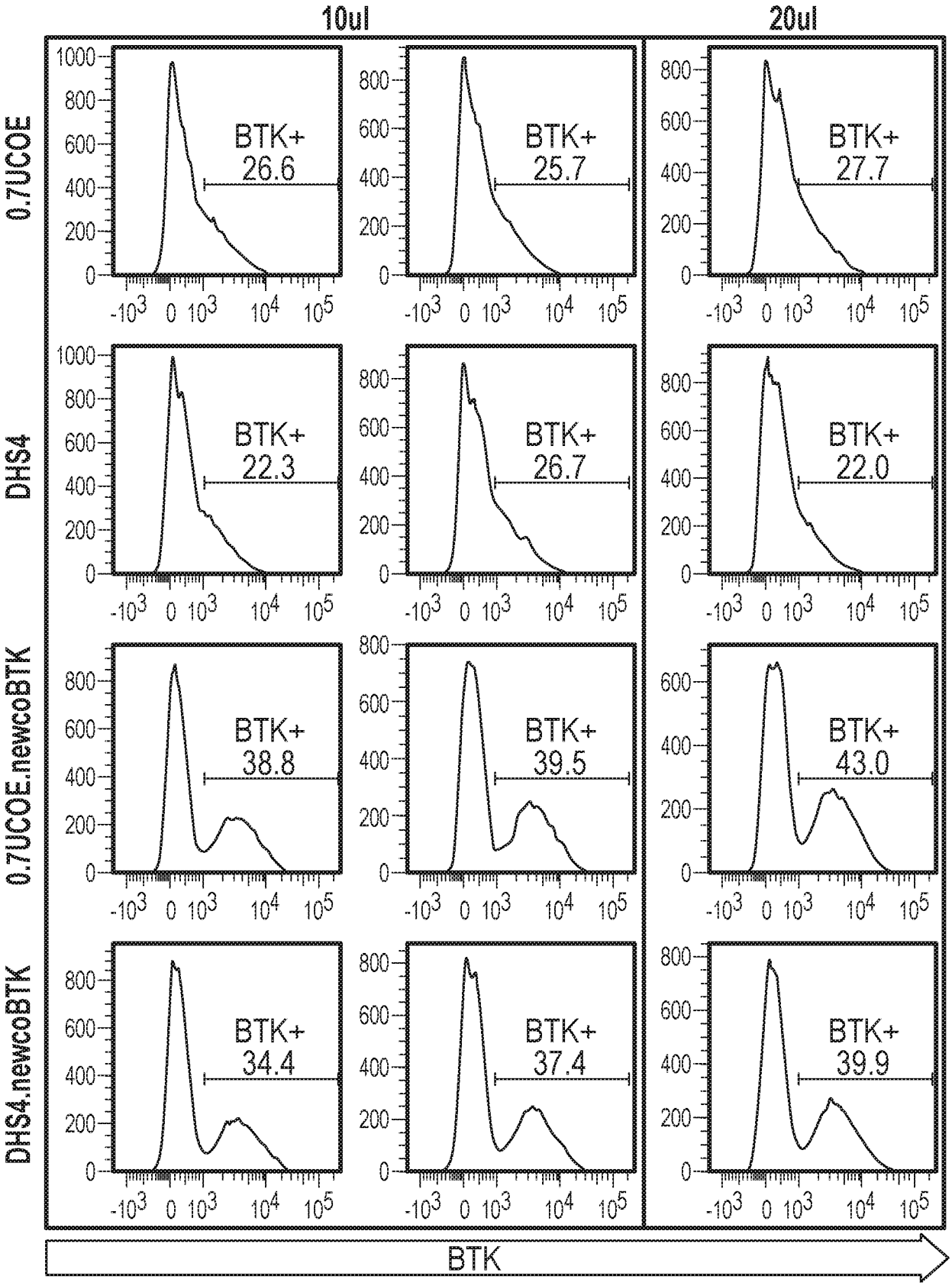


FIG. 63-4

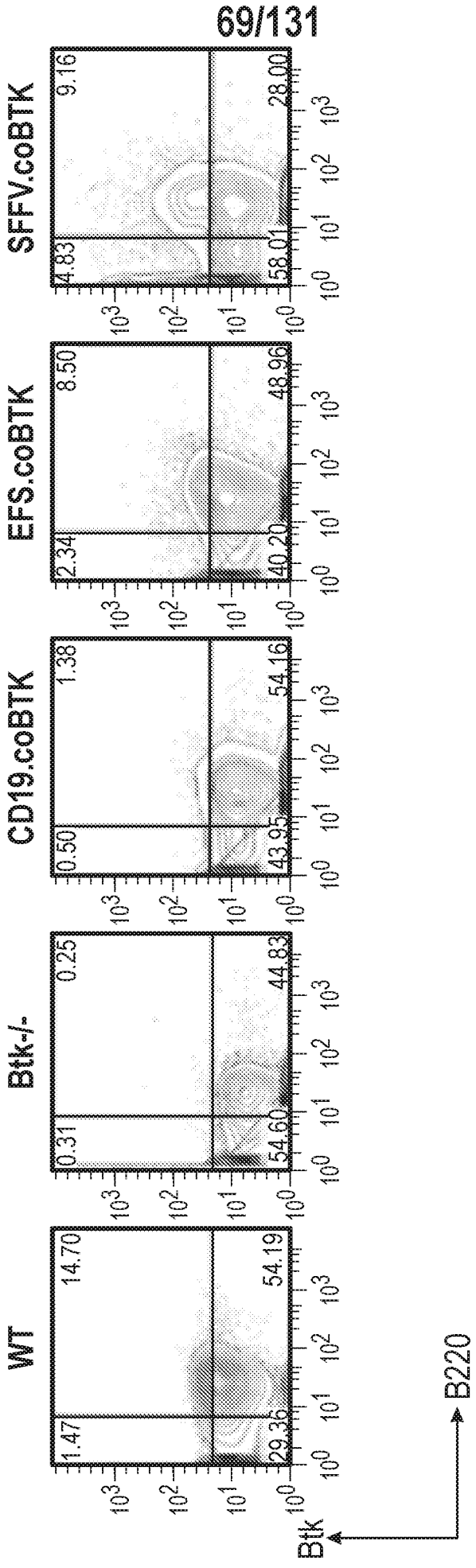

WT
Btk-/-
CD19.coBTK
EFS.coBTK
SFFV.coBTK
1.47
14.70
29.35
54.19
0.31
0.25
54.60
44.83
0.50
1.38
43.95
54.16
2.34
8.50
40.20
48.96
4.83
9.16
58.01
28.00
Btk
B220

FIG. 63-5

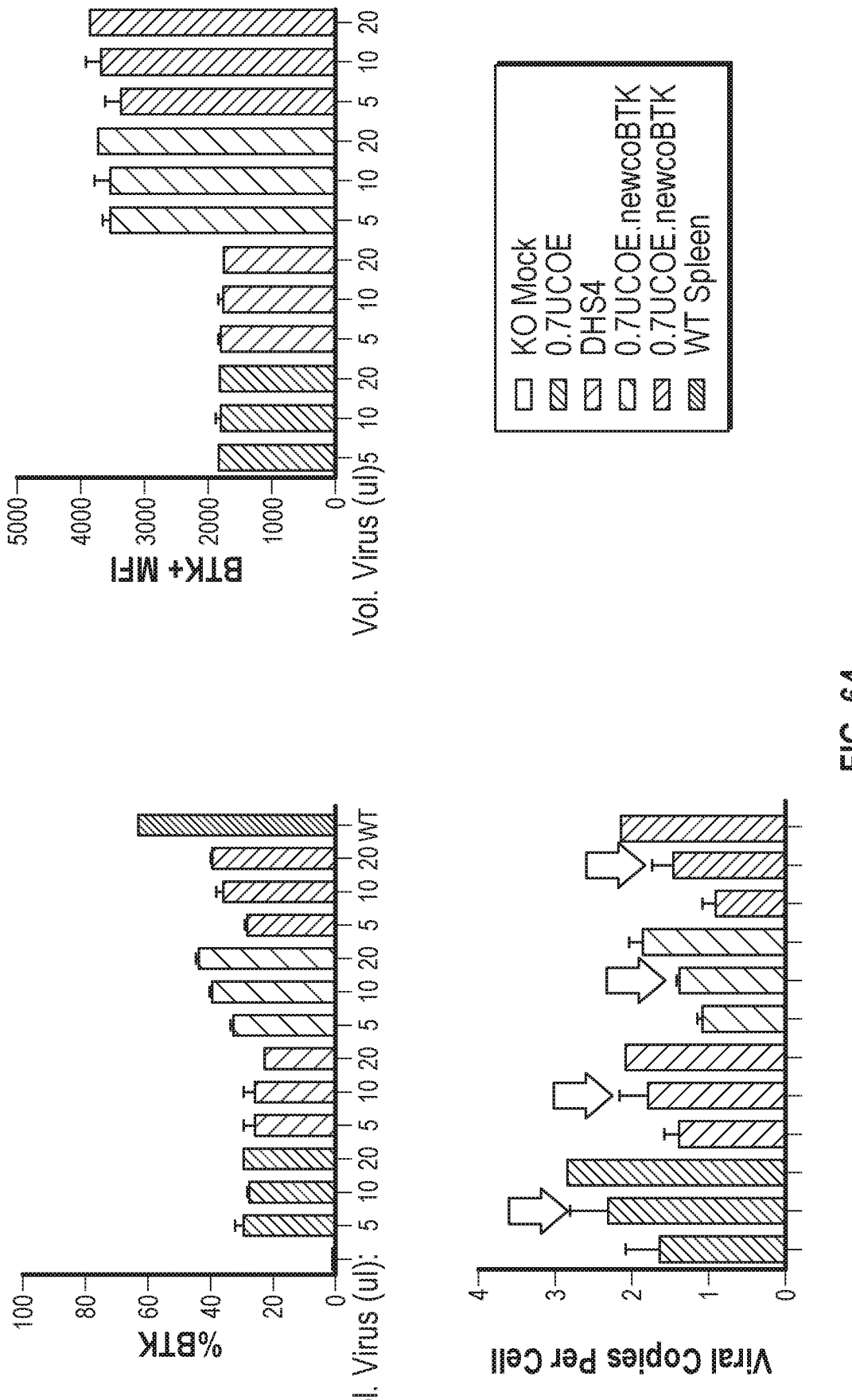

BTK+ MFI
5000
4000
3000
2000
1000
0
Vol. Virus (ul)5 10 20 5 10 20 5 10 20 5 10 20 5 10 20
KO Mock
0.7UCOE
DHS4
0.7UCOE.newcoBTK
0.7UCOE.newcoBTK
WT Spleen
%BTK
100
80
60
40
20
0
Vol. Virus (ul): 5 10 20 5 10 20 5 10 20 5 10 20 5 10 20 WT
Viral Copies Per Cell
4
3
2
1
0

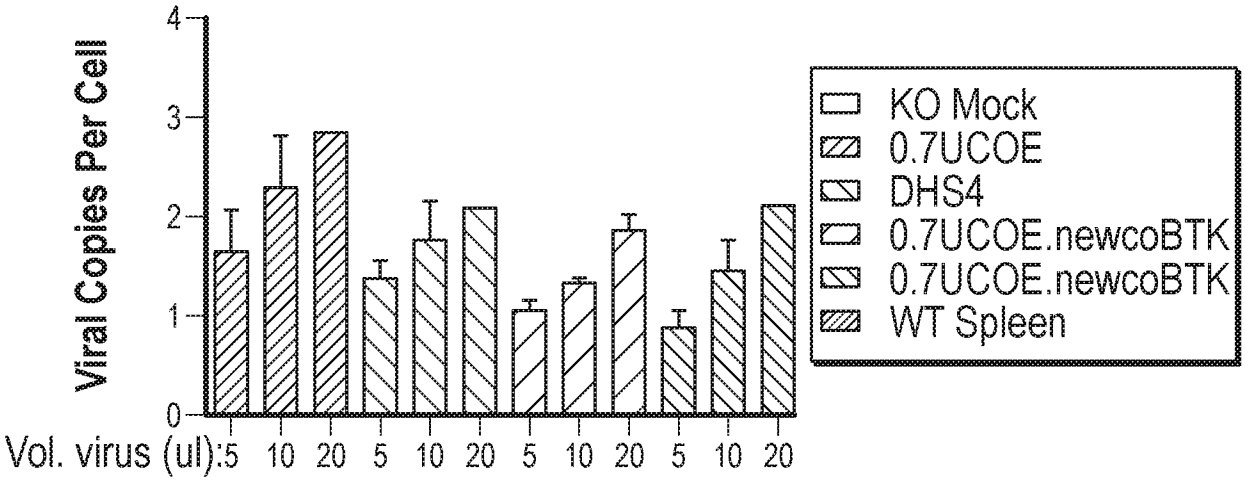
FIG. 64

Experimental Groups:

0.7UCOE.BTKp.**coBTK** (Titer: 1.17E+09) - 5 mice
0.7UCOE.DHS4.BTKp.**coBTK** (Titer: 1.09E+09) - 5 mice
0.7UCOE.BTKp.**newcoBTK** (Titer: 1.81E+08) - 5 mice
0.7UCOE.DHS4.BTKp.**newcoBTK** (Titer: 1.13E+08) - 5 mice
KO Mock - 3 mice
WT Mock - 3 mice
Unirradiated controls - 1 each
Add or subtract mice from experimental groups?

Transduction Set-Up:

Volume match - 10ul/million cells (for consistency with current in vivo experiments)



Input, BTK In Vivo #12
(Expected Matched VCN)

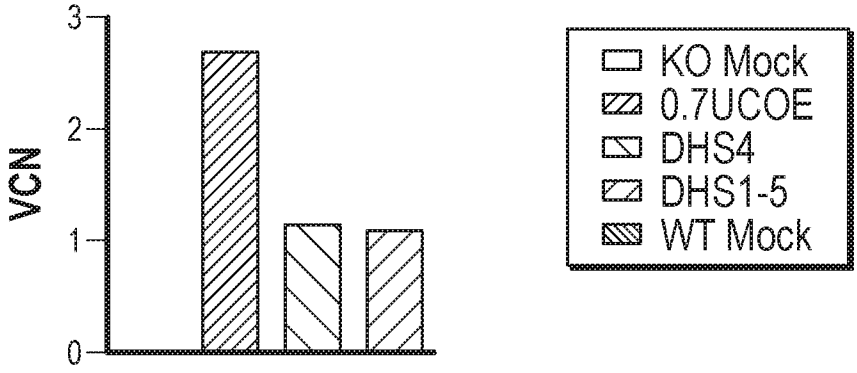
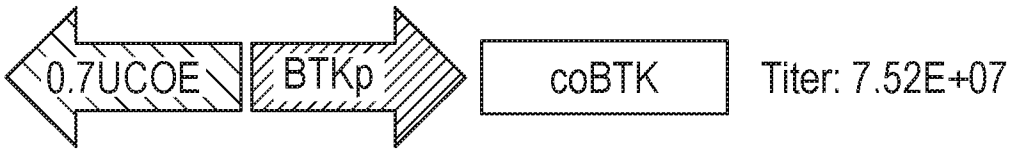


FIG. 65

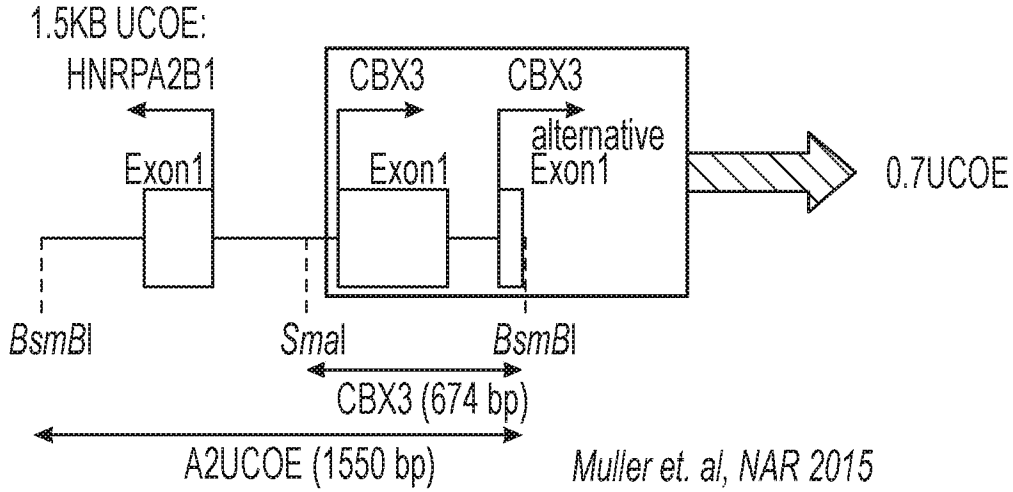
0.7UCOE.BTKp.coBTK is still a strong candidate for gene therapy, but recently titers have decreased (from 10e9 to 10e7)

Currently, our UCOE element is in the “reverse orientation”, which may be decreasing titers due to antisense transcripts:



By putting the UCOE in the forward orientation, titers have increased:

FIG. 66


1.5KB UCOE:
HNRPA2B1
CBX3
CBX3
alternative
Exon1
Exon1
Exon1
0.7UCOE
BsmBI
SmaI
BsmBI
CBX3 (674 bp)
A2UCOE (1550 bp)
Muller et. al, NAR 2015

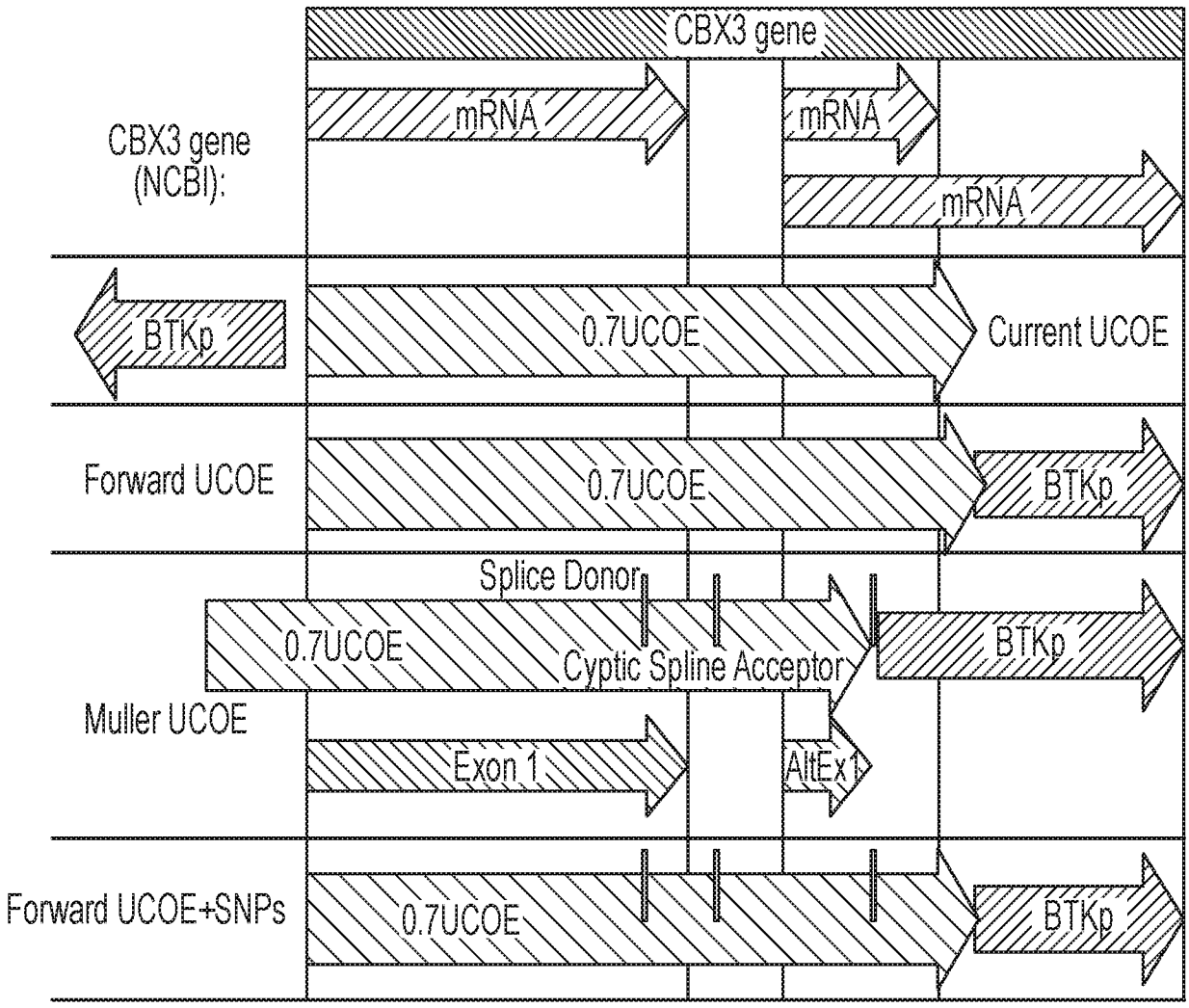

CBX3 gene
CBX3 gene (NCBI):
mRNA
mRNA
mRNA
BTKp
0.7UCOE
Current UCOE
Forward UCOE
0.7UCOE
BTKp
Splice Donor
0.7UCOE
Cyptic Spline Acceptor
BTKp
Muller UCOE
Exon 1
AltEx1
Forward UCOE+SNPs
0.7UCOE
BTKp

FIG. 67

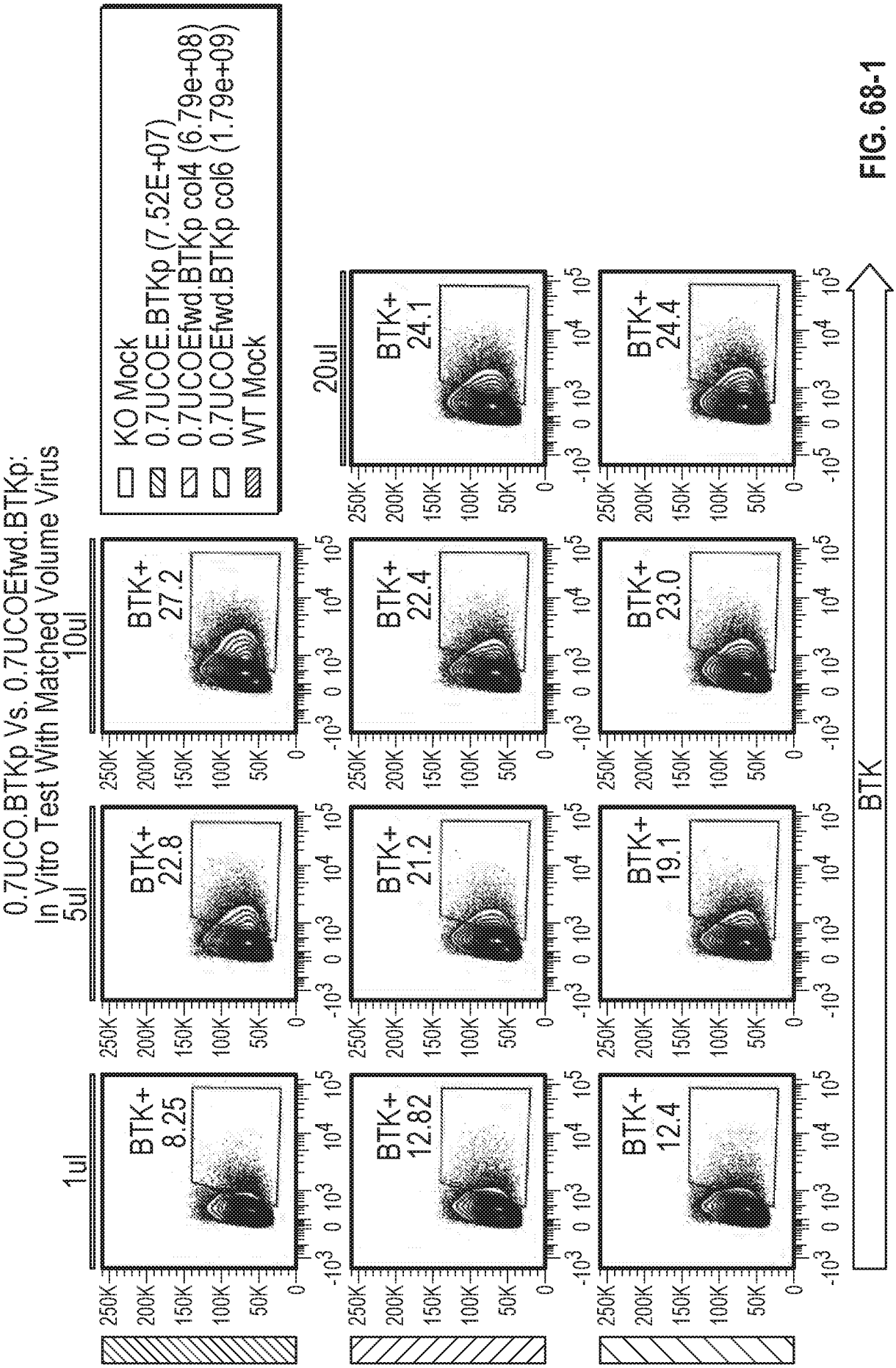

0.7UCO.BTKp Vs. 0.7UCOEfwd.BTKp:
In Vitro Test With Matched Volume Virus
1ul
5ul
10ul
20ul
KO Mock
0.7UCOE.BTKp (7.52E+07)
0.7UCOEfwd.BTKp col4 (6.79e+08)
0.7UCOEfwd.BTKp col6 (1.79e+09)
WT Mock
BTK+ 8.25
BTK+ 12.82
BTK+ 12.4
BTK+ 22.8
BTK+ 21.2
BTK+ 19.1
BTK+ 27.2
BTK+ 22.4
BTK+ 23.0
BTK+ 24.1
BTK+ 24.4
250K
200K
150K
100K
50K
0
-10^3
0
10^3
10^4
10^5
BTK

FIG. 68-1

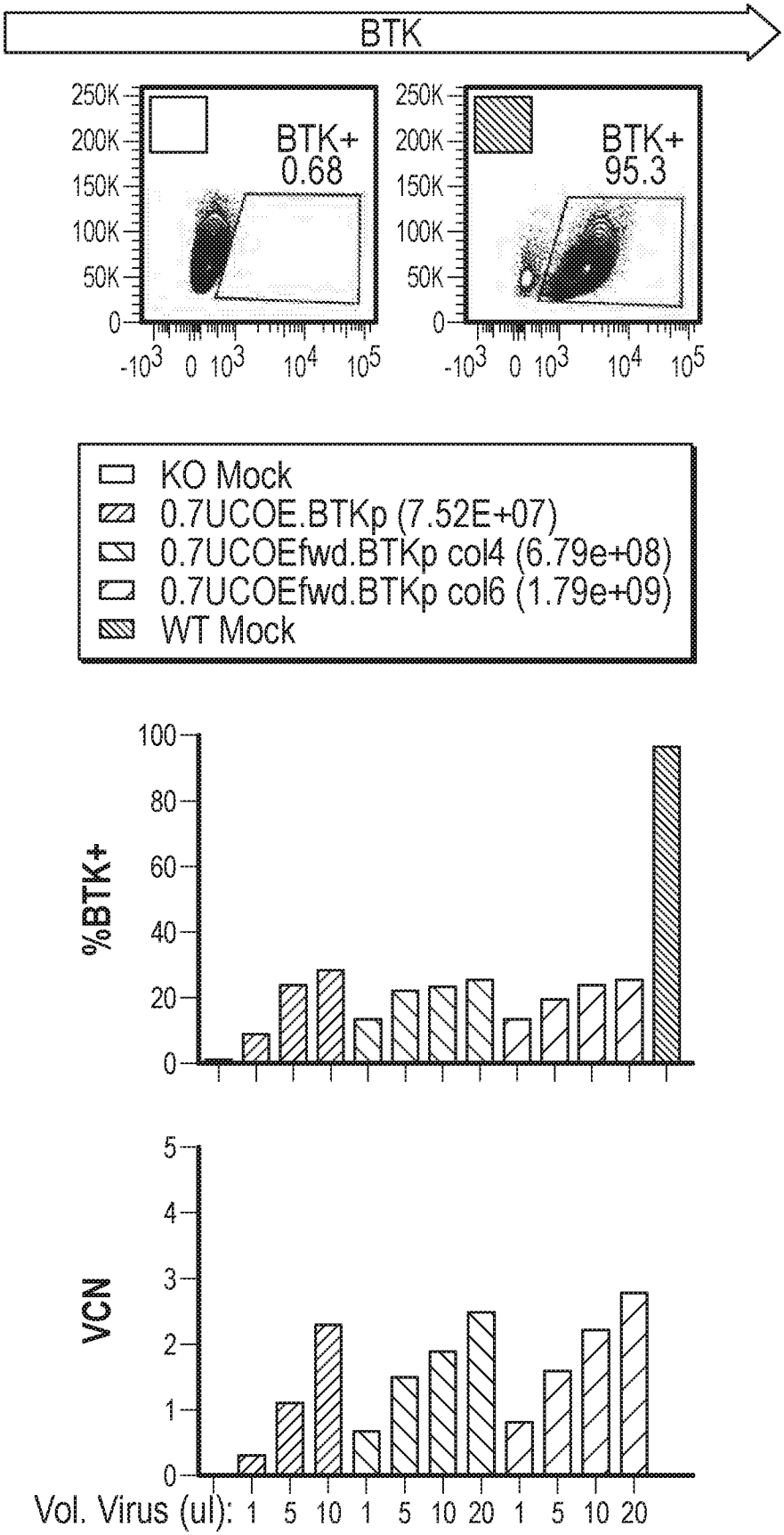

BTK
250K
200K
150K
100K
50K
0
BTK+
0.68
BTK+
95.3
-10^3 0 10^3 10^4 10^5
KO Mock
0.7UCOE.BTKp (7.52E+07)
0.7UCOEfwd.BTKp col4 (6.79e+08)
0.7UCOEfwd.BTKp col6 (1.79e+09)
WT Mock
%BTK+
100
80
60
40
20
0
VCN
5
4
3
2
1
0
Vol. Virus (ul): 1 5 10 1 5 10 20 1 5 10 20

FIG. 68-2

Plans For Finalizing Clinical BTK LV Construct

- **Promoter:**
  - **BTK promoter** is optimal promoter
- **UCOE elements:**
  - **0.7kb UCOE** effectively prevents silencing of BTK expression and leads to increased vector titer
  - Placing the UCOE to the forward orientation increases titer significantly, but does not alter BTK expression
  - This suggests that our **current (reverse) UCOE** performs equivalente to high titer constructs
  - Currently comparing both orientations in determining final vector choice
- **Enhancer Elements:**
  - 0.7UCOE.IE.Btkp exhibits rescue of Btk expression function with fewer viral integrations compared to 0.7UCOE.Btkp
  - Addition of smaller enhancer elements (DHS sites) has not increased titer compared to larger IE construct
  - However, UCOE (forward) increases IE titer by >1 log, suggesting that forward UCOE will increase titer in all constructs.
  - 0.7UCOE.**DHS4**.Btkp exhibits increased BTK expression in B and myeloid cells compared to 0.7UCOE.IE.Btkpro implying that 0.7UCOE.**DHS4**.Btkp vector is likely optimal
- **Codon Optimizer BTK:**
  - 'Dutch construct' leads to significant increase in BTK expression compared to our previous co-Btk construct- and will be used in optimal vector

FIG. 69

BTK In Vivo #12:
- Immunized with NP-CGG on 2/27, Day 7 bleed on 3/6
  - ELISA for total IgG, IgM, and NP-specific IgG/M
  - Possibly secondary immunization in March (3/27)
- Sac in early-mid April, depending on immunization

BTK In Vivo #13:
- (Comparing 0.7UCOE to 0.7UCOEfwd, 6 mice each)
- 12 week bleed and NP-CGG immunization on 3/8

New (Dutch) codon-optimized BTK:
- Cloned into 0.7UCOE, 0.7UCOEfwd, and 0.7UCOE.DHS4 constructs
- In vivo testing in progress

FIG. 70

XLA Patient CD34+ HSC Cell Bank
Institutional Review Board (IRB) Approved Apheresis Of XLA Patient's Stem Cells.

Patient ID	Gender	Location	Type	cDNA	Protein	Sample	BTK EXPRESSION	Apheresed	Comments
XLA P1	M	-	-	-	-	CD34	+	NIH	
XLA P2	M	Intron 12	Presumed Splice Varient	Del Exon 13	Presumed None, Due To Non Sense Mediated mRNA Decay	CD34, PBMC	-	Seattle Children's	
XLA P3	M	Coding	Missence	C.1766A >G	p>E589G	CD34, PBMC	+	Seattle Children's	XLA P3 And XLA P4 Are Relatives
XLA P4	M	Coding	Missence	C.1766A >G	p>E589G	CD34, PBMC	+		

FIG. 71

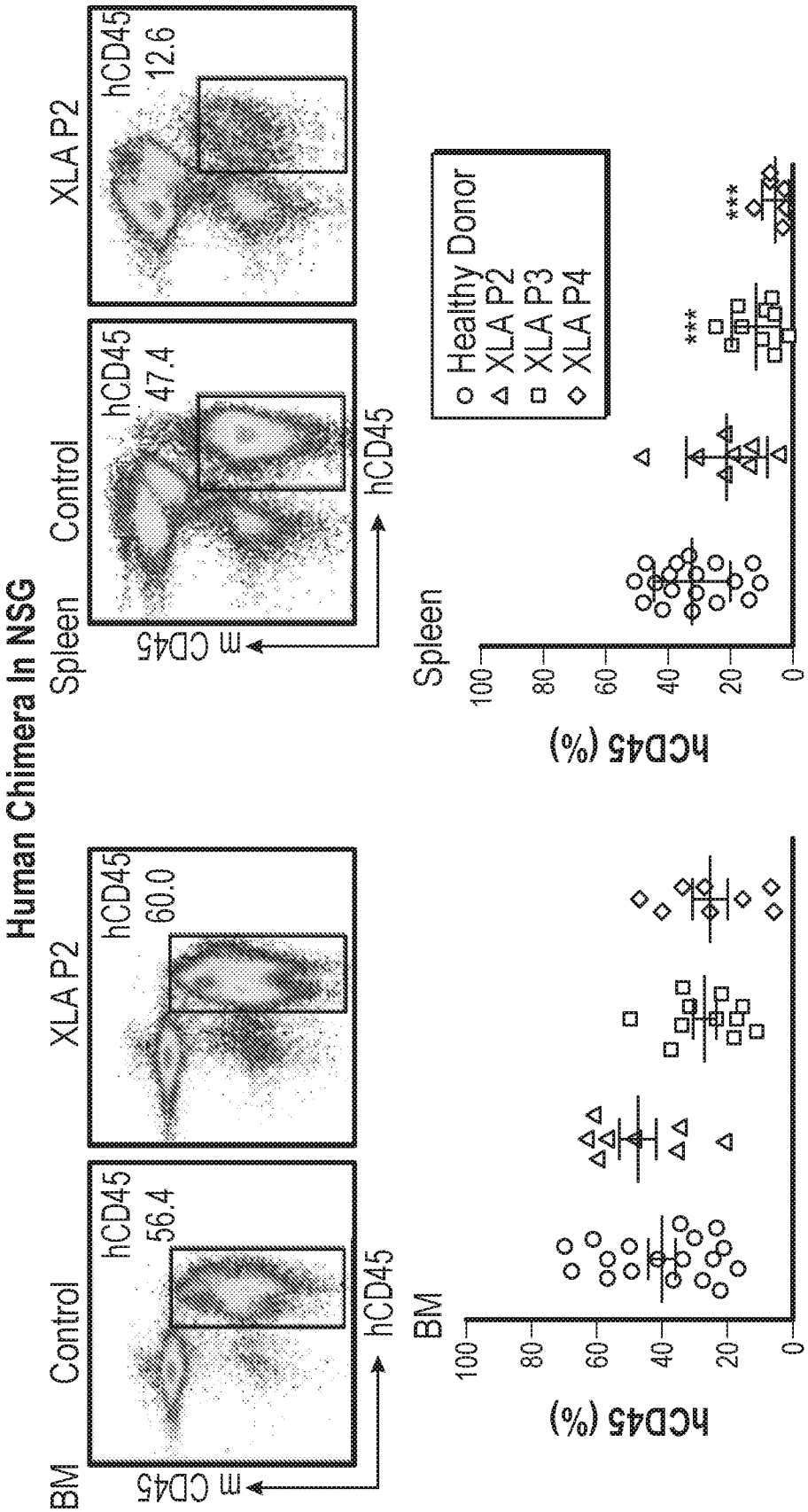
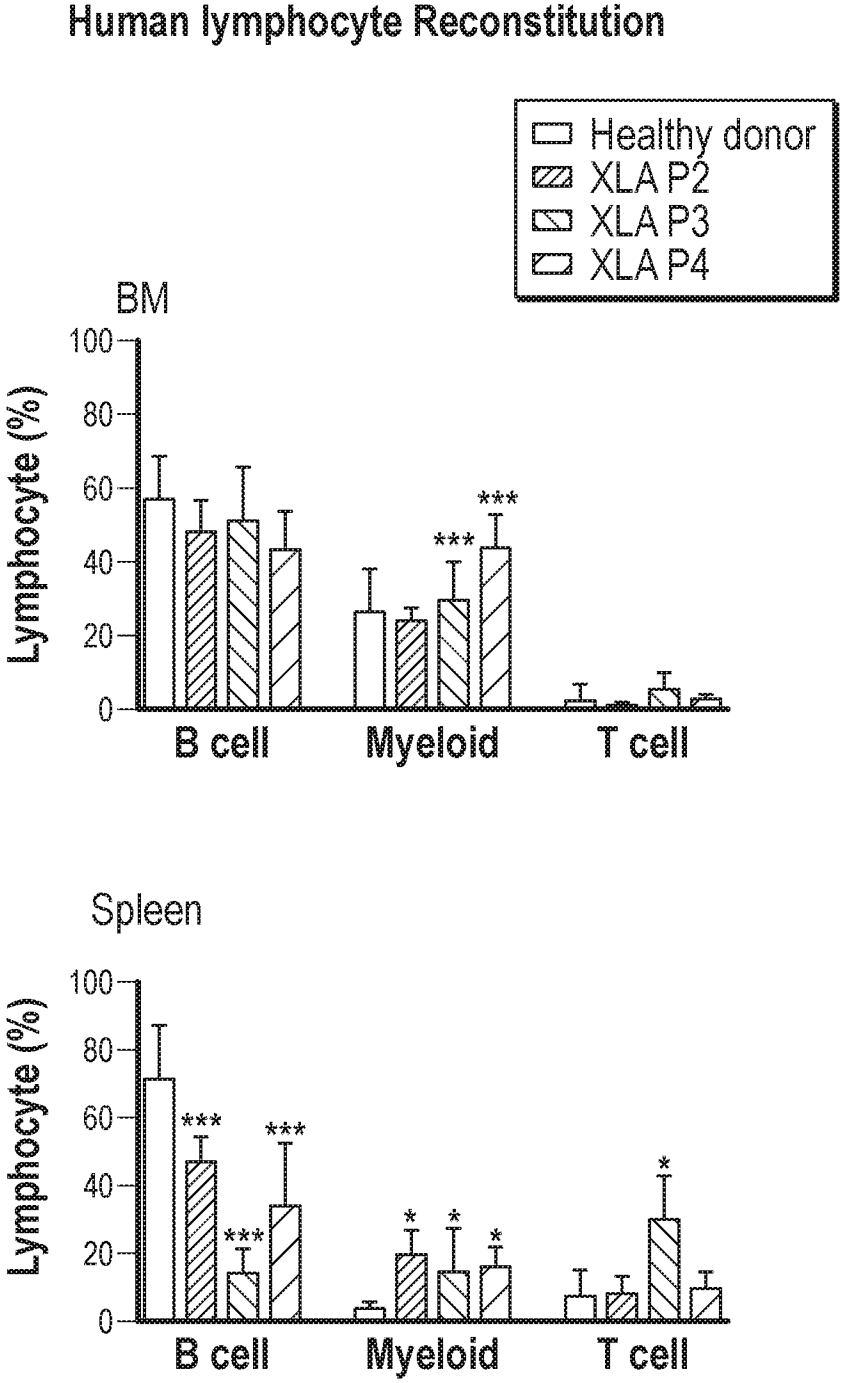

Human Chimera In NSG
BM
Control
XLA P2
hCD45
56.4
60.0
m CD45
hCD45
Spleen
Control
XLA P2
hCD45
47.4
12.6
m CD45
hCD45
BM
hCD45 (%)
100
80
60
40
20
0
Spleen
hCD45 (%)
Healthy Donor
XLA P2
XLA P3
XLA P4
***
***
Equivalent engraftment of hCD45 cells in BM, however significantly lower percentage of differentiated hCD45 cells in the periphery.
n (HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

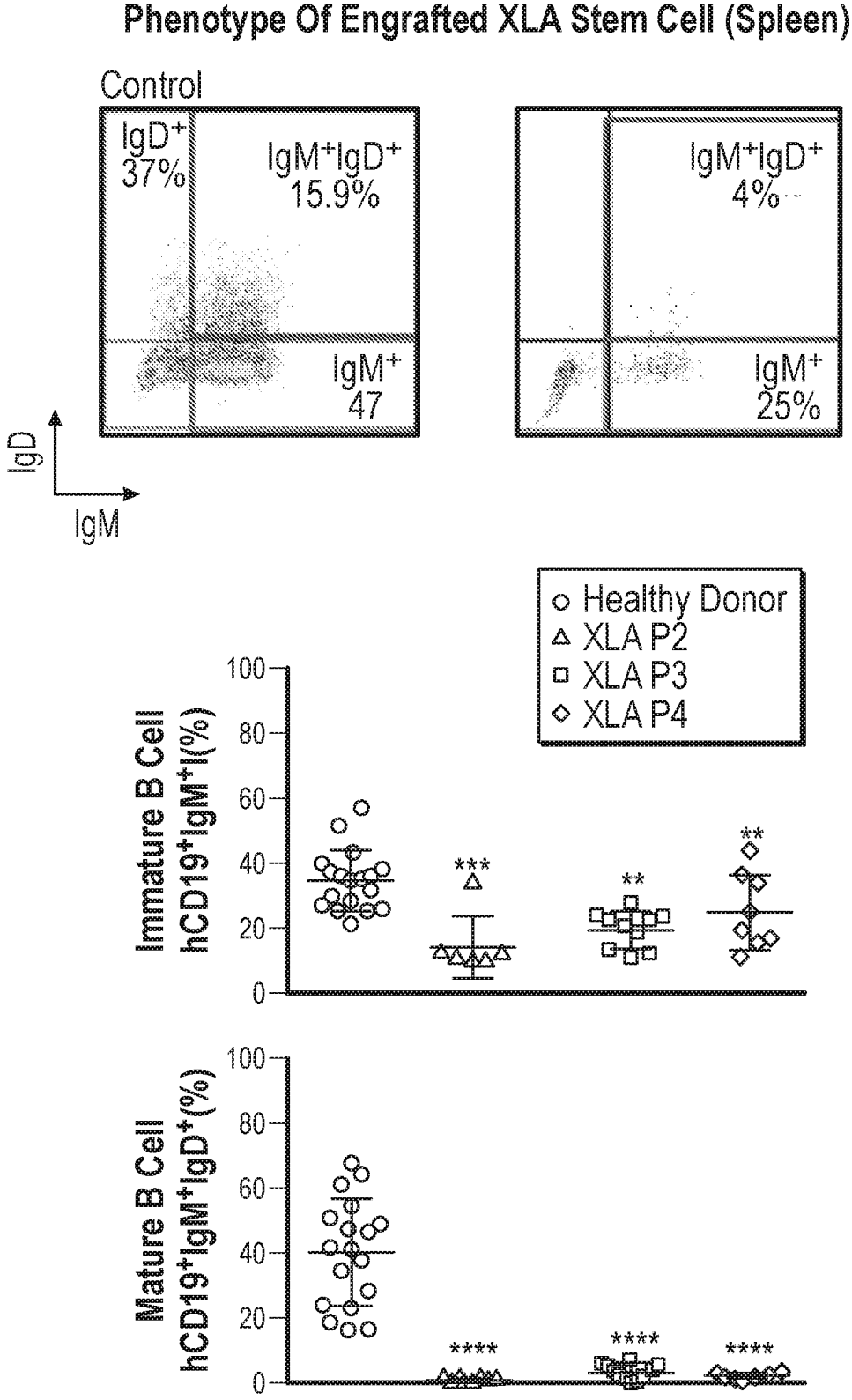
FIG. 72



% B cells is equivalent in BM however significantly lower in spleen with relative increase in myeloid and T cells

n (HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

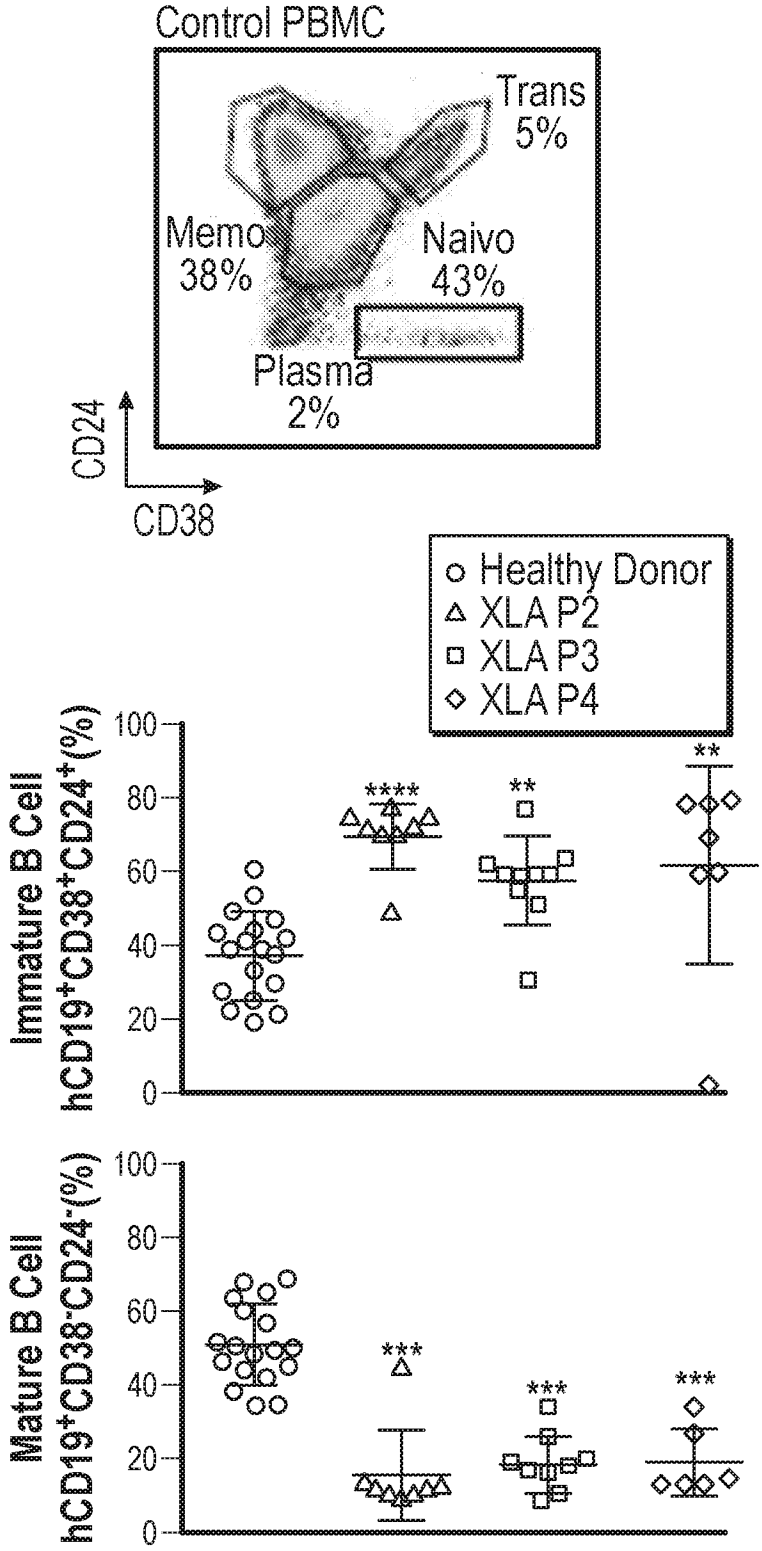
FIG. 73



n (HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

FIG. 74

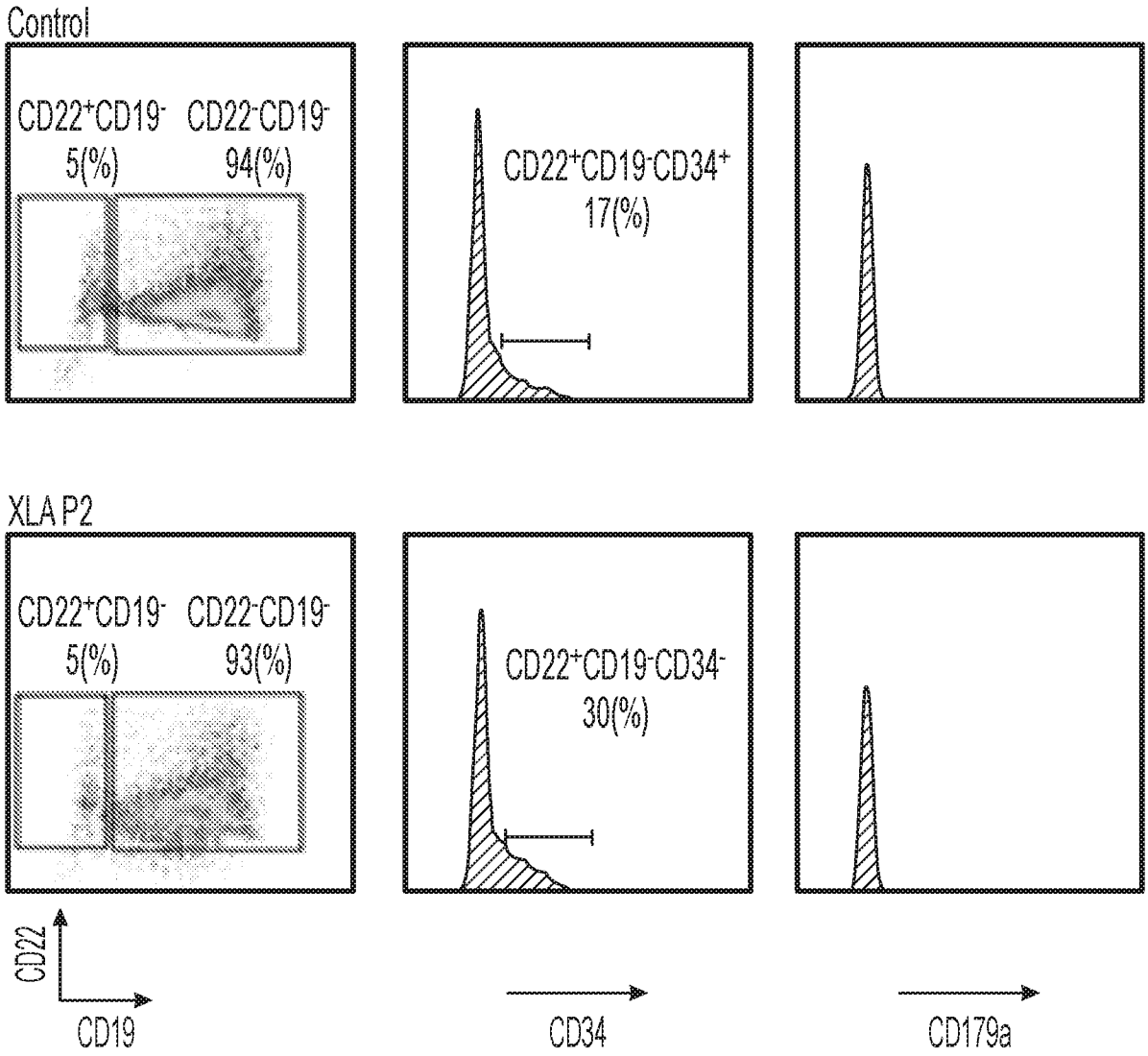
Phenotype Of Engrafted XLA Stem Cell (Spleen)

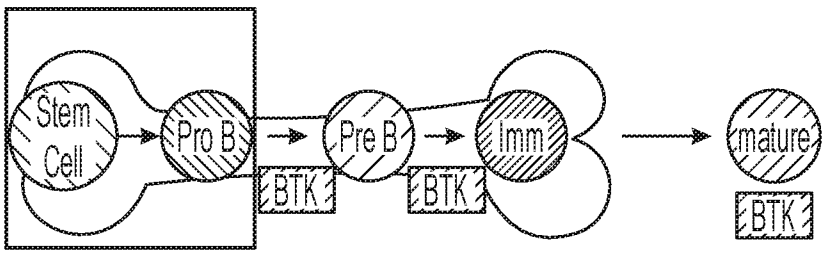


XLA experimental group has significantly higher percent of immature B cell and lack mature B cell.

n (HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

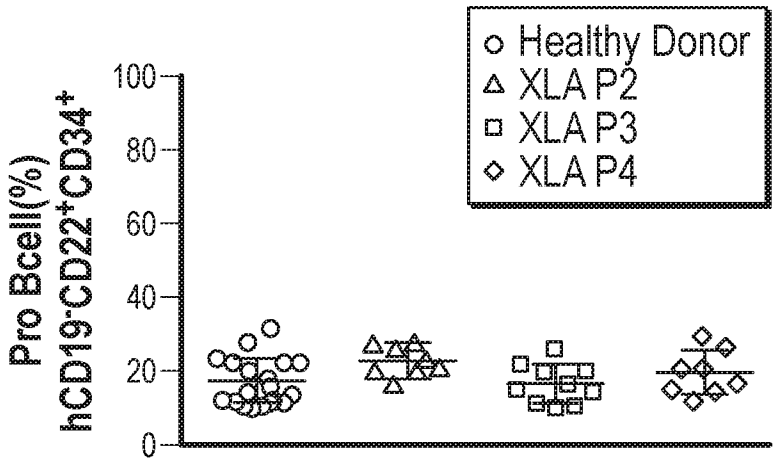
FIG. 75





Pro B cell	CD22+	CD19-	CD34+	CD179a-	IgM-	CD10-

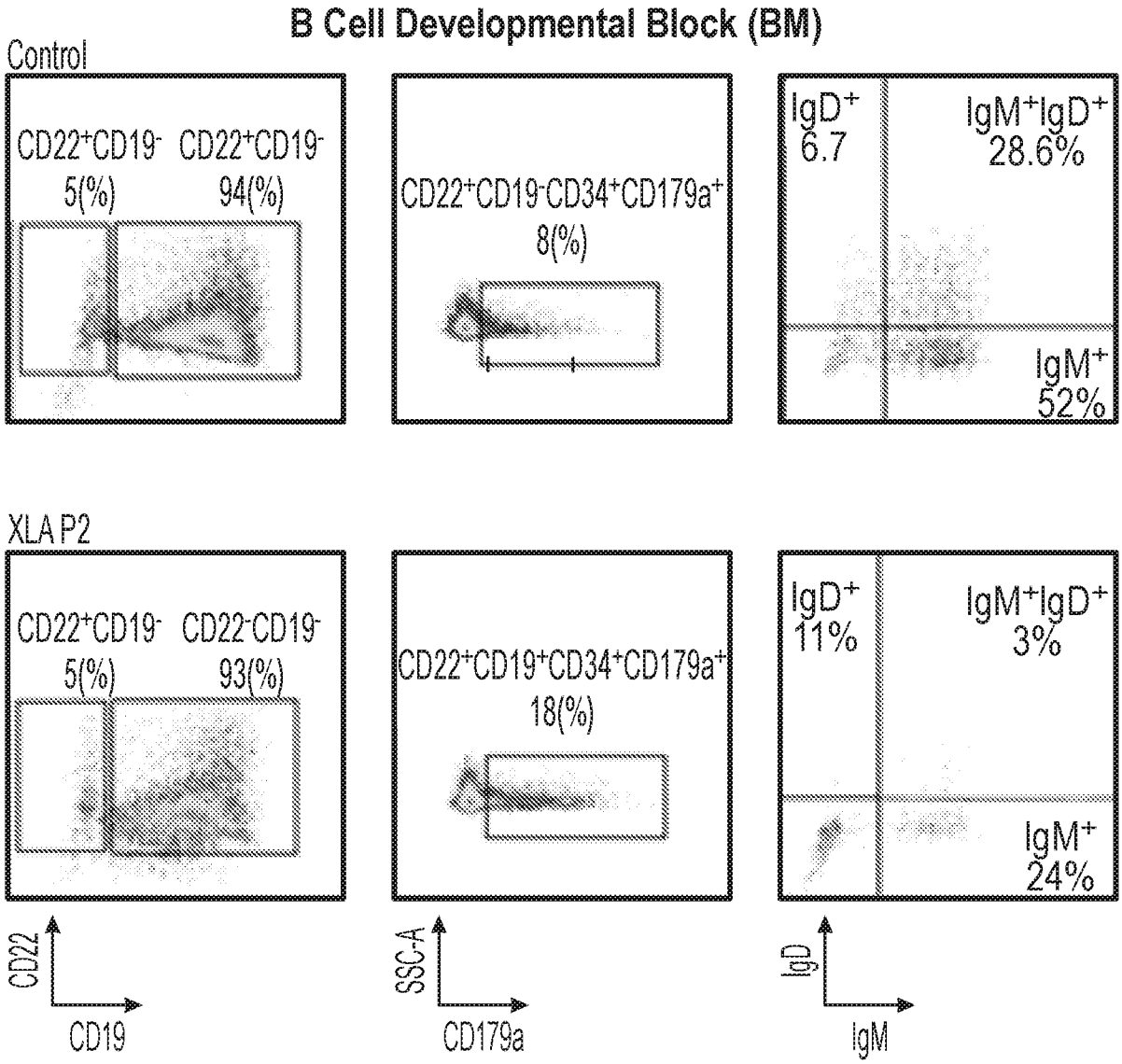
FIG. 76-1

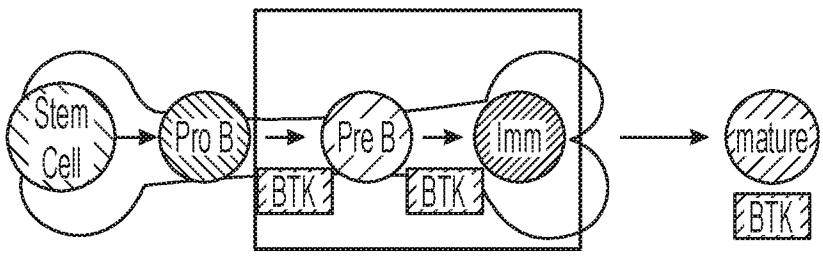


Equivalent %Pro B cell between the XLA and healthy group.

n (HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

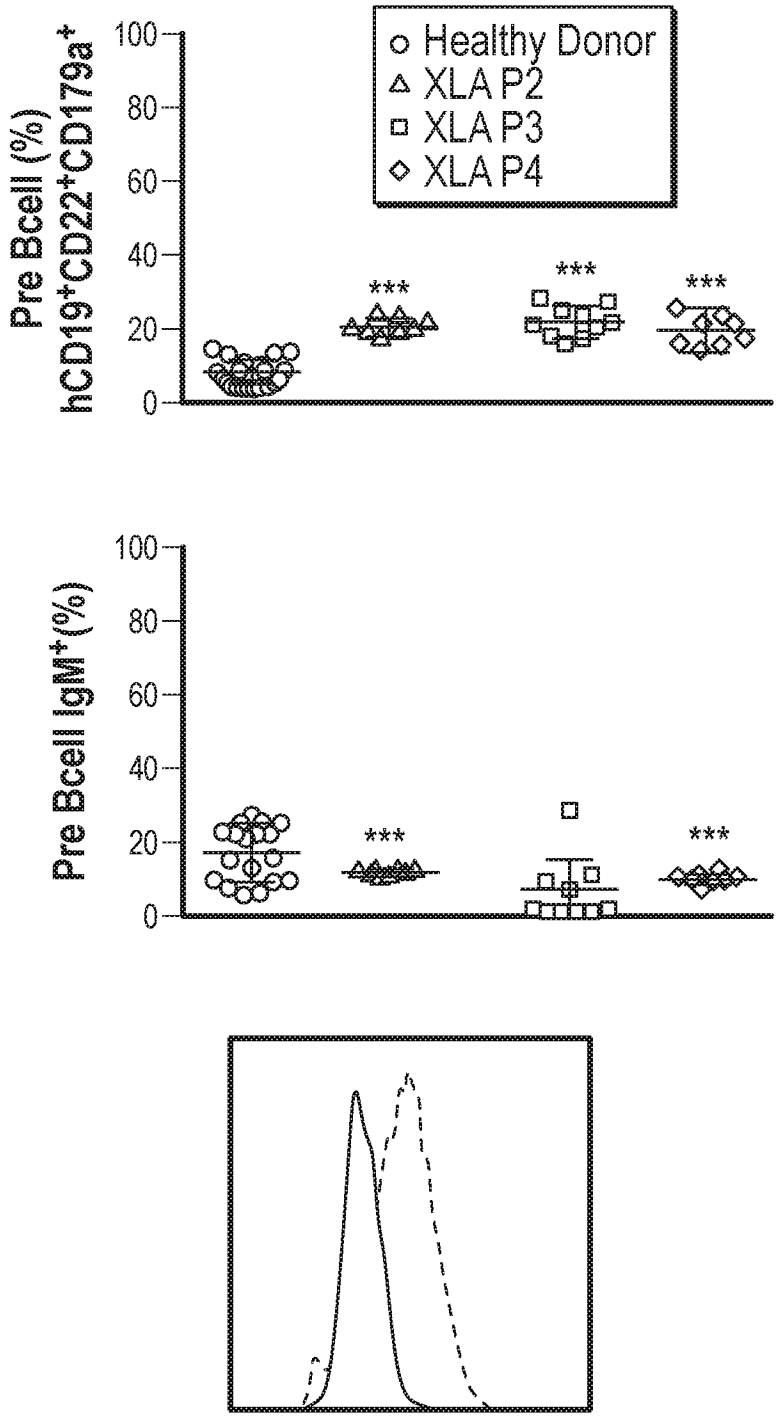
FIG. 76-2





Pro B cell	CD22+	CD19+	CD34+/-	CD179a+	IgM+	CD10 high

FIG. 77-1



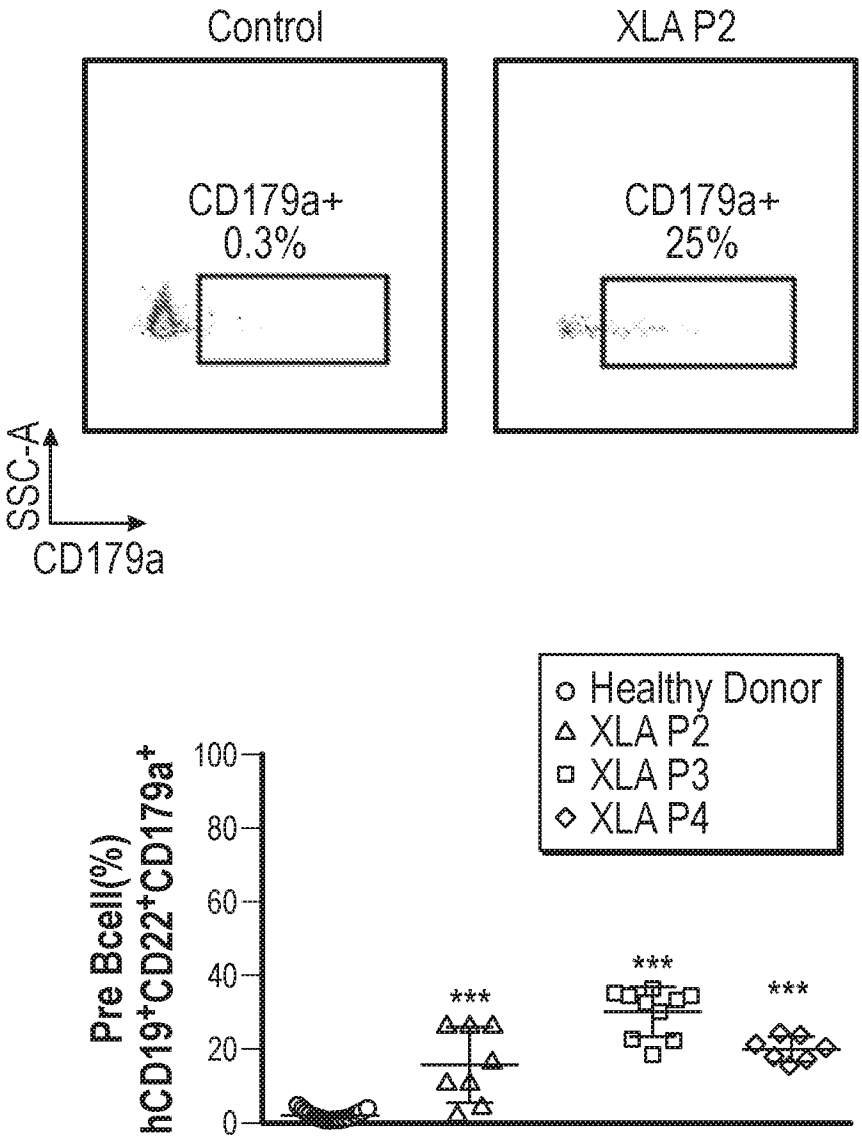
XLA has significantly higher % pre-B cells compared to healthy control.

n(HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

FIG. 77-2

B Cell Developmental Block (Spleen)

Pro B cell	CD22+	CD19+	CD34+/-	CD179a+	IgM+	CD10 high+



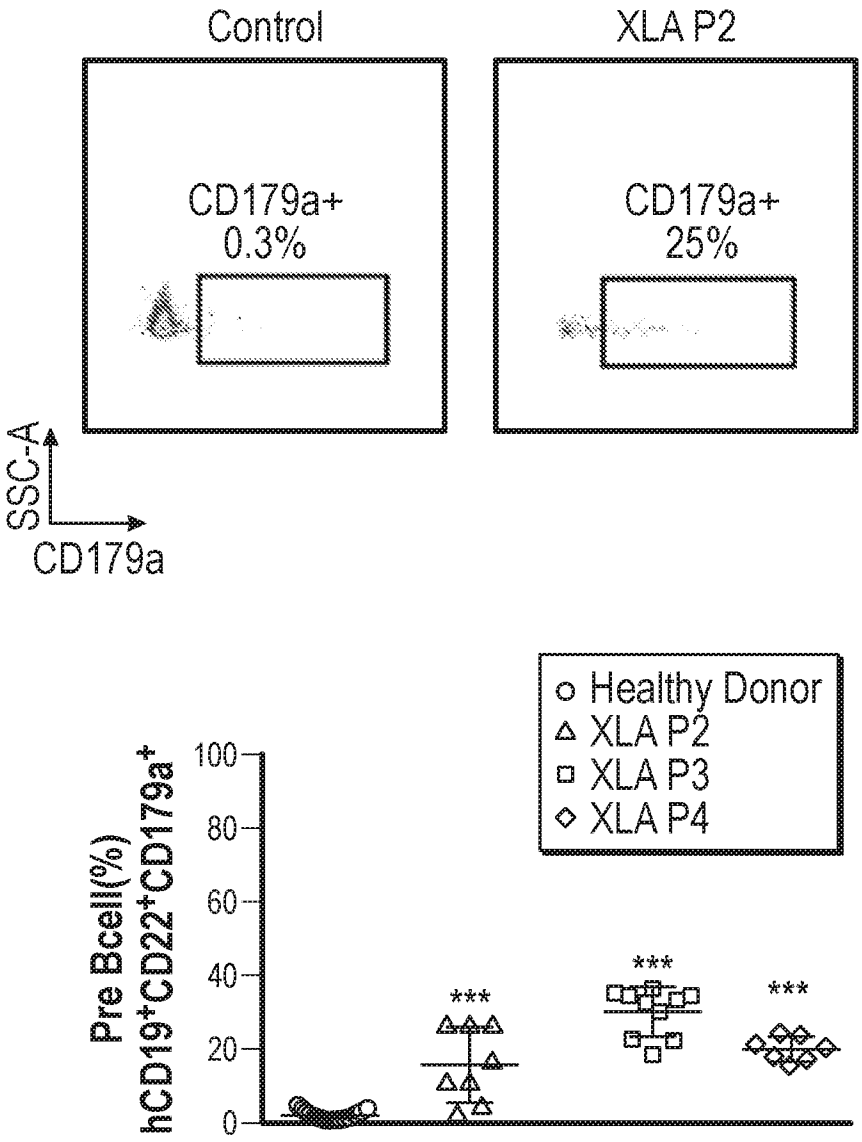
Development of XLA B cells blocked at Pre B cell stage. Pre B cells are able to migrate to spleen.

n (HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

FIG. 78

B Cell Developmental Block (Spleen)

Pro B cell	CD22+	CD19+	CD34+/-	CD179a+	IgM+	CD10 high+



Development of XLA B cells blocked at Pre B cell stage. Pre B cells are able to migrate to spleen.

n (HD=18, XLA P2=8, XLA P3=11, XLA P4=8)
Stat: one way ANOVA compare to HD

FIG. 79

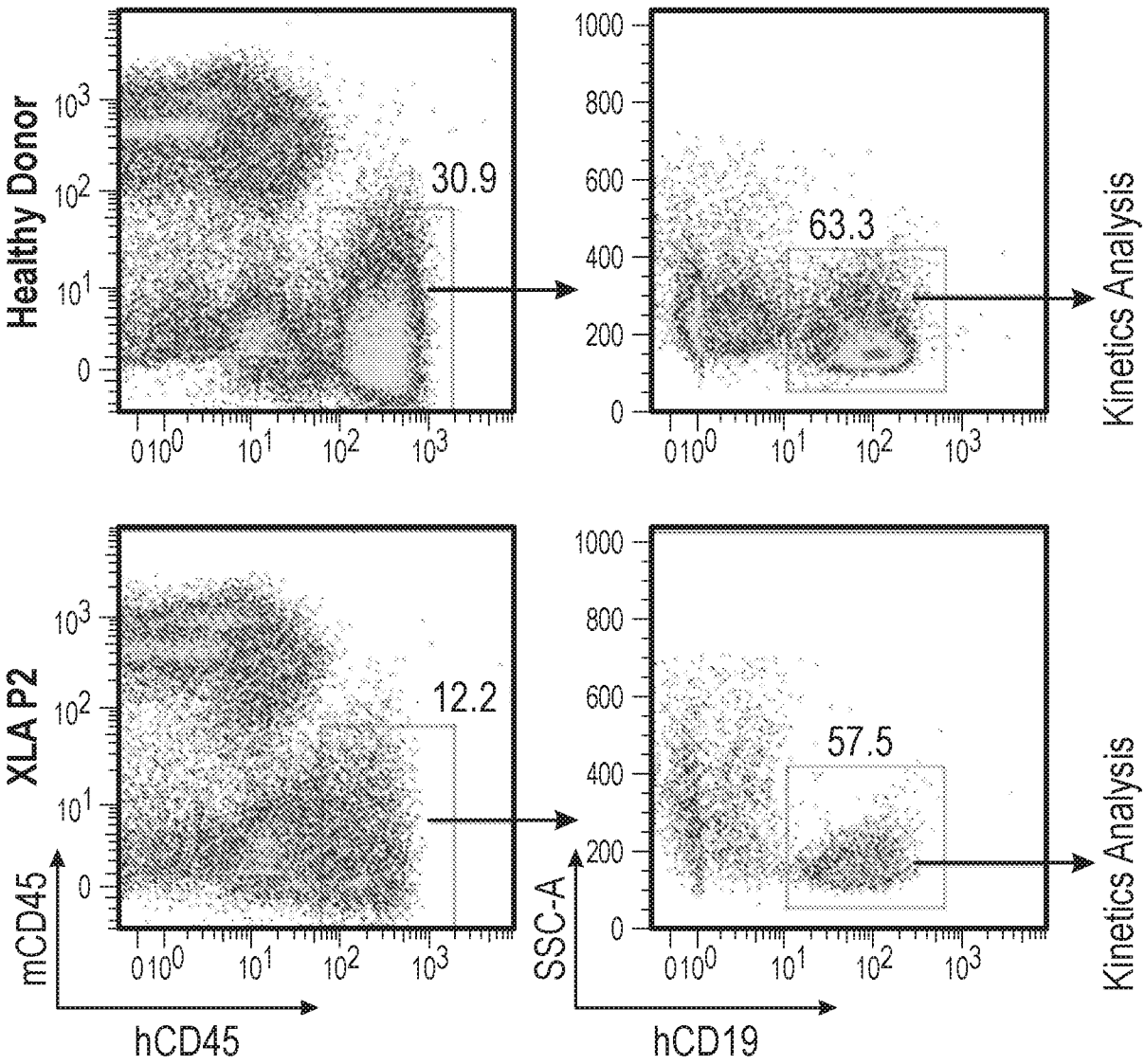

Healthy Donor
30.9
63.3
Kinetics Analysis
XLA P2
12.2
57.5
Kinetics Analysis
mCD45
hCD45
SSC-A
hCD19

FIG. 80-1

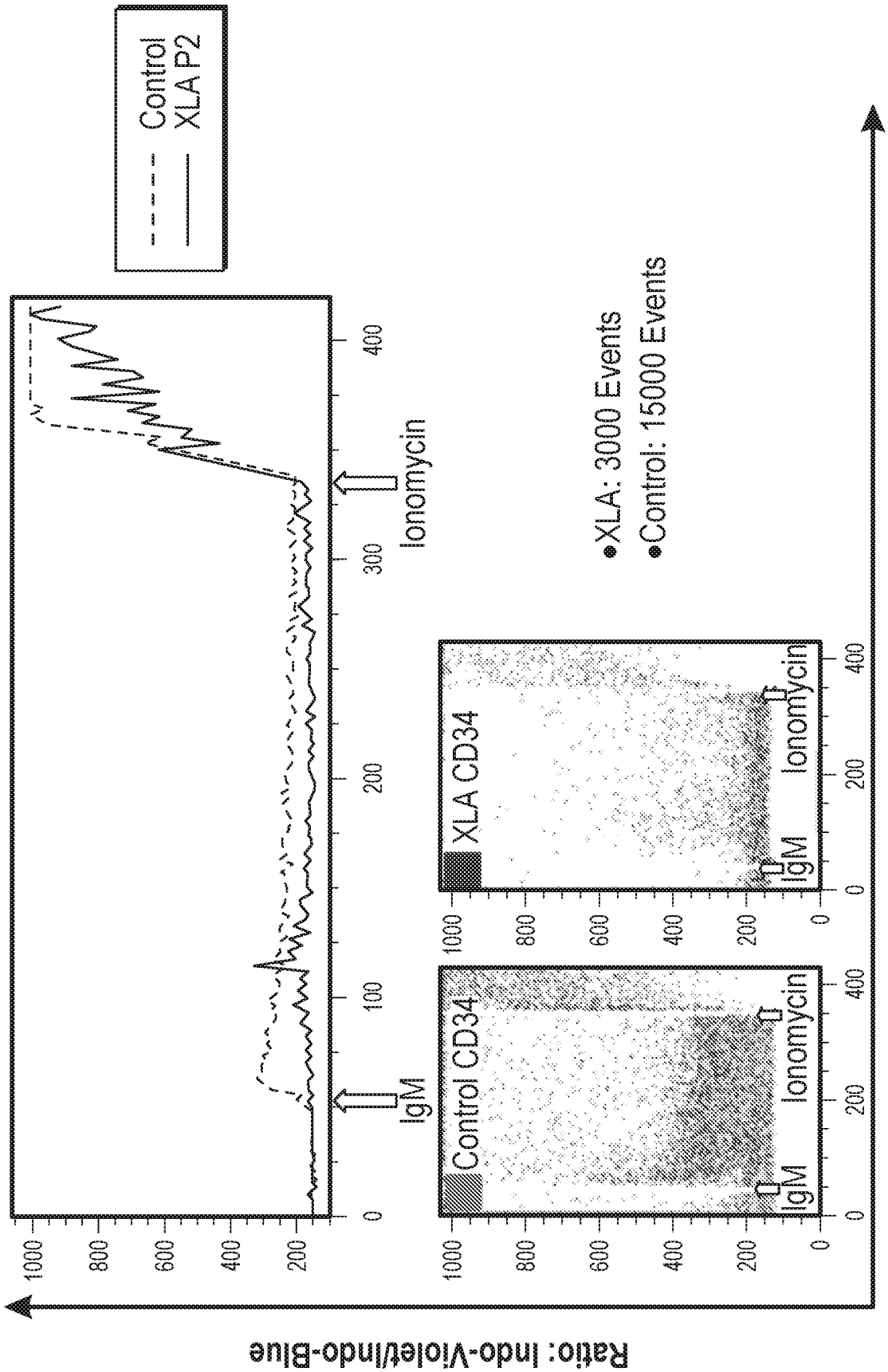
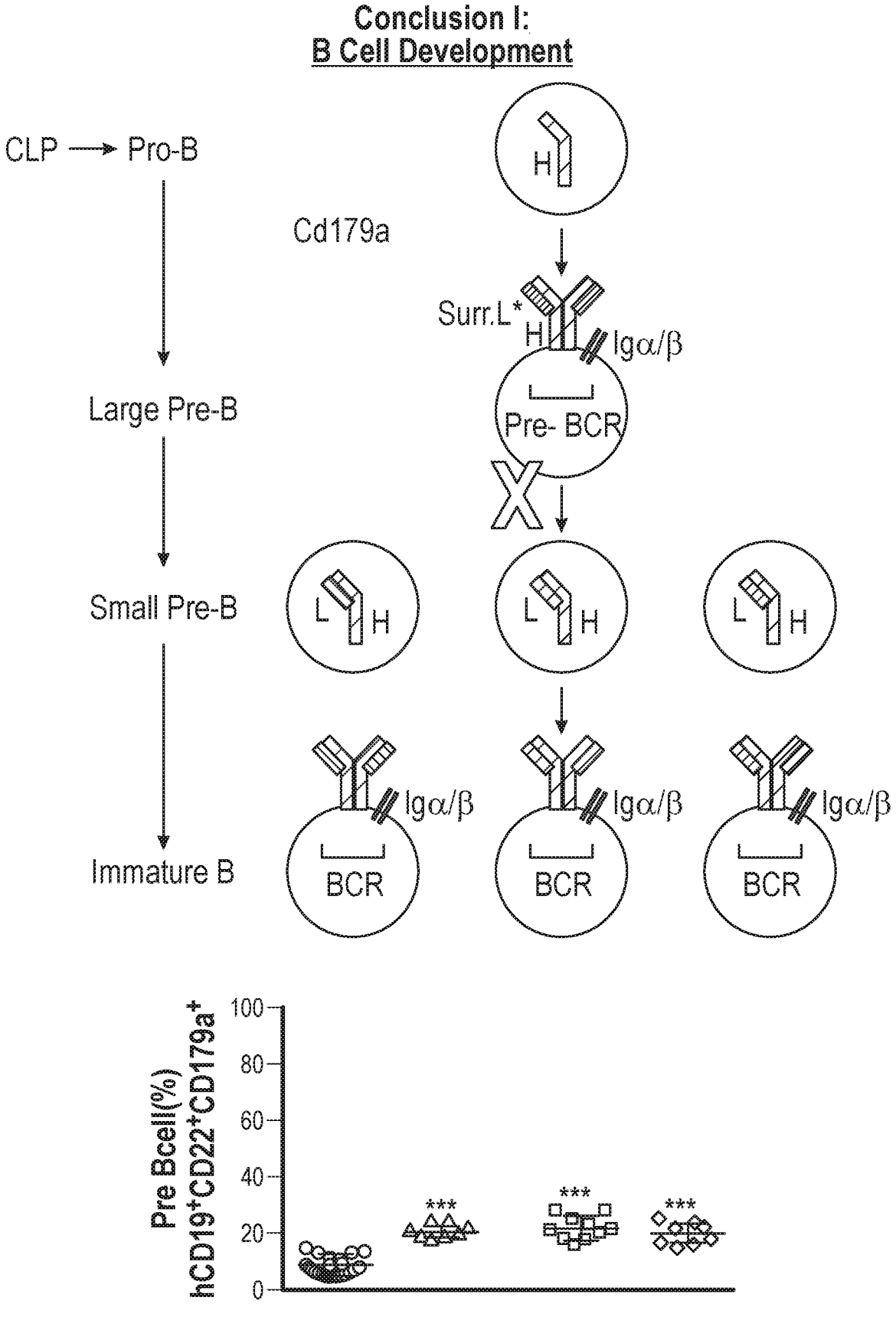

Control
XLA P2
Ratio: Indo-Violet/Indo-Blue
1000
800
600
400
200
0
100
200
300
400
IgM
Ionomycin
Control CD34
XLA CD34
•XLA: 3000 Events
•Control: 15000 Events

FIG. 80-2



XLA Cells have B cell blocked at Pre B cell.

FIG. 81

Conclusion I:

°Are we able to recapitulate XLA patient's B cell phenotype in NSG mice?

- Lower number and percentage of B cells in Spleen.
- B cell development is arrest at pre B cell stage in BM.
- Pre B cell are not able to differentiate into mature B cells.
- Immature B cells from the bone marrow also migrate to spleen.
- XLA splenic B cell are functionally impaired.

FIG. 82

Human Lentiviral Transduction of Stem Cells:

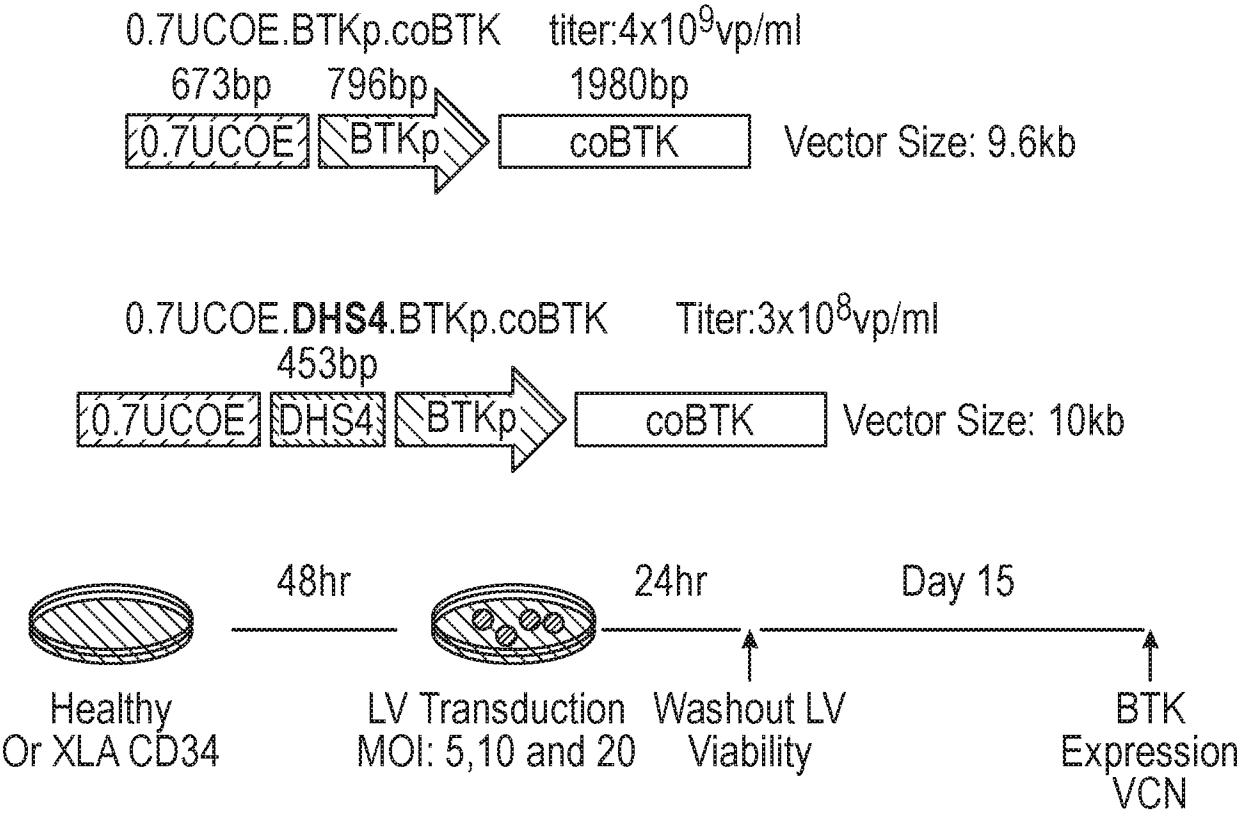


FIG. 83

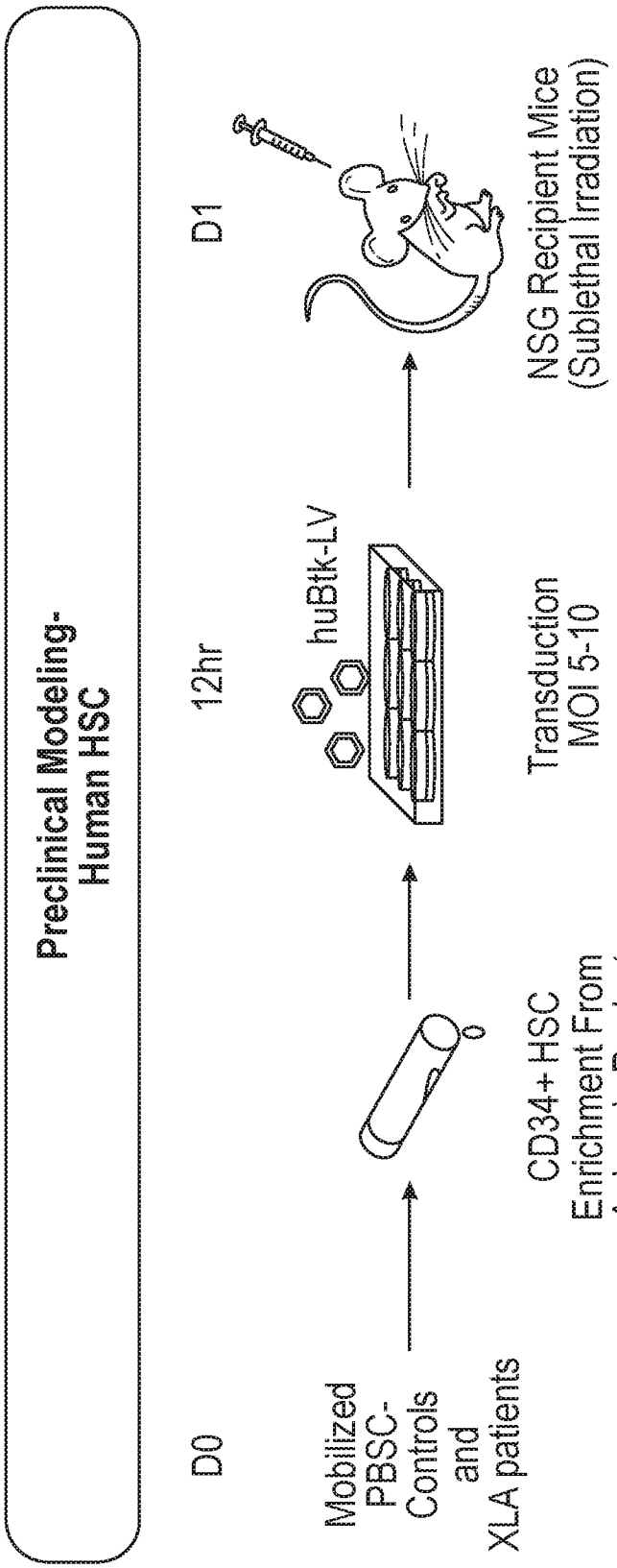
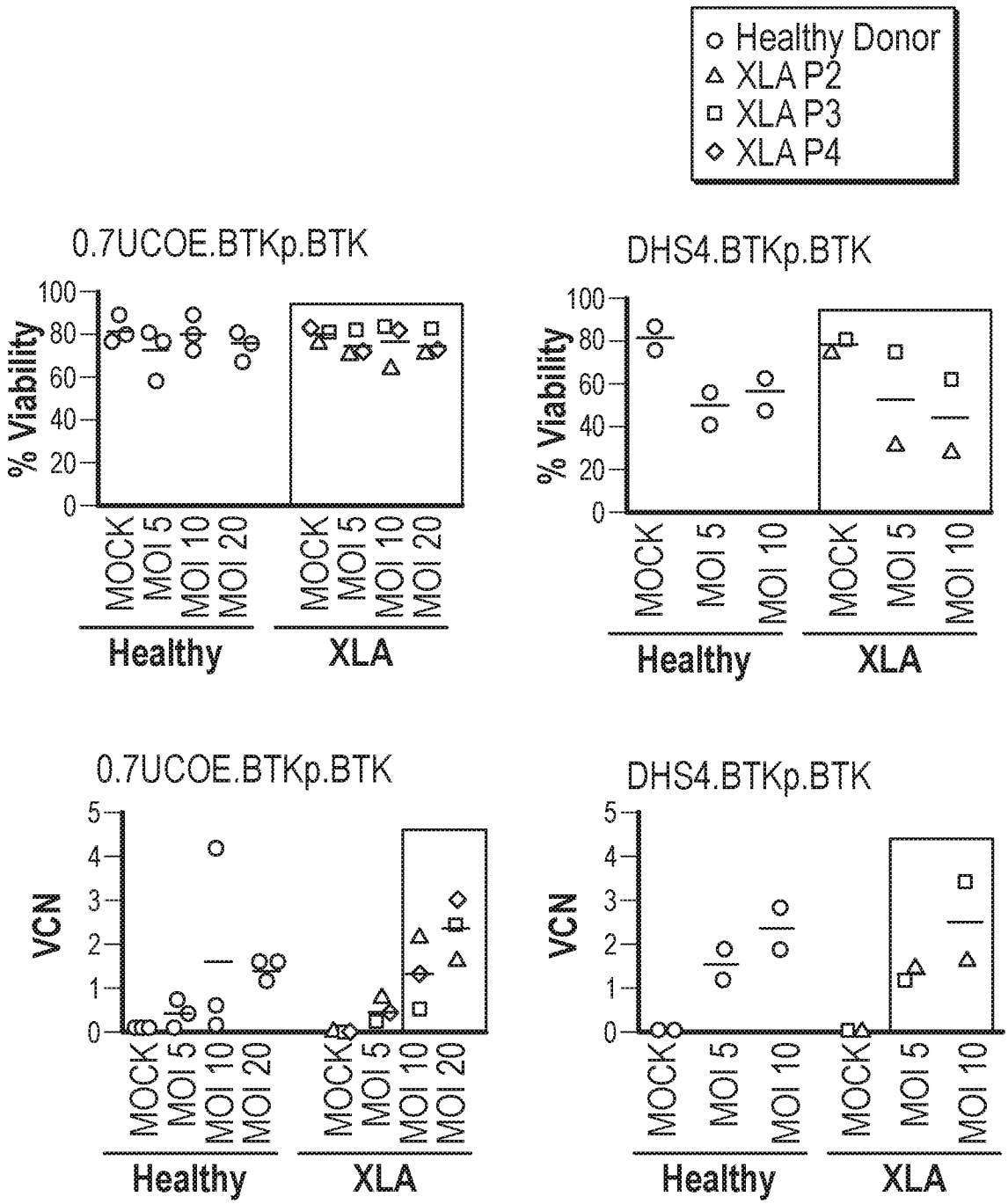

Precinical Modeling-
Human HSC
D0
Mobilized
PBSC-
Controls
and
XLA patients
CD34+ HSC
Enrichment From
Aphereis Product
12hr
huBtk-LV
Transduction
MOI 5-10
D1
NSG Recipient Mice
(Sublethal Irradiation)

FIG. 84

Human Lentiviral Transduction of Stem Cells:



70% viability with 0.7UCOE.BTKp.BTK compare to DHS4. Clinically relevant VCN 1-2 at MOI 10 and 20.

FIG. 85

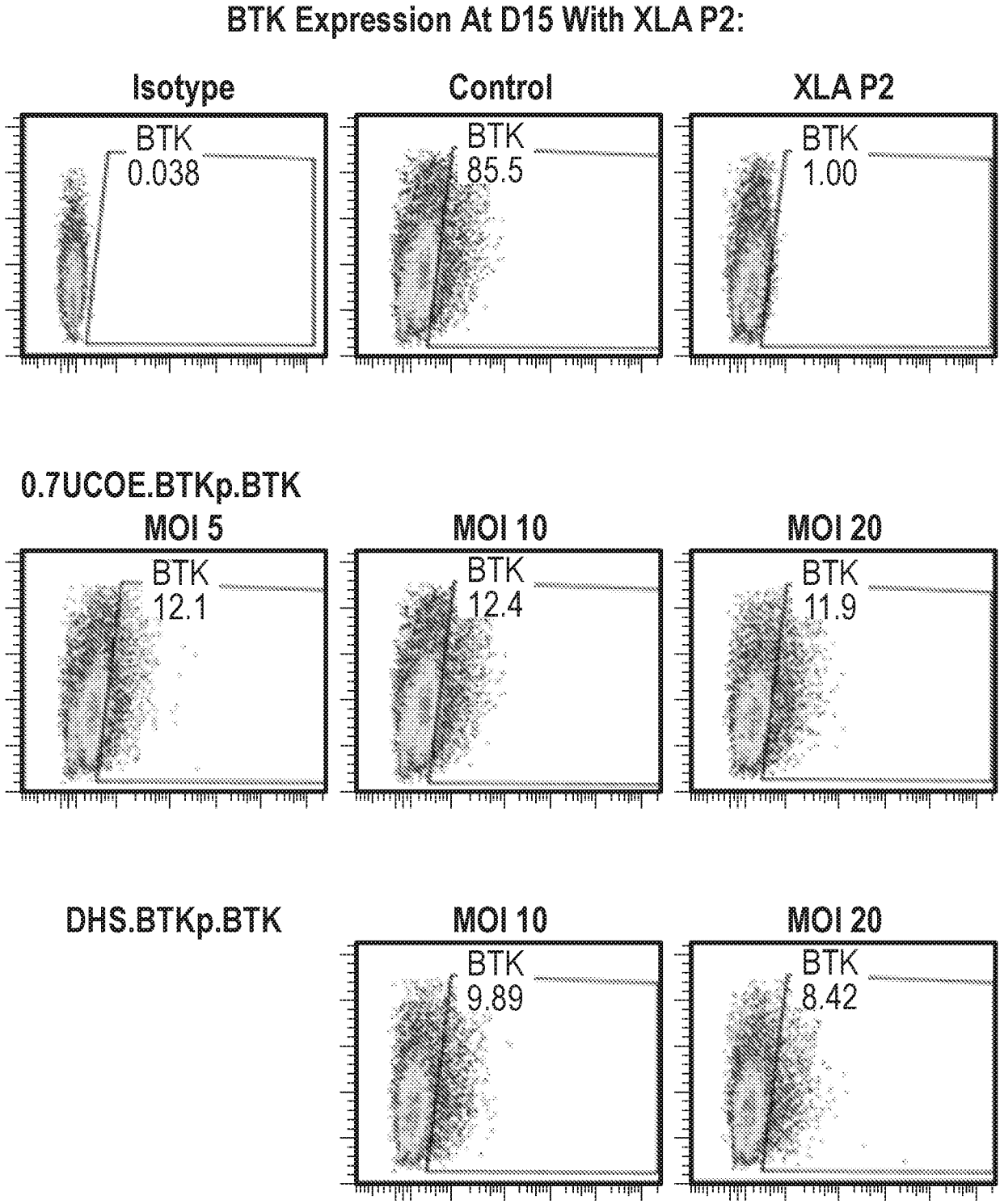
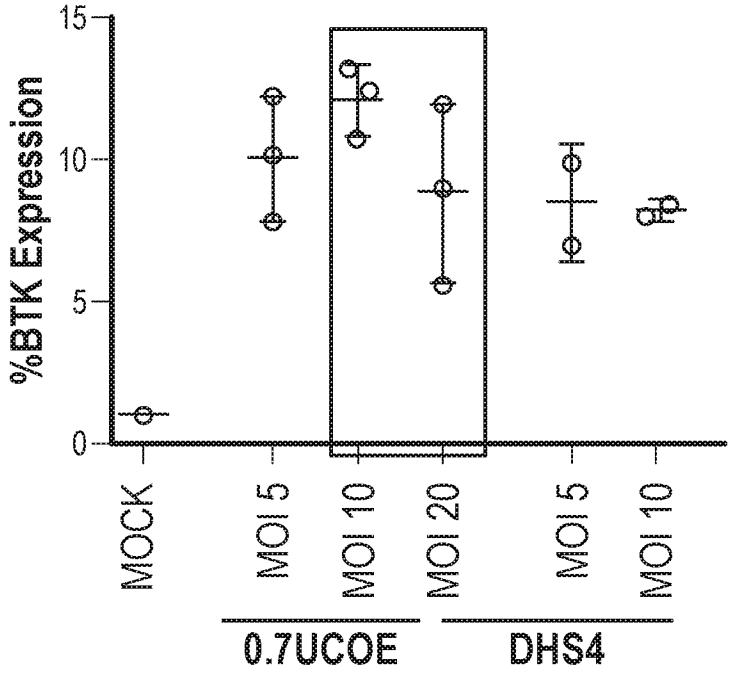

BTK Expression At D15 With XLA P2:
Isotype
Control
XLA P2
BTK
0.038
BTK
85.5
BTK
1.00
0.7UCOE.BTKp.BTK
MOI 5
MOI 10
MOI 20
BTK
12.1
BTK
12.4
BTK
11.9
DHS.BTKp.BTK
MOI 10
MOI 20
BTK
9.89
BTK
8.42

FIG. 86-1



In non selective environment 0.7UCOE.BTKpBTK leads to higher expression of BTK compare to DHS4.

FIG. 86-2

Conclusion II:

- Are we able to rescue the B cell development with lentiviral transduction of XLA stem cells in-vivo?
  - XLA stem cells transduced with 0.7UCOE.BTKp.BTK and 0.7UCOE.DHS4.BTKp.BTK at MOI10, leads to clinically relevant viral copy 1-2.

- In-vivo experiment: comparing B cell reconstitution and development with 0.7UCOE.BTKp.BTK and 0.7UCOE.DHS4.BTKp.BTK

FIG. 87

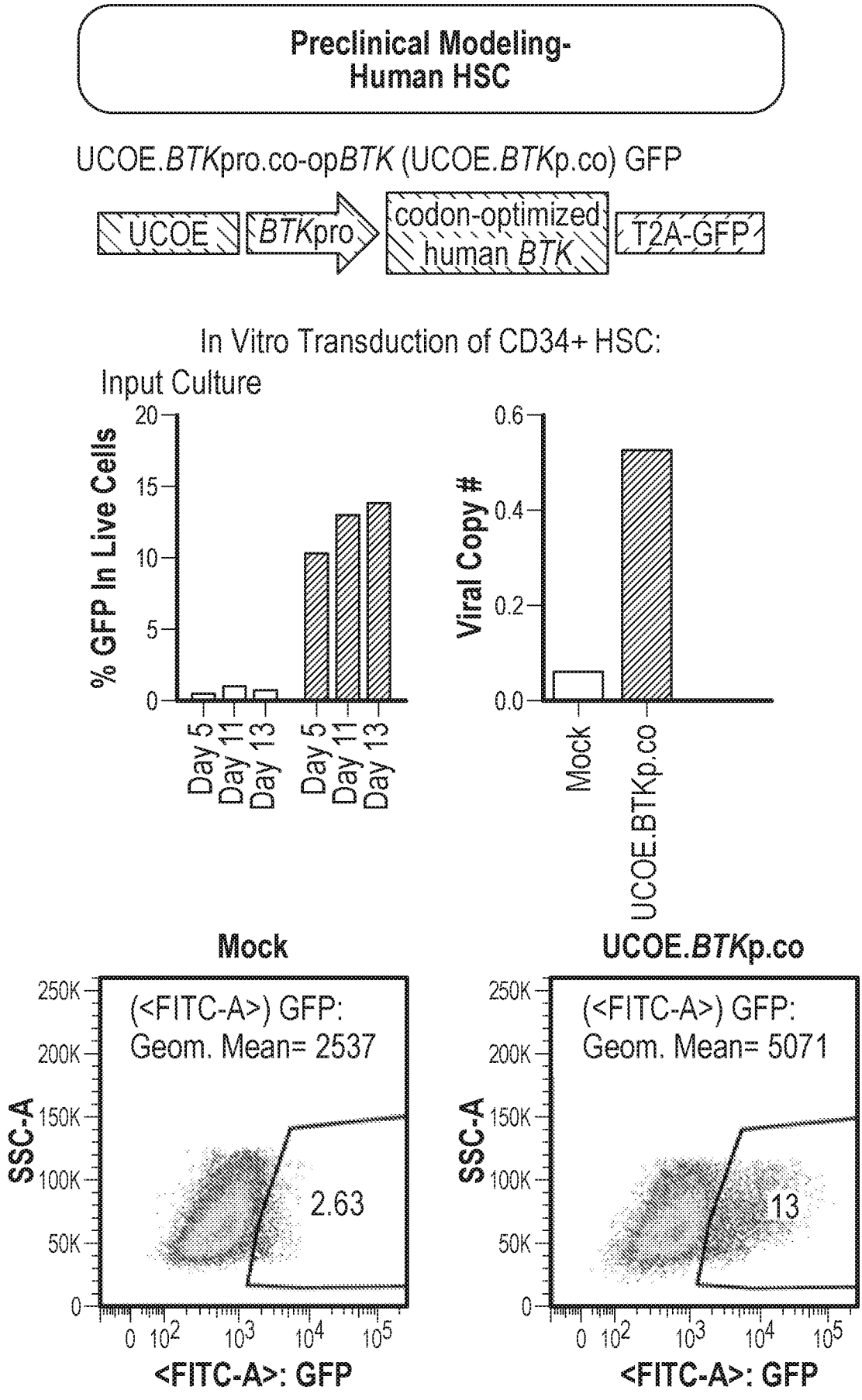

Preclinical Modeling-
Human HSC
UCOE.BTKpro.co-opBTK (UCOE.BTKp.co) GFP
UCOE
BTKpro
codon-optimized human BTK
T2A-GFP
In Vitro Transduction of CD34+ HSC:
Input Culture
% GFP In Live Cells
20
15
10
5
0
Day 5
Day 11
Day 13
Day 5
Day 11
Day 13
Viral Copy #
0.6
0.4
0.2
0.0
Mock
UCOE.BTKp.co
Mock
UCOE.BTKp.co
250K
200K
150K
100K
50K
0
SSC-A
(<FITC-A>) GFP:
Geom. Mean= 2537
2.63
(<FITC-A>) GFP:
Geom. Mean= 5071
13
0 10^2 10^3 10^4 10^5
<FITC-A>: GFP

FIG. 88

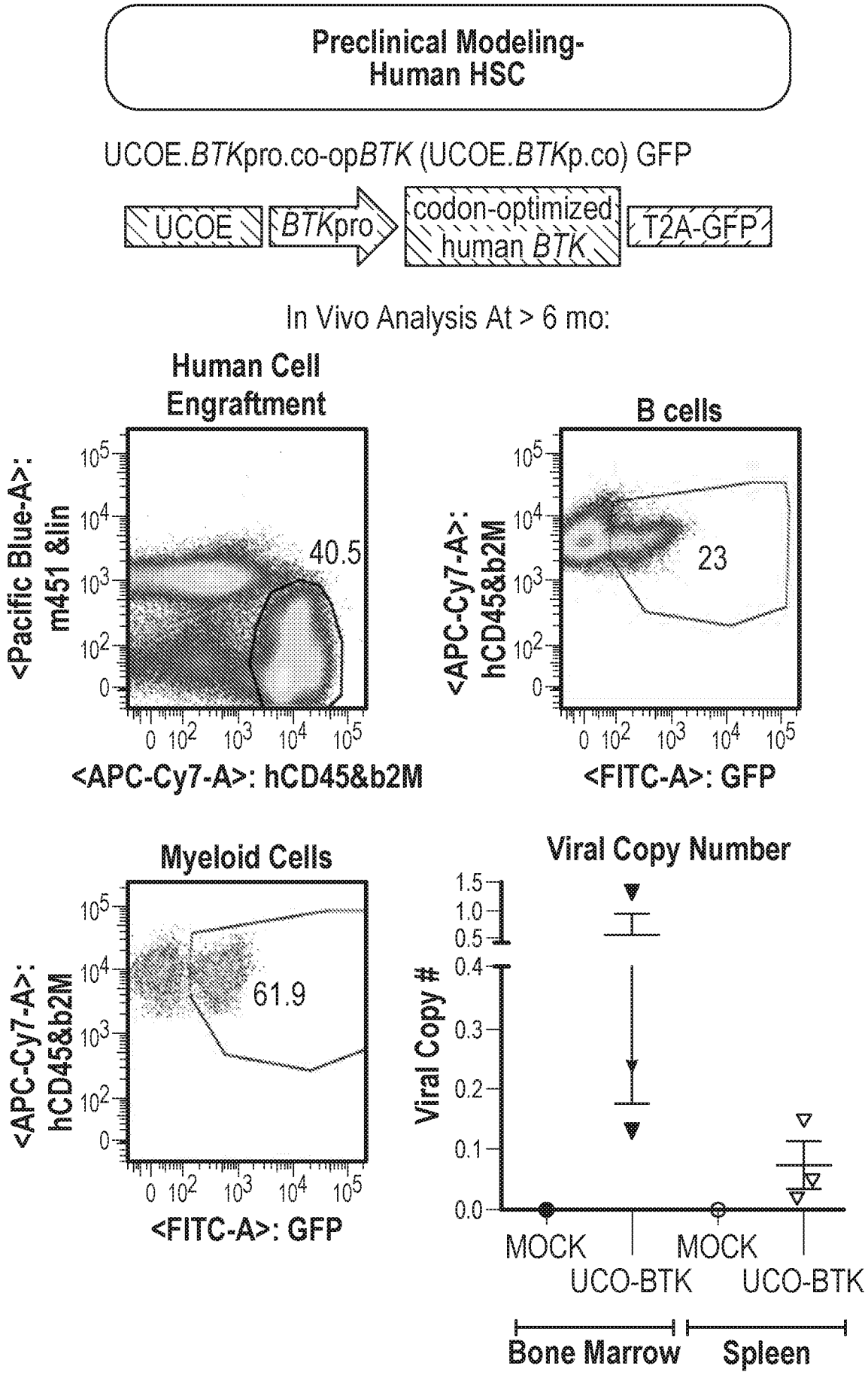

Preclinical Modeling-
Human HSC
UCOE.BTKpro.co-opBTK (UCOE.BTKp.co) GFP
UCOE
BTKpro
codon-optimized human BTK
T2A-GFP
In Vivo Analysis At > 6 mo:
Human Cell Engraftment
<Pacific Blue-A>: m451 &lin
40.5
<APC-Cy7-A>: hCD45&b2M
B cells
<APC-Cy7-A>: hCD45&b2M
23
<FITC-A>: GFP
Myeloid Cells
<APC-Cy7-A>: hCD45&b2M
61.9
<FITC-A>: GFP
Viral Copy Number
Viral Copy #
MOCK
MOCK
UCO-BTK
UCO-BTK
Bone Marrow
Spleen

FIG. 89

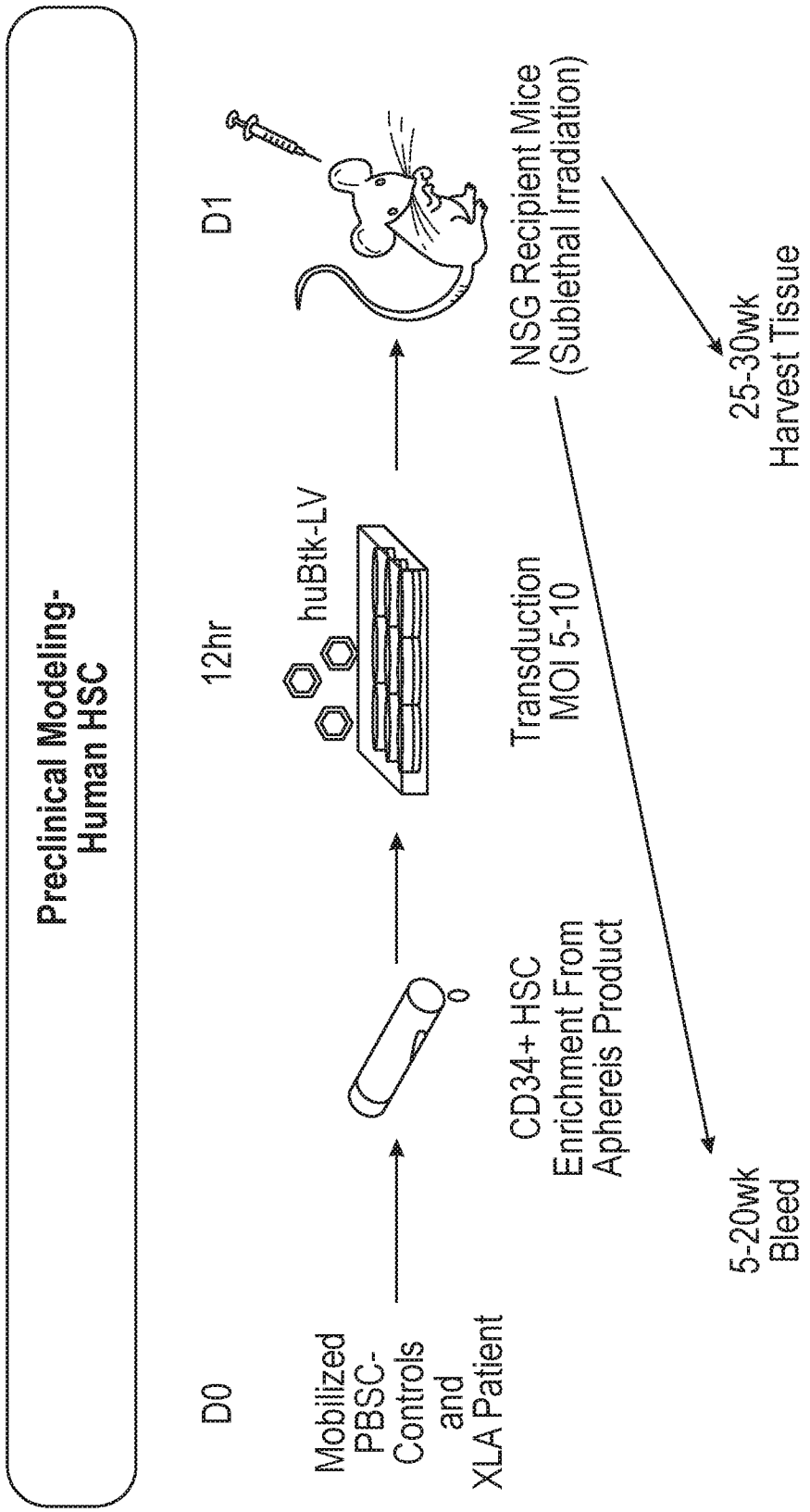

Precinical Modeling-
Human HSC
D0
Mobilized
PBSC-
Controls
and
XLA Patient
CD34+ HSC
Enrichment From
Aphereis Product
12hr
huBtk-LV
Transduction
MOI 5-10
D1
NSG Recipient Mice
(Sublethal Irradiation)
5-20wk
Bleed
25-30wk
Harvest Tissue

FIG. 90

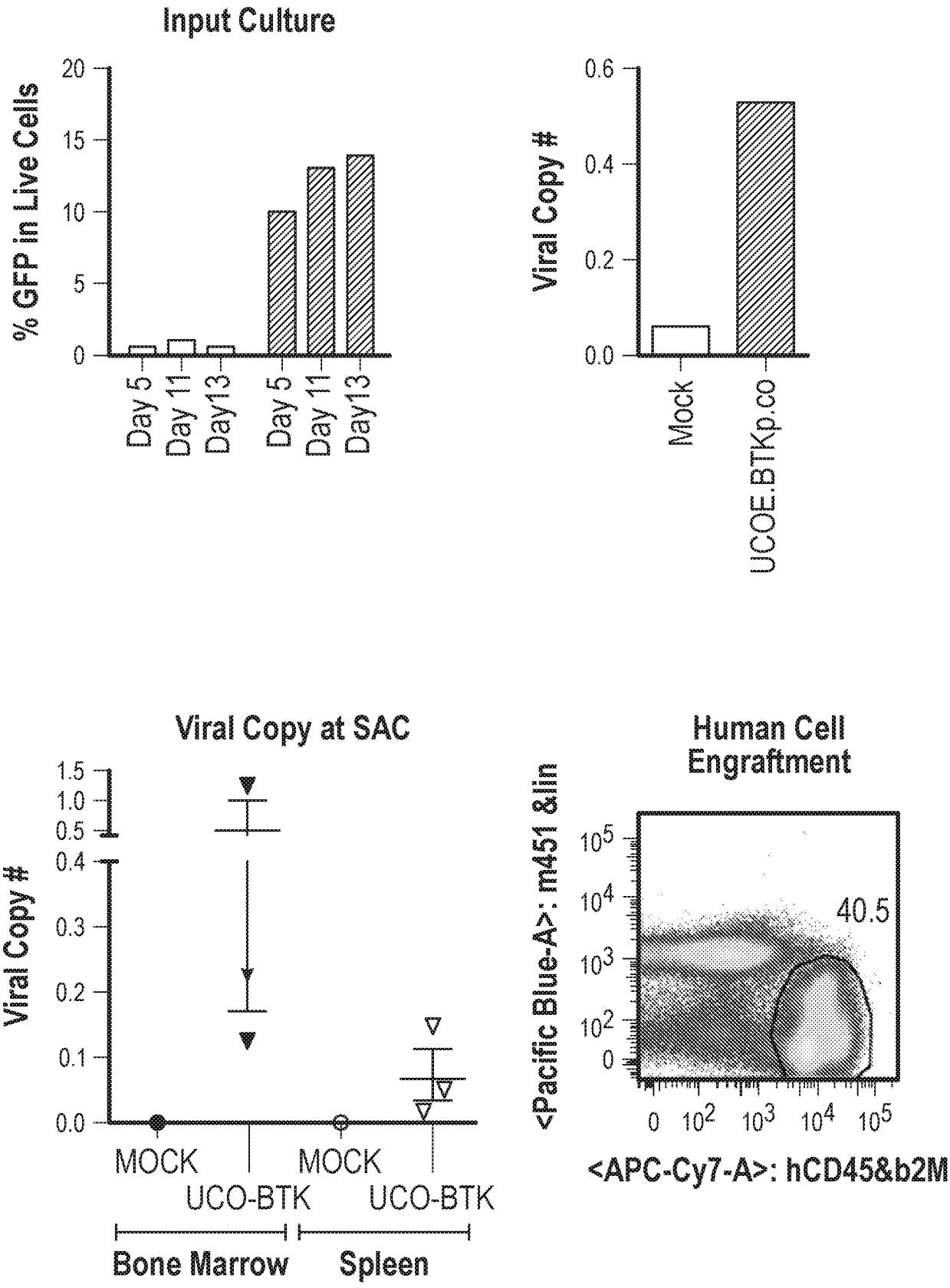

Input Culture
% GFP in Live Cells
20
15
10
5
0
Day 5
Day 11
Day13
Day 5
Day 11
Day13
Viral Copy #
0.6
0.4
0.2
0.0
Mock
UCOE.BTKp.co
Viral Copy at SAC
Viral Copy #
1.5
1.0
0.5
0.4
0.3
0.2
0.1
0.0
MOCK
MOCK
UCO-BTK
UCO-BTK
Bone Marrow
Spleen
Human Cell Engraftment
<Pacific Blue-A>: m451 &lin
10^5
10^4
10^3
10^2
0
40.5
0
10^2
10^3
10^4
10^5
<APC-Cy7-A>: hCD45&b2M

FIG. 91-1

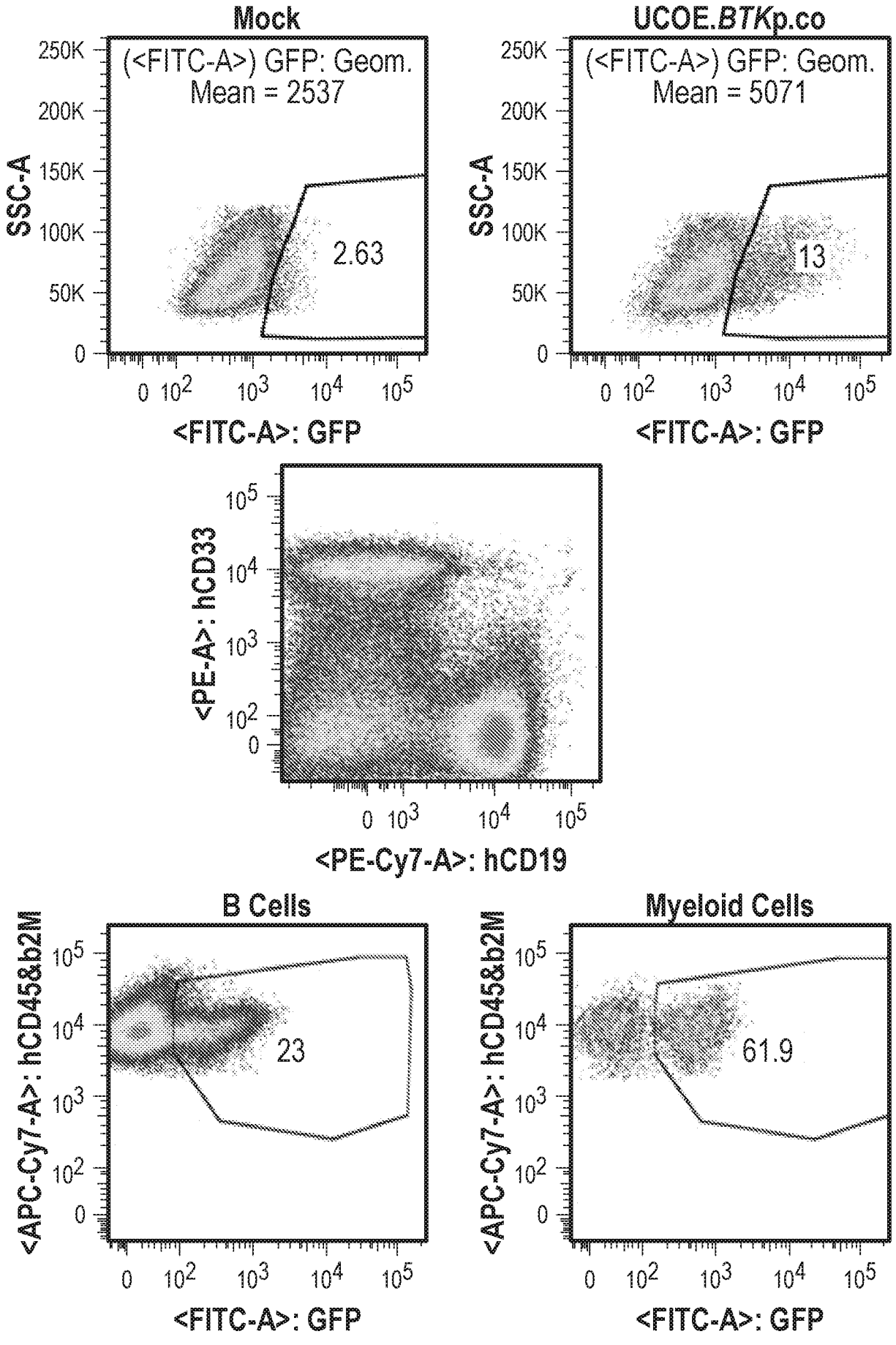

Mock
(<FITC-A>) GFP: Geom. Mean = 2537
2.63
SSC-A
<FITC-A>: GFP
UCOE.BTKp.co
(<FITC-A>) GFP: Geom. Mean = 5071
13
SSC-A
<FITC-A>: GFP
<PE-A>: hCD33
<PE-Cy7-A>: hCD19
B Cells
23
<APC-Cy7-A>: hCD45&b2M
<FITC-A>: GFP
Myeloid Cells
61.9
<APC-Cy7-A>: hCD45&b2M
<FITC-A>: GFP

FIG. 91-2

Alignment 1
sequence 2
mock genomic (+)
1-50201
Criteria: 70%. 100 bp
Regions: 73

X-axis: sequence1
Resolution: 15
Window size: 100 bp

gene
exon
UTR
CNS
mRNA
Repeats
LINE
LTR
SINE
RNA
DNA
Other

Sequencel hBTK:1- 47244

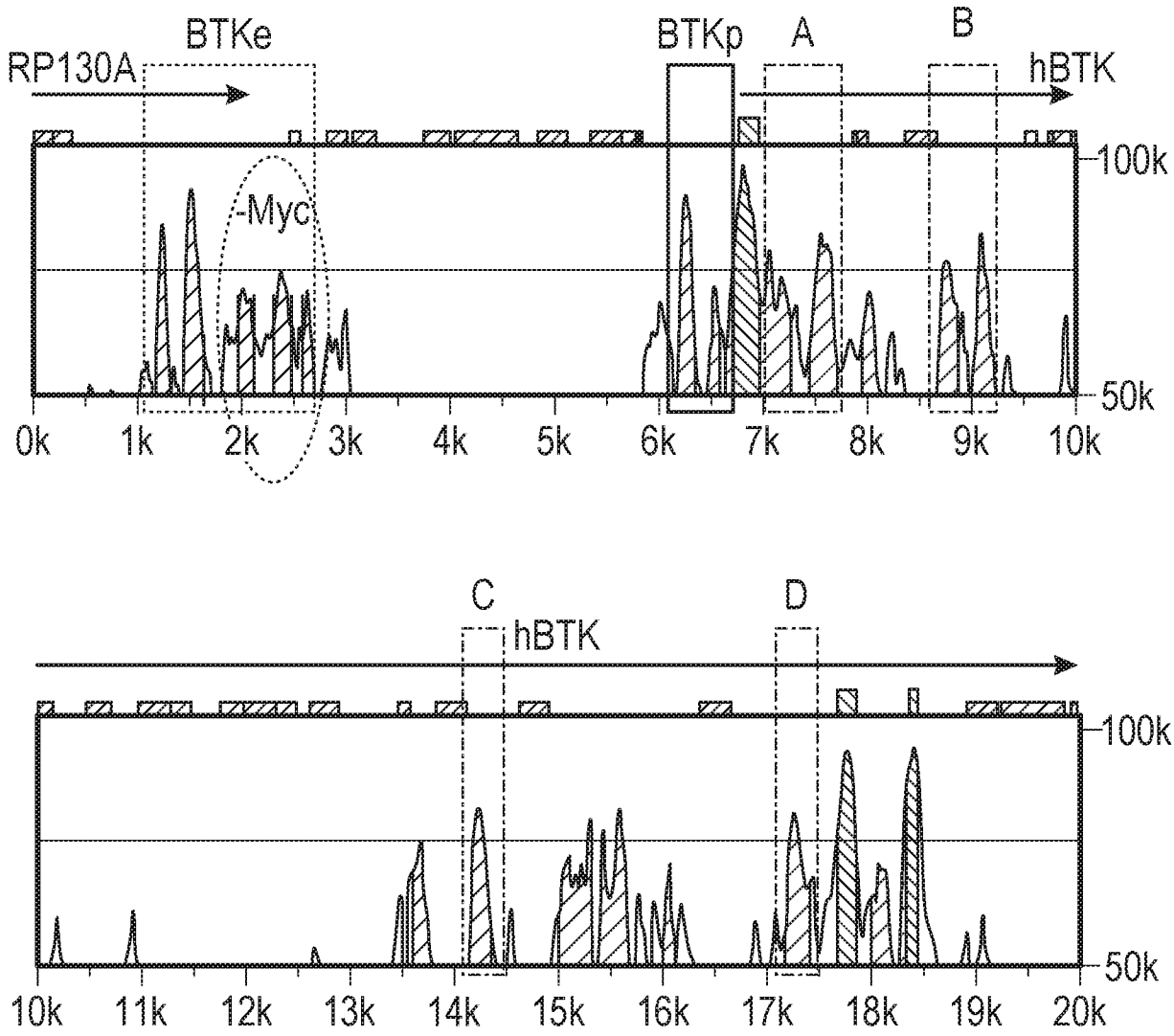


FIG. 92-1

Alignment 1
sequence 2
mock genomic (+)
1-50201
Criteria: 70%. 100 bp
Regions: 73

X-axis: sequence1
Resolution: 15
Window size: 100 bp

gene
exon
UTR
CNS
mRNA
Repeats
LINE
LTR
SINE
RNA
DNA
Other

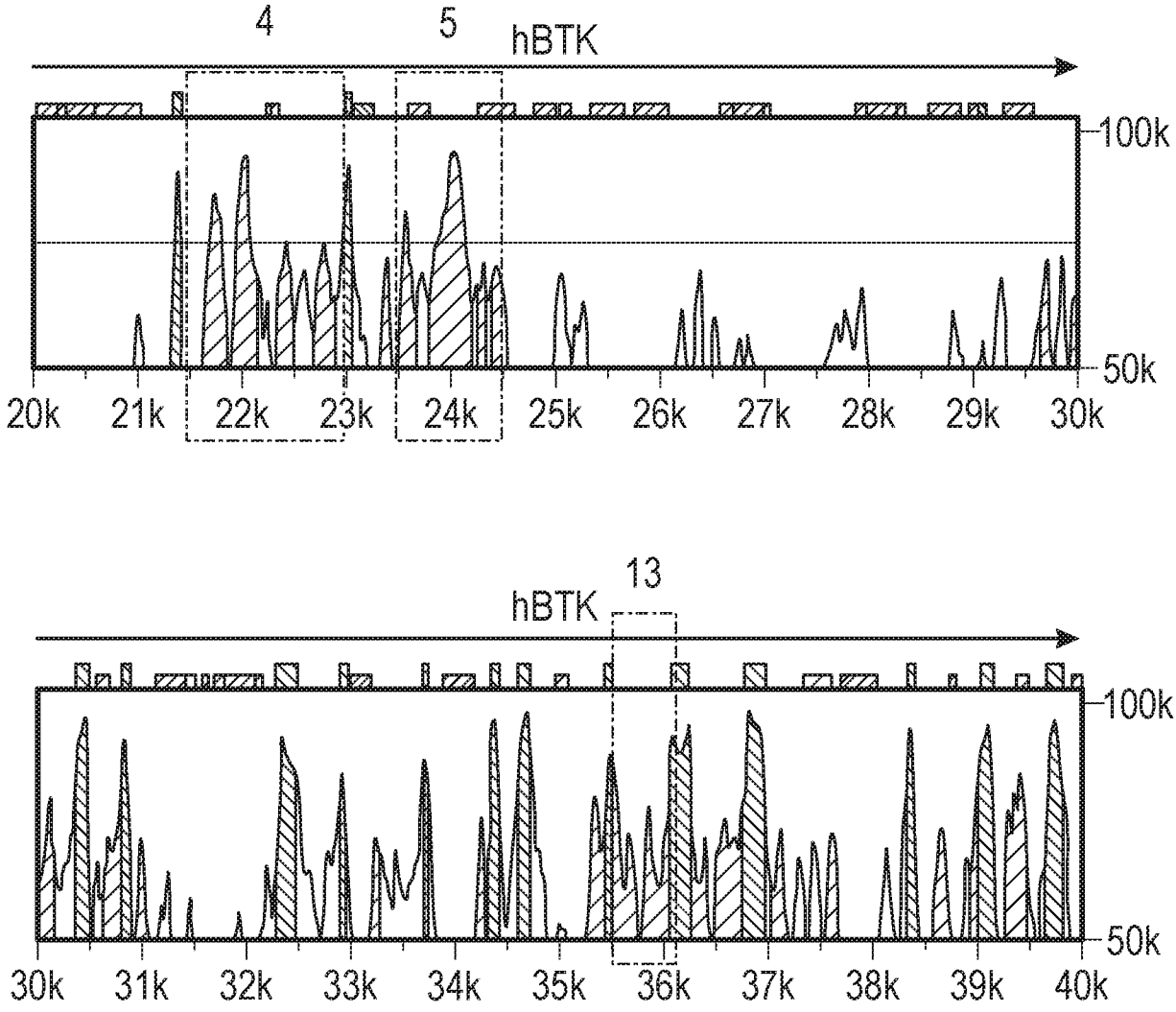
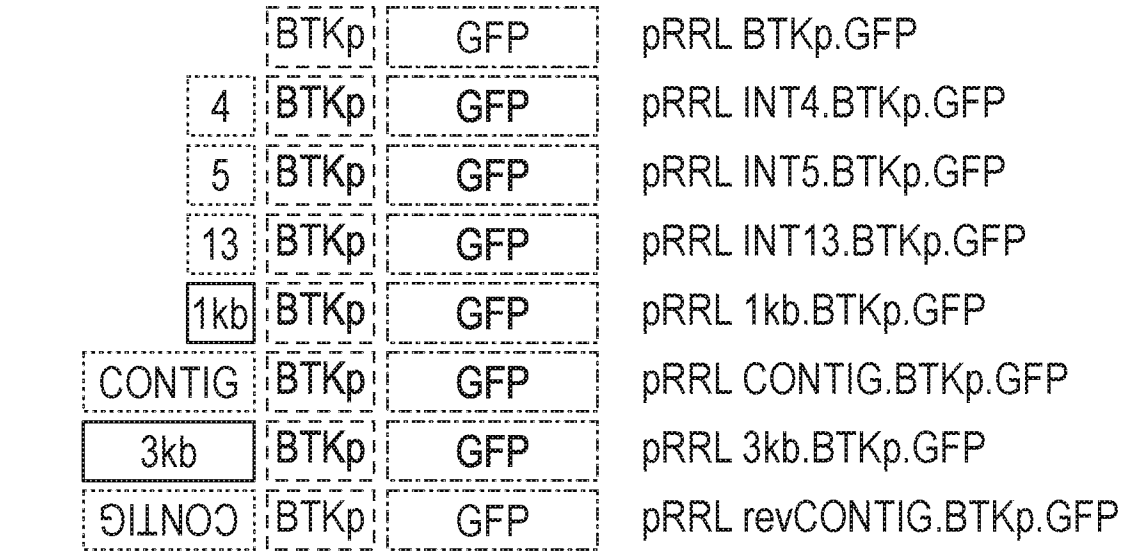


FIG. 92-2

SET 1: TEST INTROS 4, 5, 13 (CONTIG = ALL 3)

Test 1:



NOTE: "1kb" and "3kb" are non-conserved intron 1 sequences, to control for size or enhancer

Test 2:

* INT4-5 element aka "IE"

Test 3 (in mice):

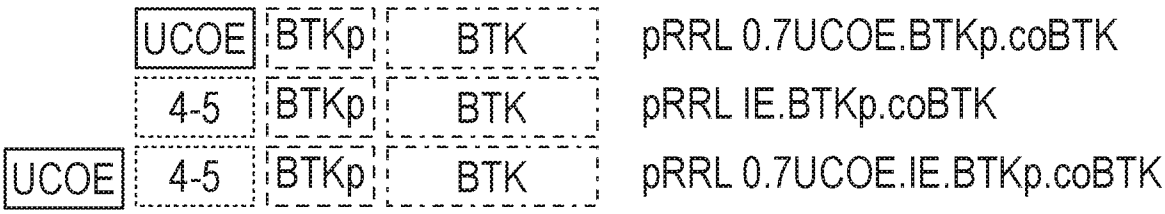
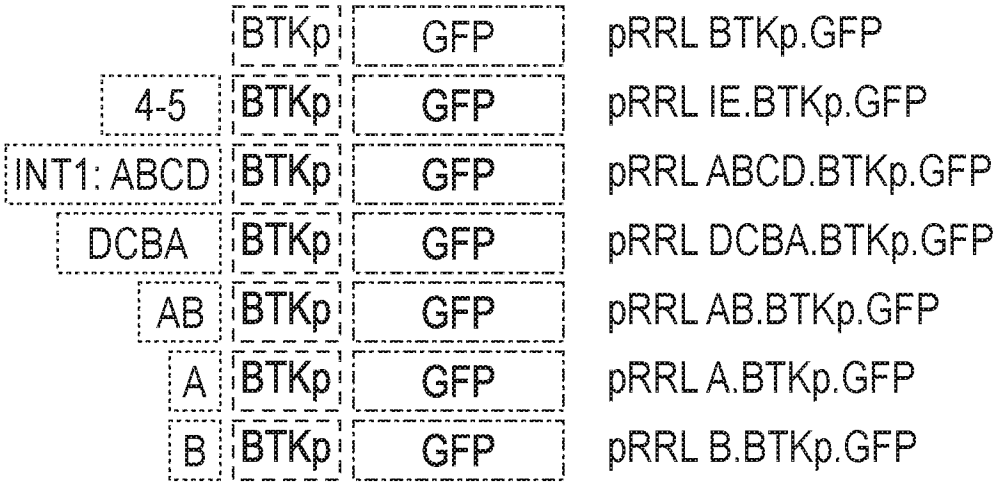


FIG. 92-3

SET 2: TEST INTRON1 (4 segments: A, B, C and D)



SET 3: TEST UPSTREAM ENHANCERS (BTKe)

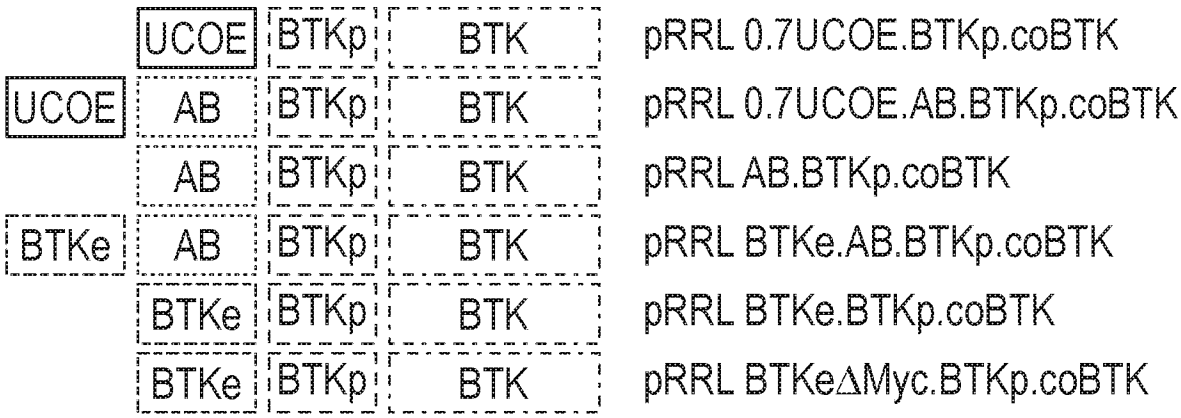


FIG. 92-4

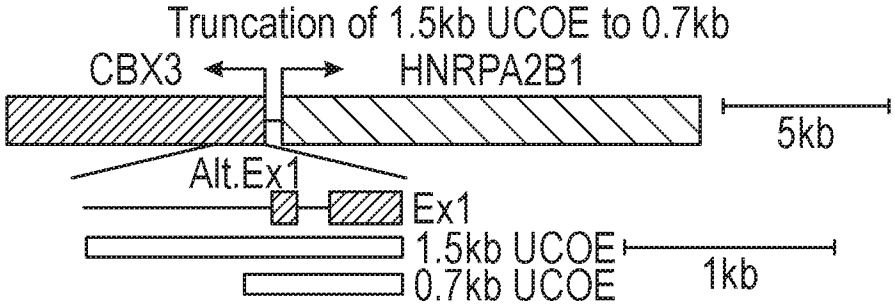


FIG. 93A

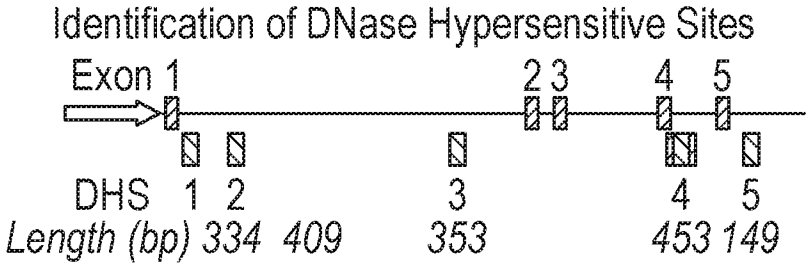


FIG. 93B

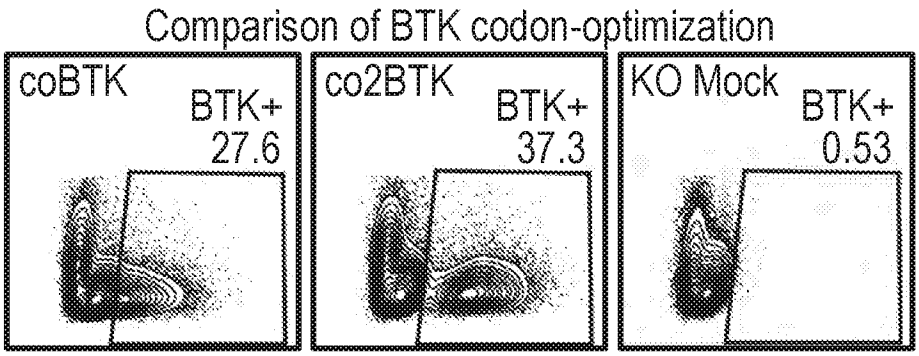


FIG. 93C

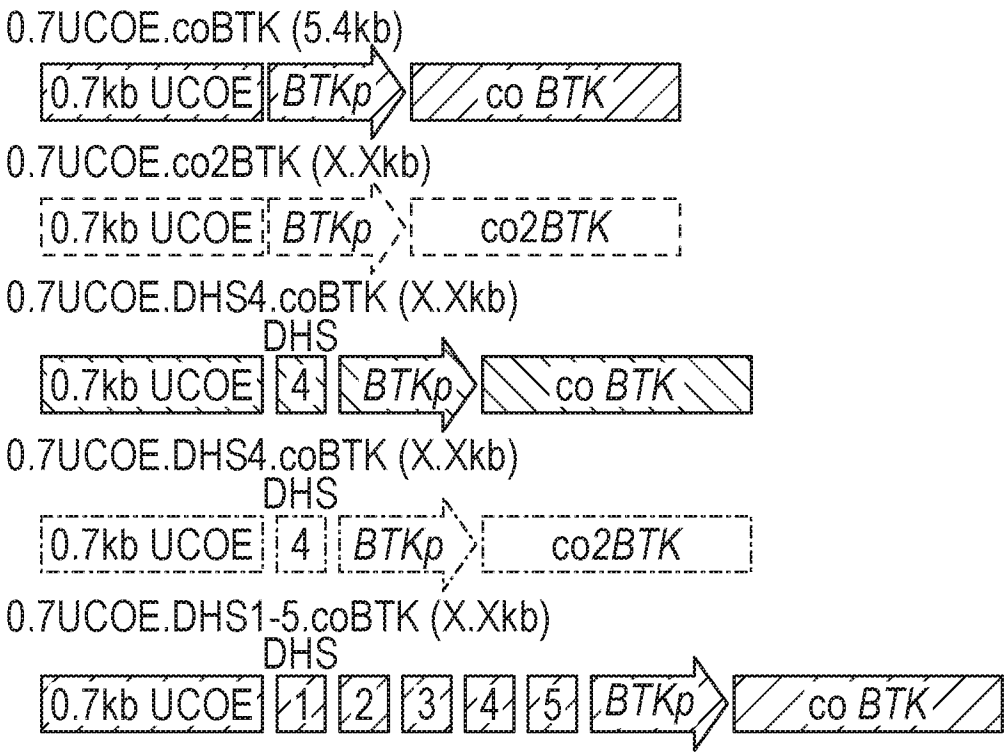


FIG. 93D

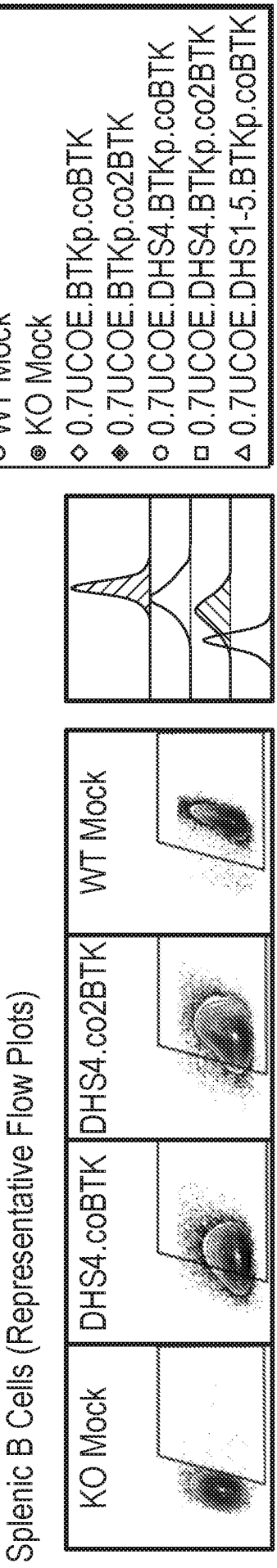


FIG. 94A

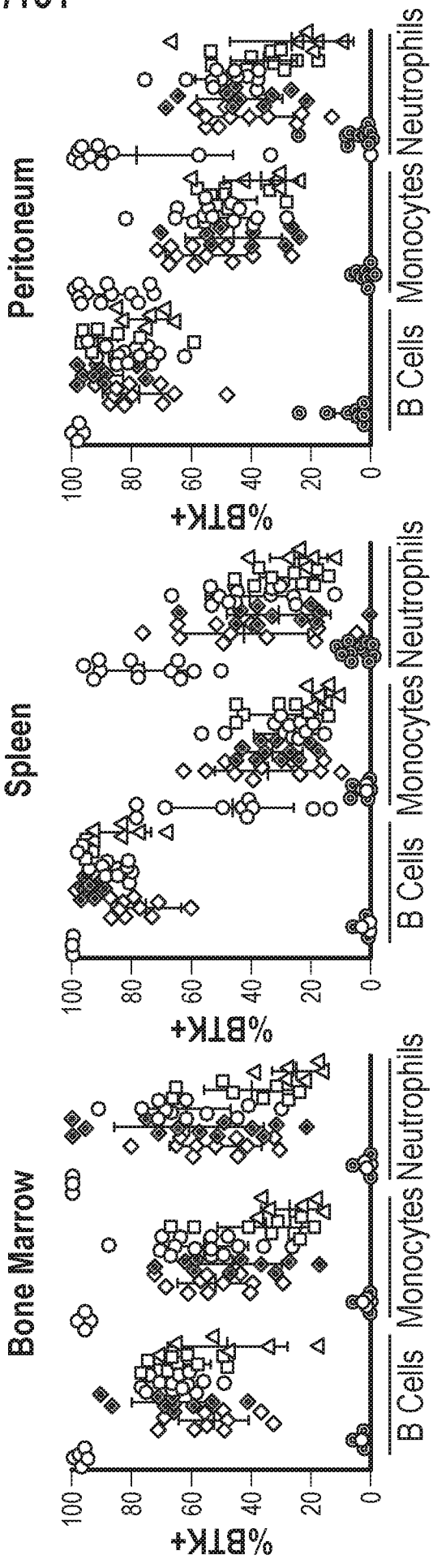
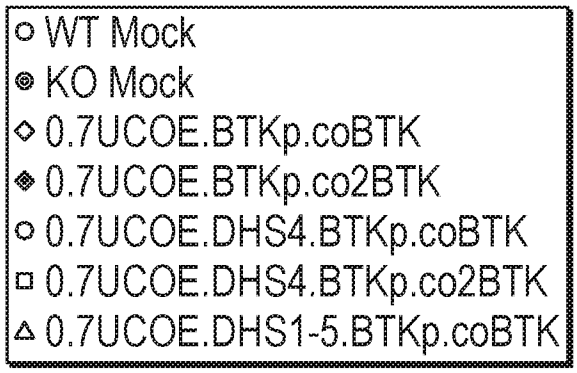


FIG. 94B

FIG. 94C

FIG. 94D



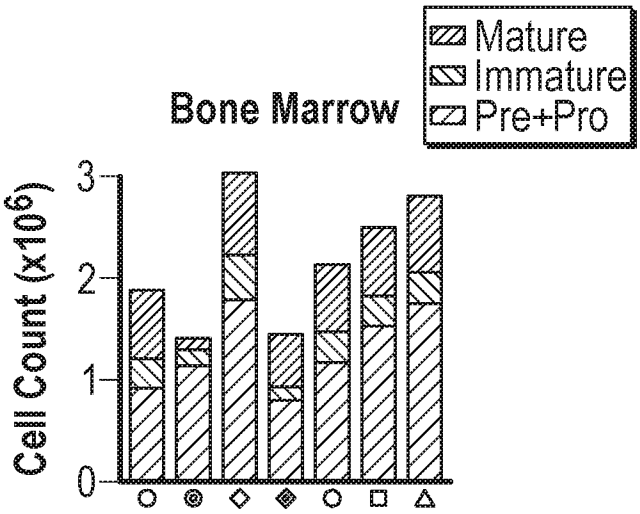


FIG. 94E

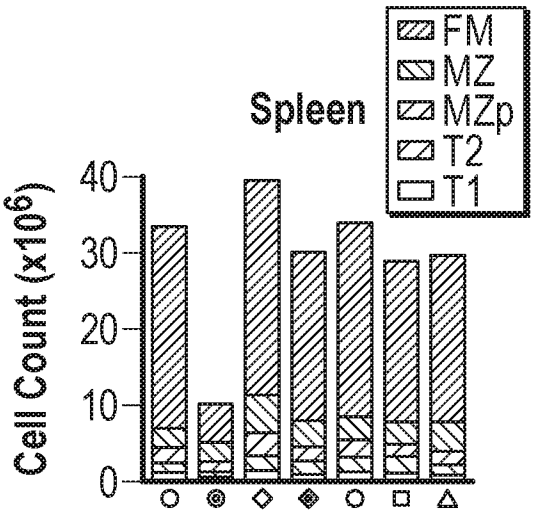


FIG. 94F

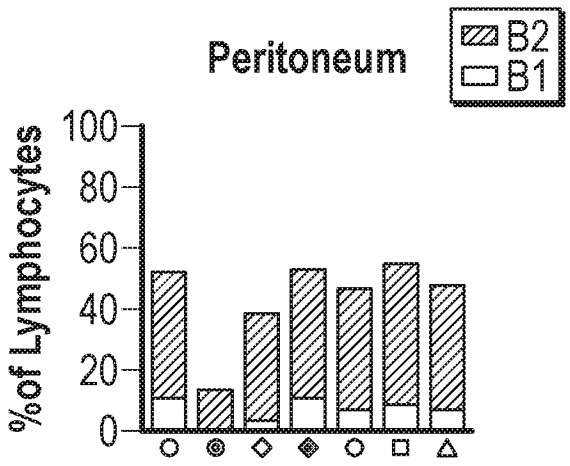


FIG. 94G

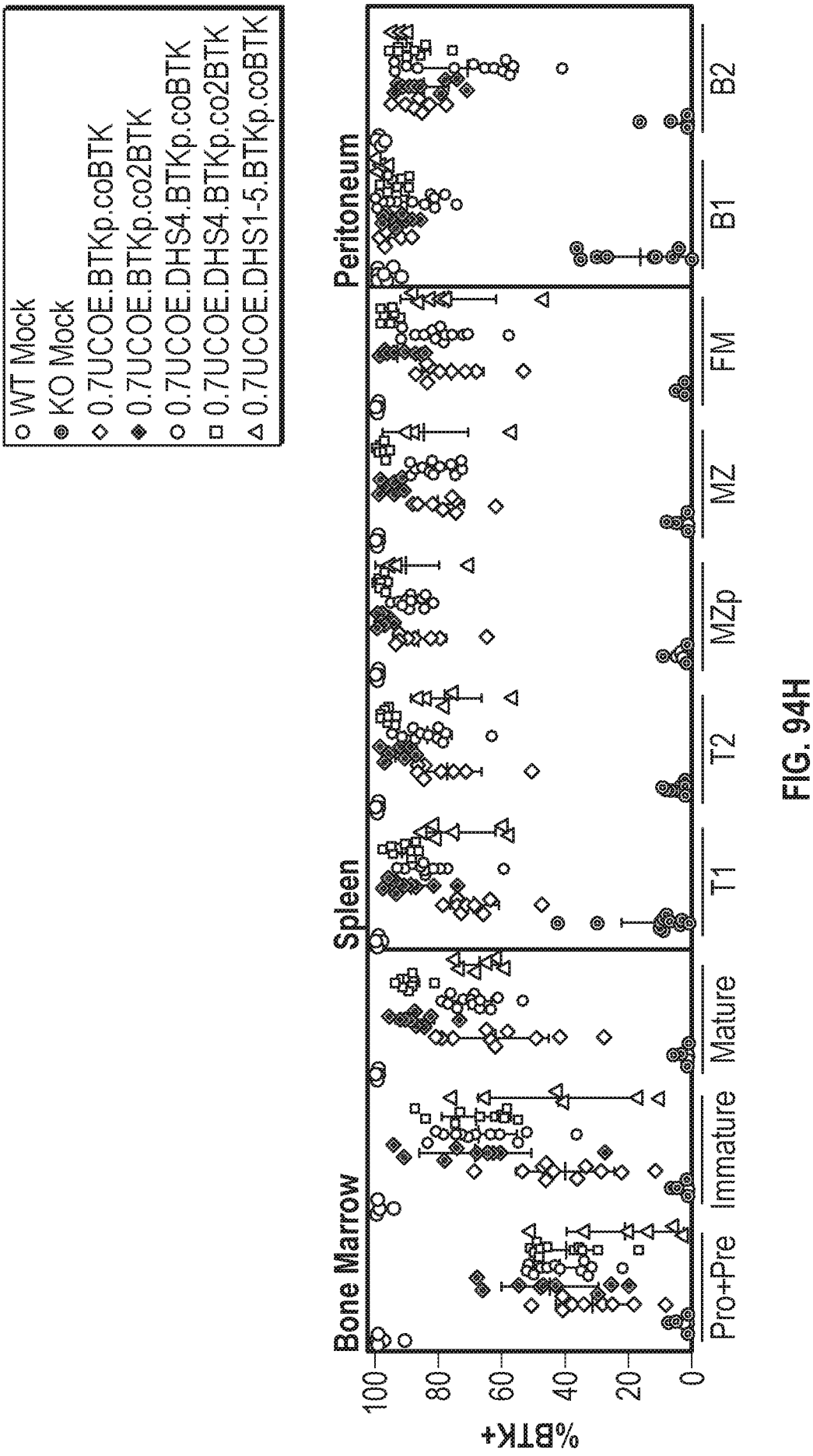

WT Mock
KO Mock
0.7UCOE.BTKp.coBTK
0.7UCOE.BTKp.co2BTK
0.7UCOE.DHS4.BTKp.coBTK
0.7UCOE.DHS4.BTKp.co2BTK
0.7UCOE.DHS1-5.BTKp.coBTK
Bone Marrow
Spleen
Peritoneum
Pro+Pre
Immature
Mature
T1
T2
MZp
MZ
FM
B1
B2
%BTK+
0
20
40
60
80
100

FIG. 94H

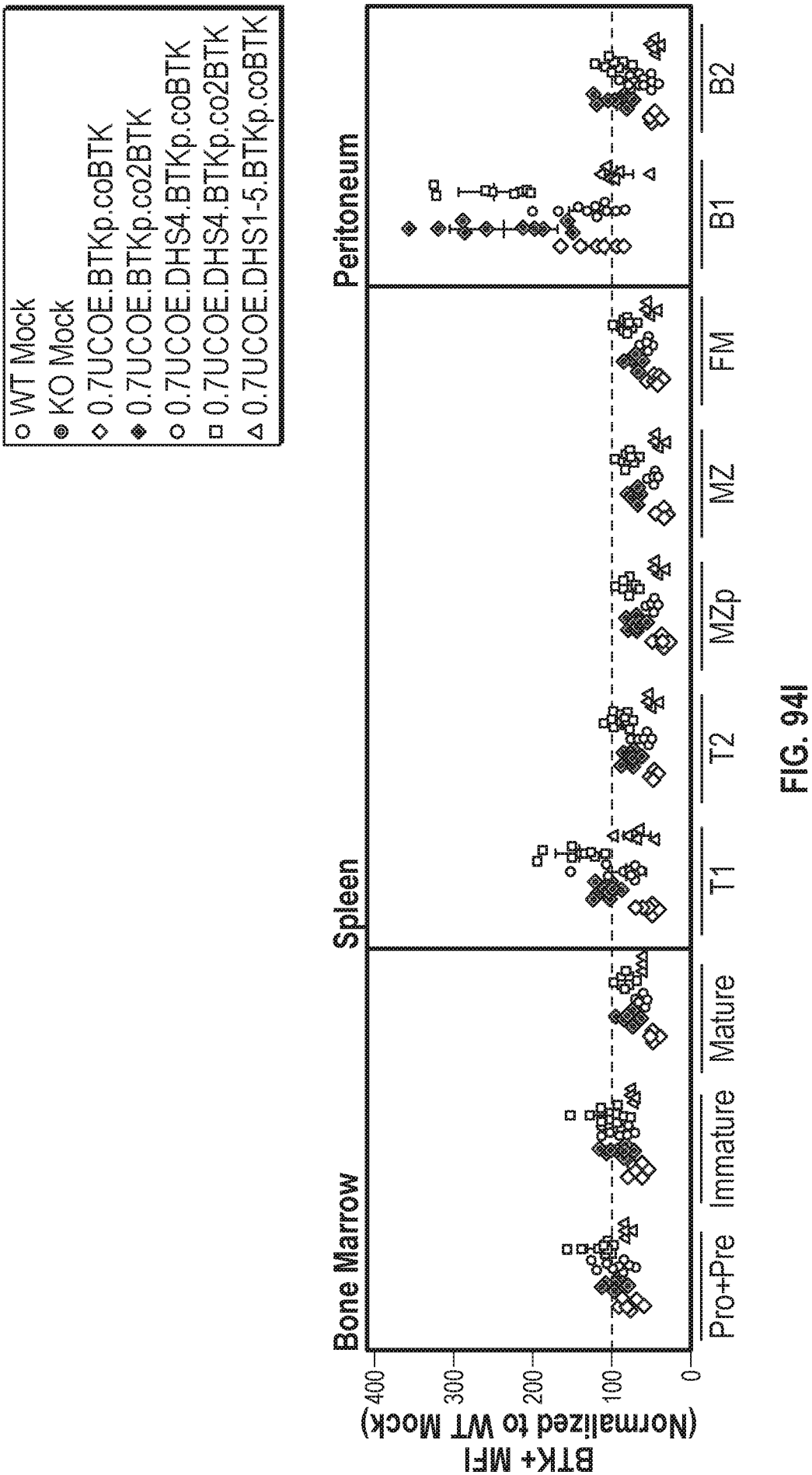
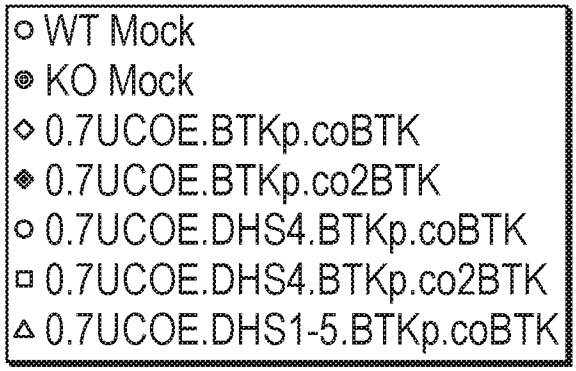

WT Mock
KO Mock
0.7UCOE.BTKp.coBTK
0.7UCOE.BTKp.co2BTK
0.7UCOE.DHS4.BTKp.coBTK
0.7UCOE.DHS4.BTKp.co2BTK
0.7UCOE.DHS1-5.BTKp.coBTK
BTK+ MFI (Normalized to WT Mock)
0
100
200
300
400
Bone Marrow
Spleen
Peritoneum
Pro+Pre
Immature
Mature
T1
T2
MZp
MZ
FM
B1
B2

FIG. 94I



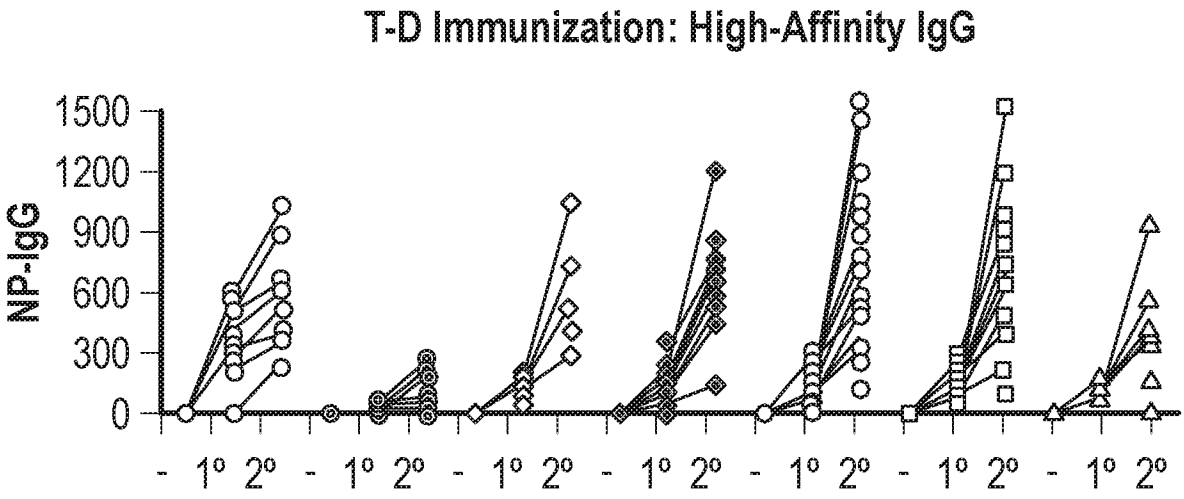


FIG. 95A

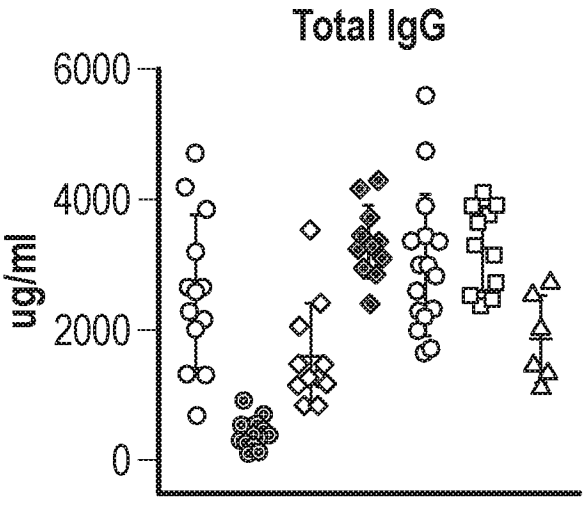


FIG. 95B

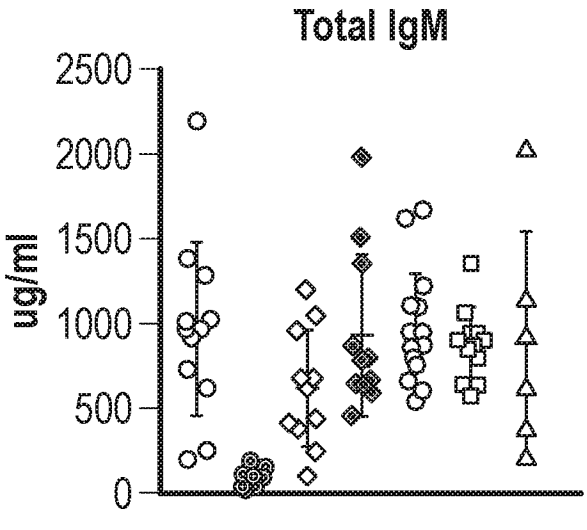


FIG. 95C

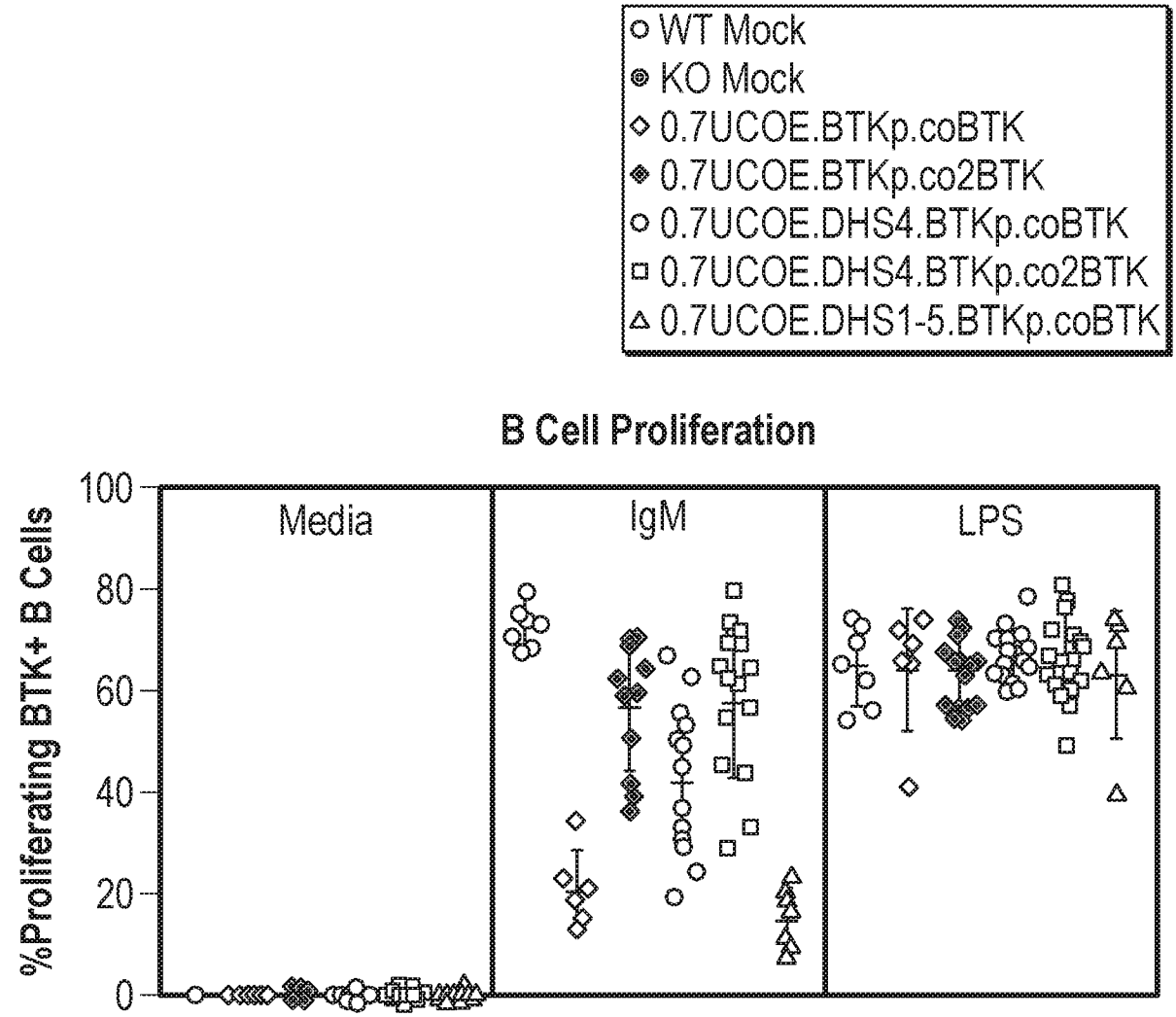


FIG. 95D

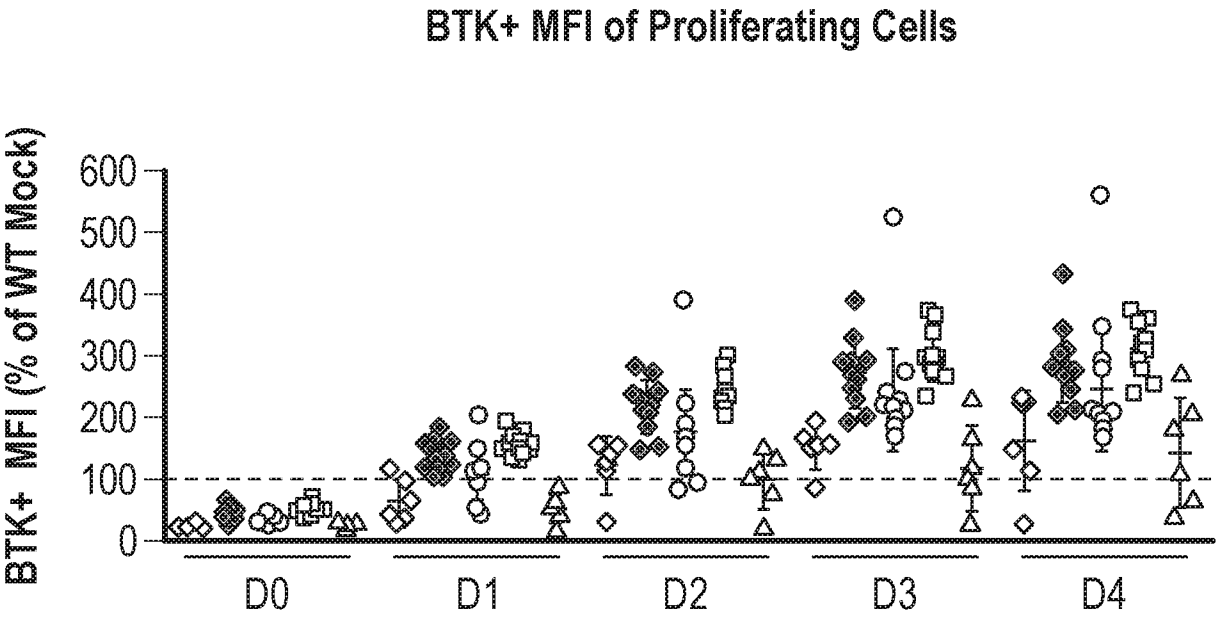


FIG. 95E

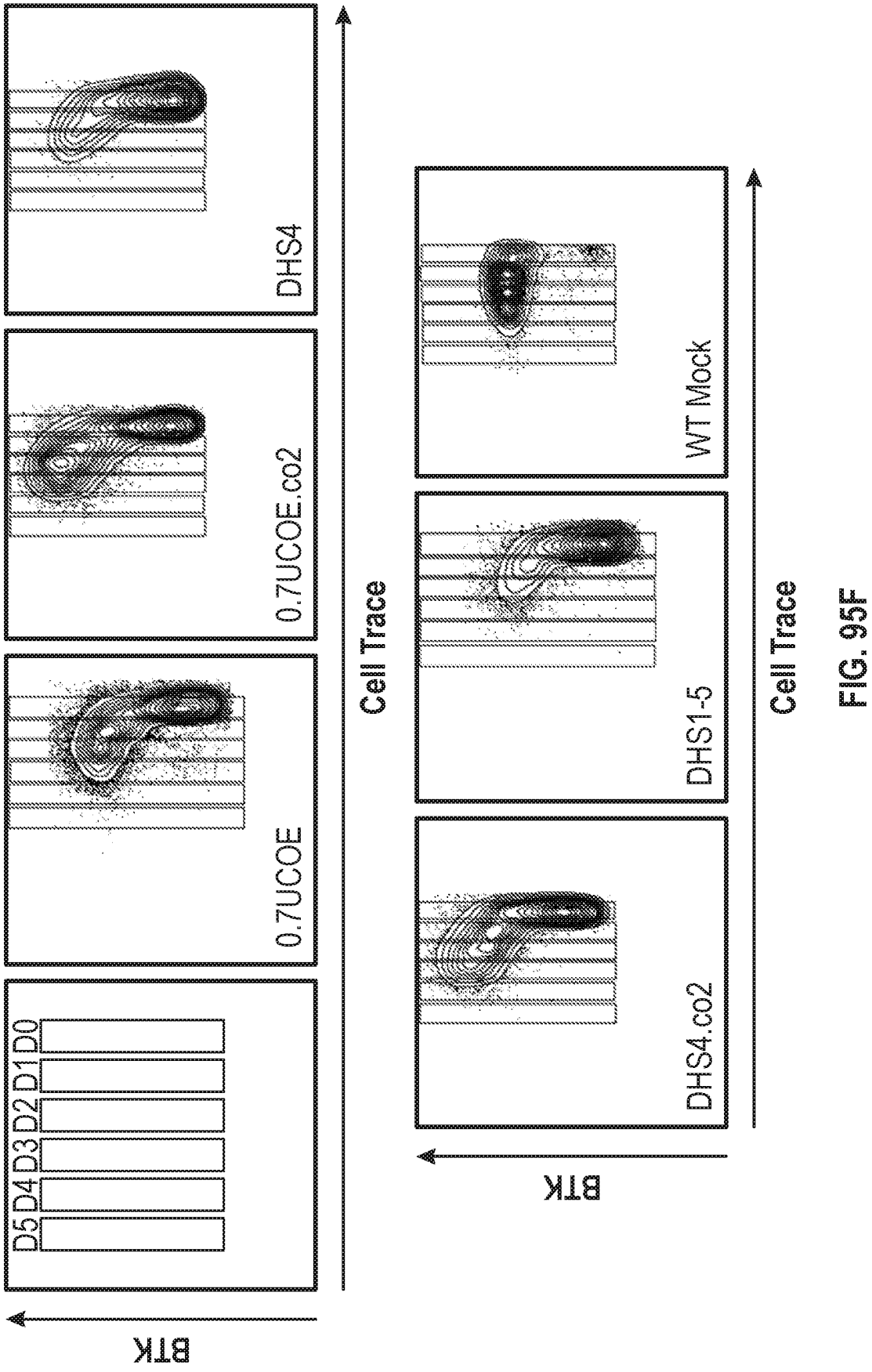

D5
D4
D3
D2
D1
D0
0.7UCOE
0.7UCOE.co2
DHS4
BTK
Cell Trace
DHS4.co2
DHS1-5
WT Mock
BTK
Cell Trace

FIG. 95F

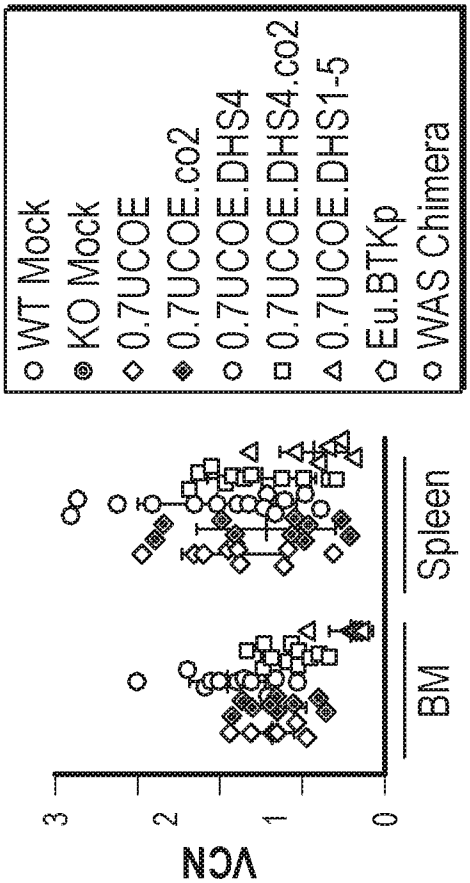
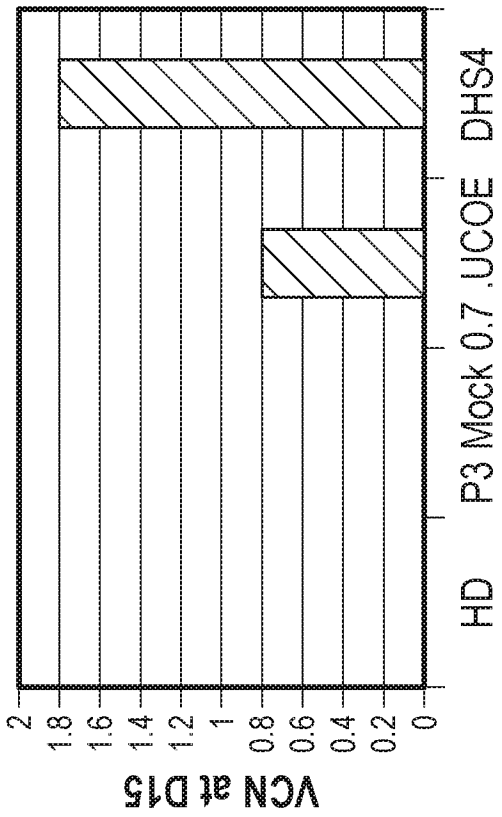


FIG. 96C



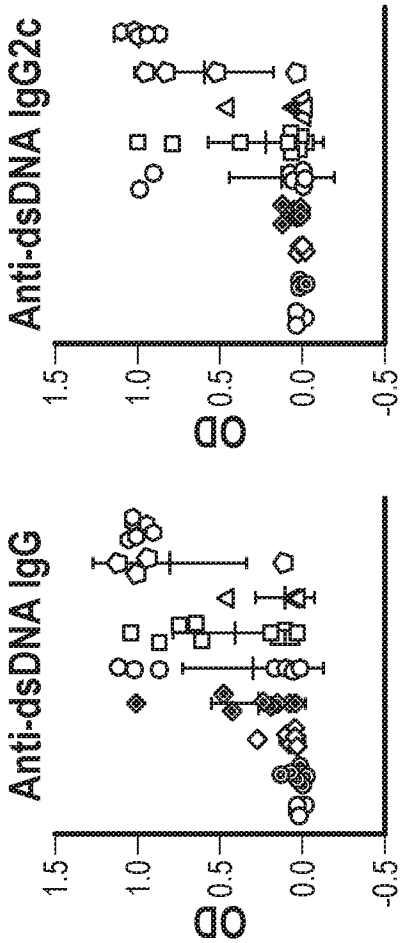


FIG. 96B

FIG. 96A

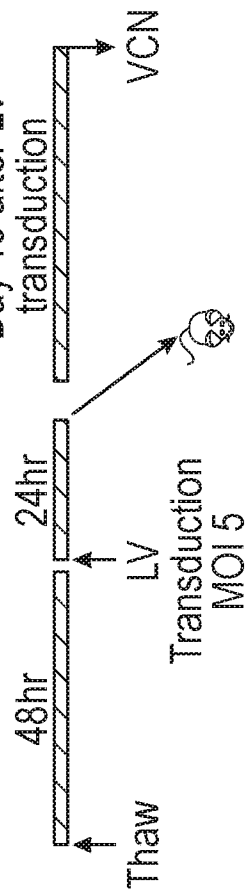


FIG. 97

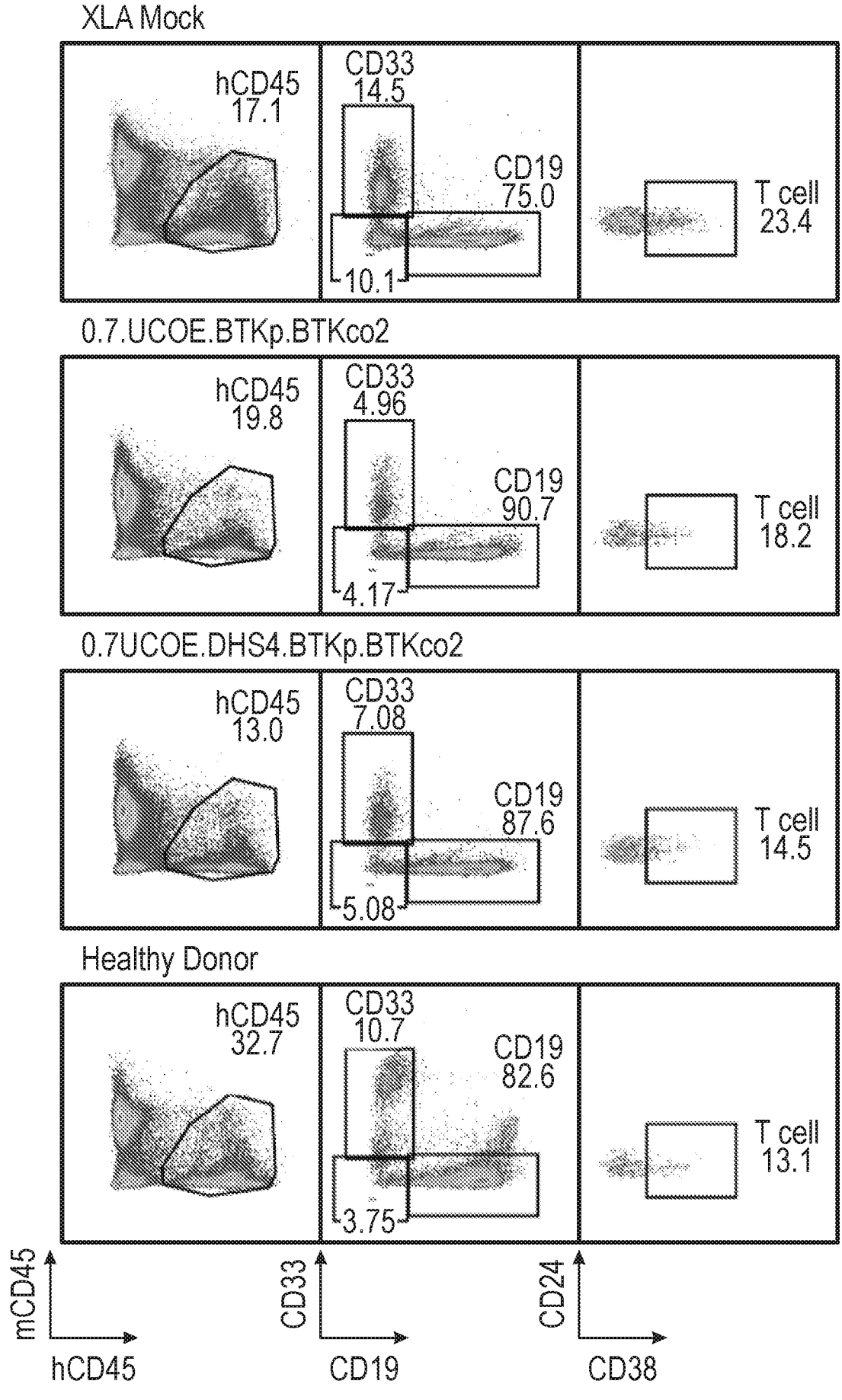

XLA Mock
hCD45
17.1
CD33
14.5
CD19
75.0
10.1
T cell
23.4
0.7.UCOE.BTKp.BTKco2
hCD45
19.8
CD33
4.96
CD19
90.7
4.17
T cell
18.2
0.7UCOE.DHS4.BTKp.BTKco2
hCD45
13.0
CD33
7.08
CD19
87.6
5.08
T cell
14.5
Healthy Donor
hCD45
32.7
CD33
10.7
CD19
82.6
3.75
T cell
13.1
mCD45
hCD45
CD33
CD19
CD24
CD38

FIG. 98A

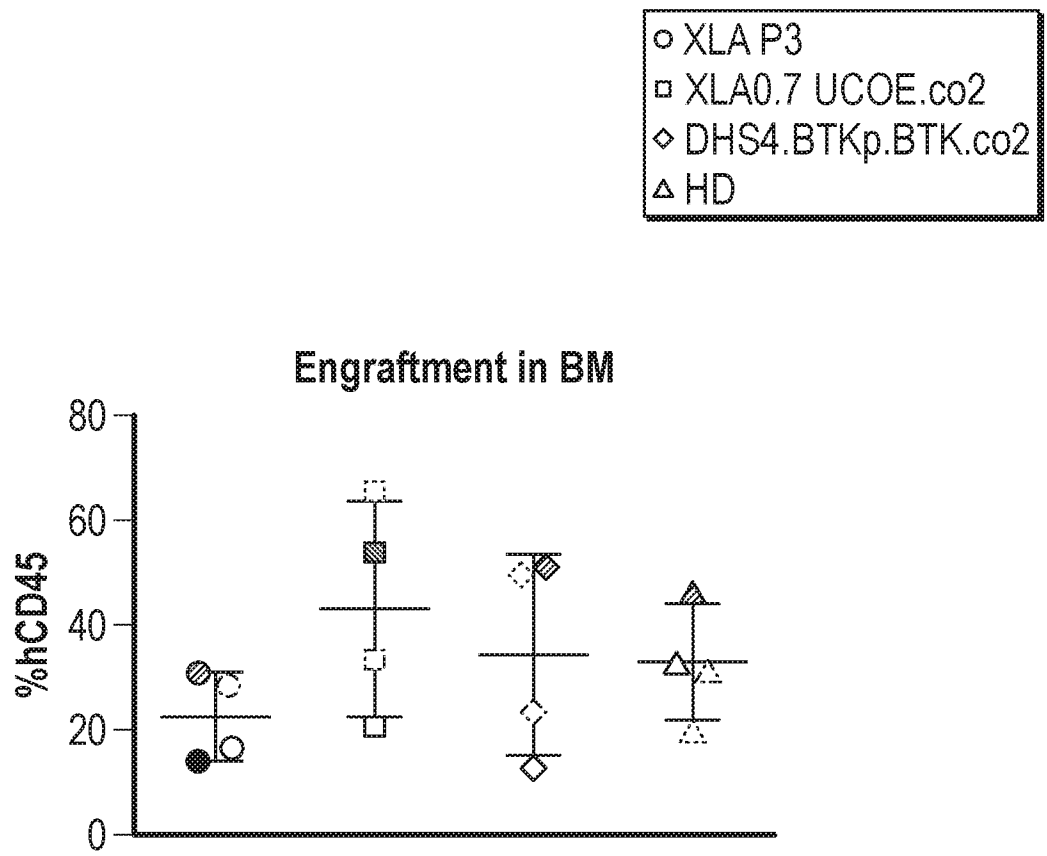


FIG. 98B

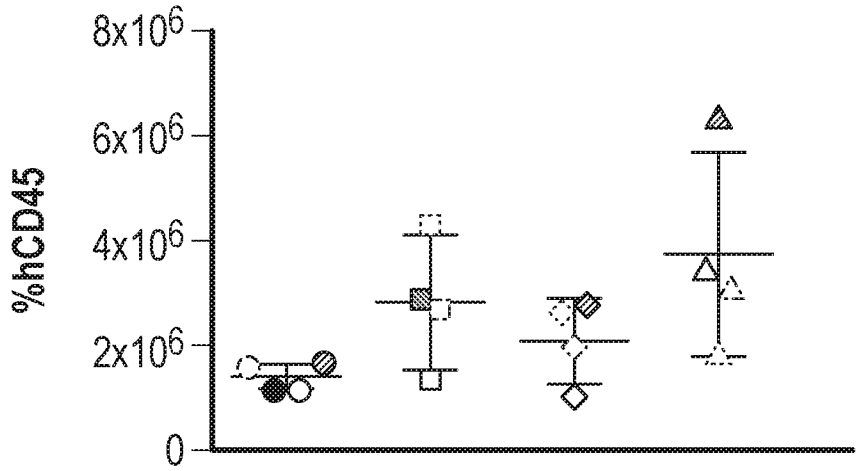


FIG. 98C

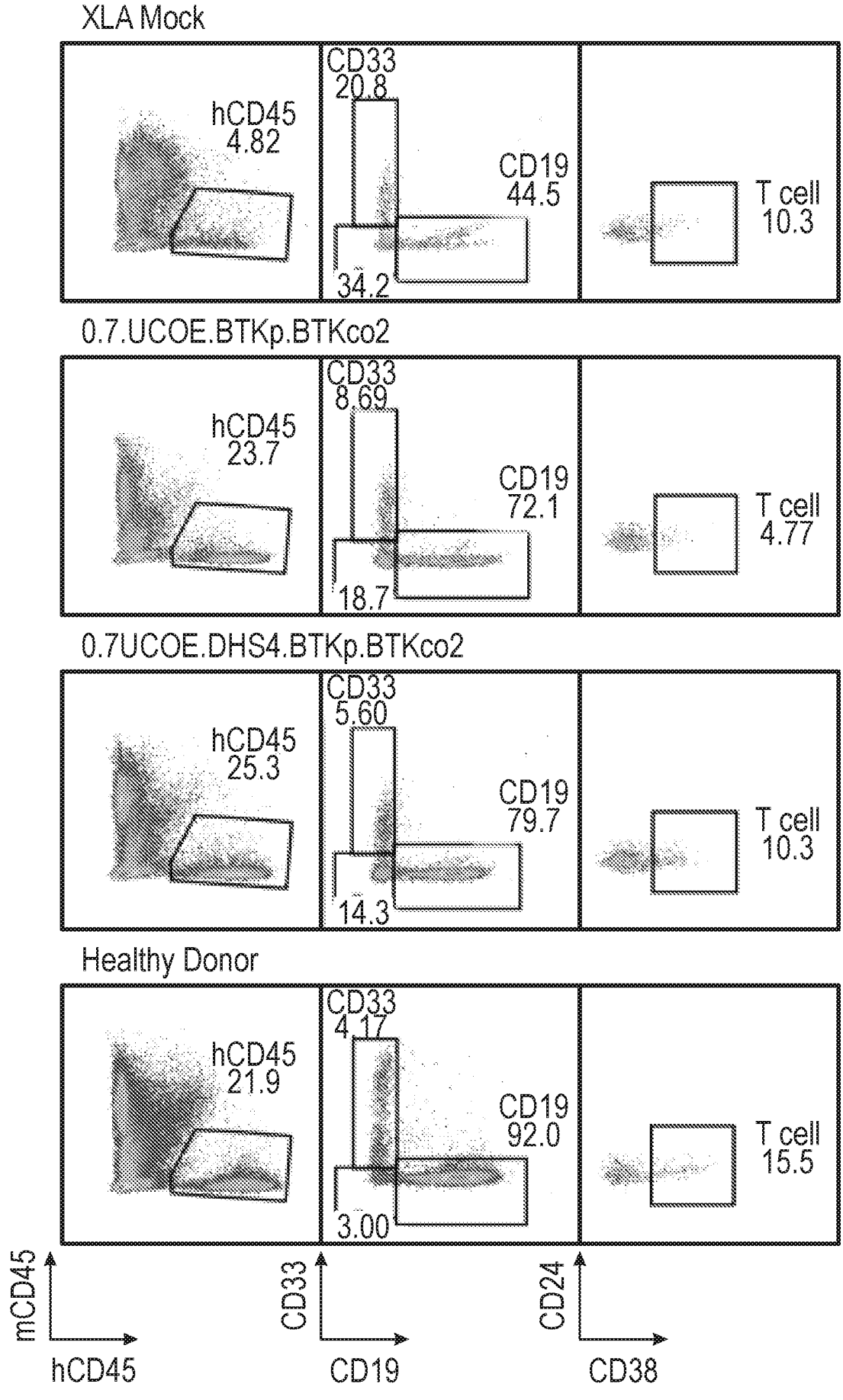

XLA Mock
hCD45
4.82
CD33
20.8
CD19
44.5
34.2
T cell
10.3
0.7.UCOE.BTKp.BTKco2
hCD45
23.7
CD33
8.69
CD19
72.1
18.7
T cell
4.77
0.7UCOE.DHS4.BTKp.BTKco2
hCD45
25.3
CD33
5.60
CD19
79.7
14.3
T cell
10.3
Healthy Donor
hCD45
21.9
CD33
4.17
CD19
92.0
3.00
T cell
15.5
mCD45
hCD45
CD33
CD19
CD24
CD38

FIG. 99A

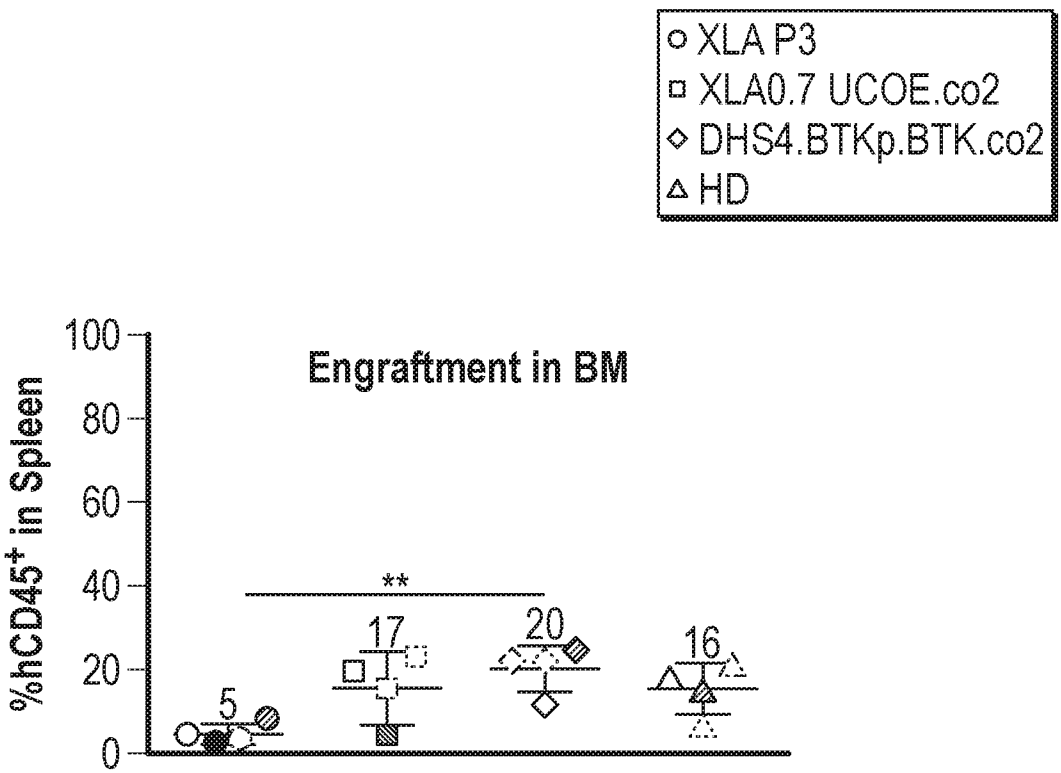


FIG. 99B

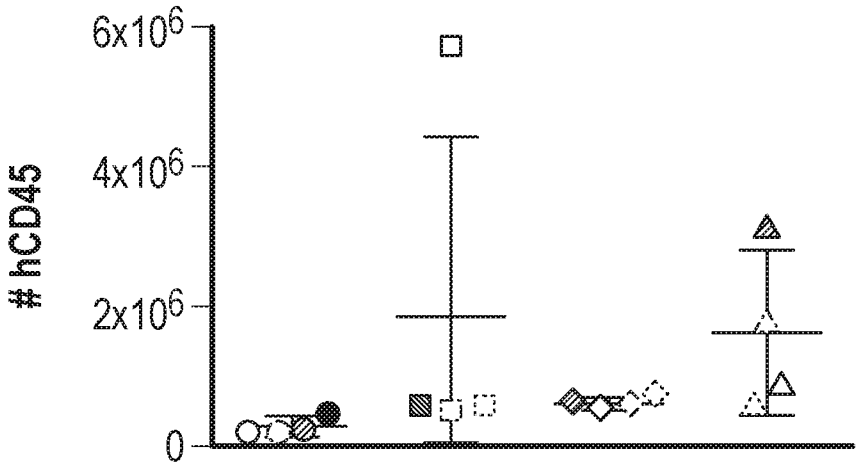
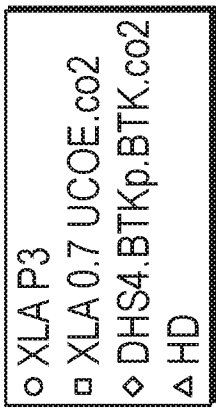


FIG. 99C



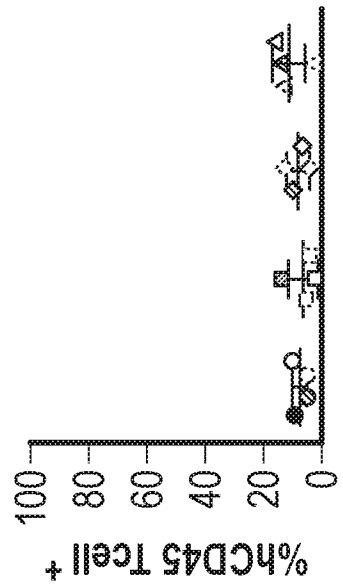


FIG. 100C

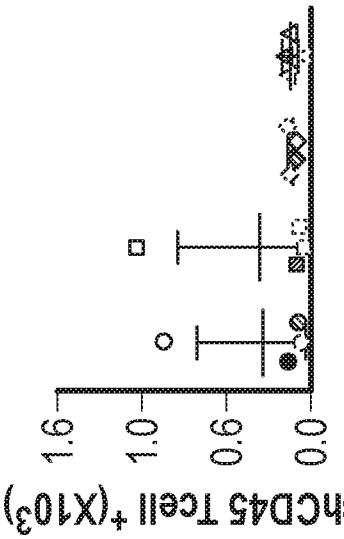


FIG. 100F

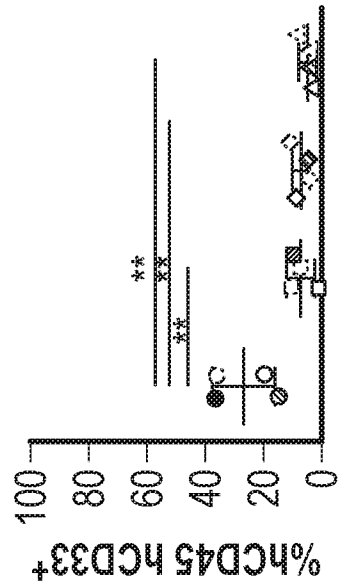


FIG. 100B

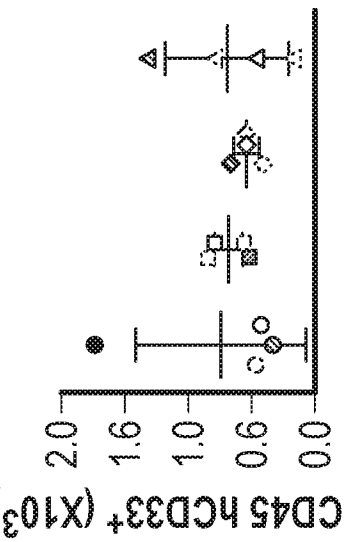


FIG. 100E

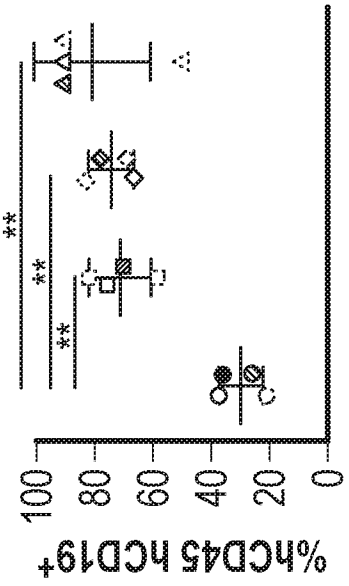


FIG. 100A

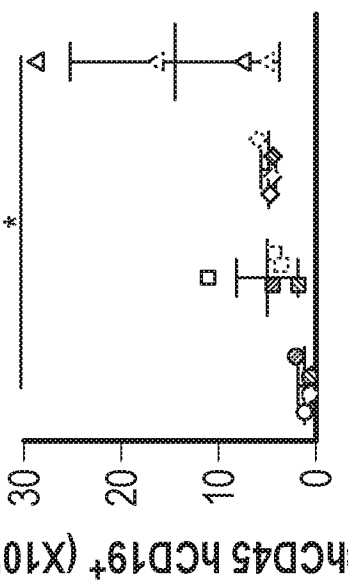


FIG. 100D

120/131

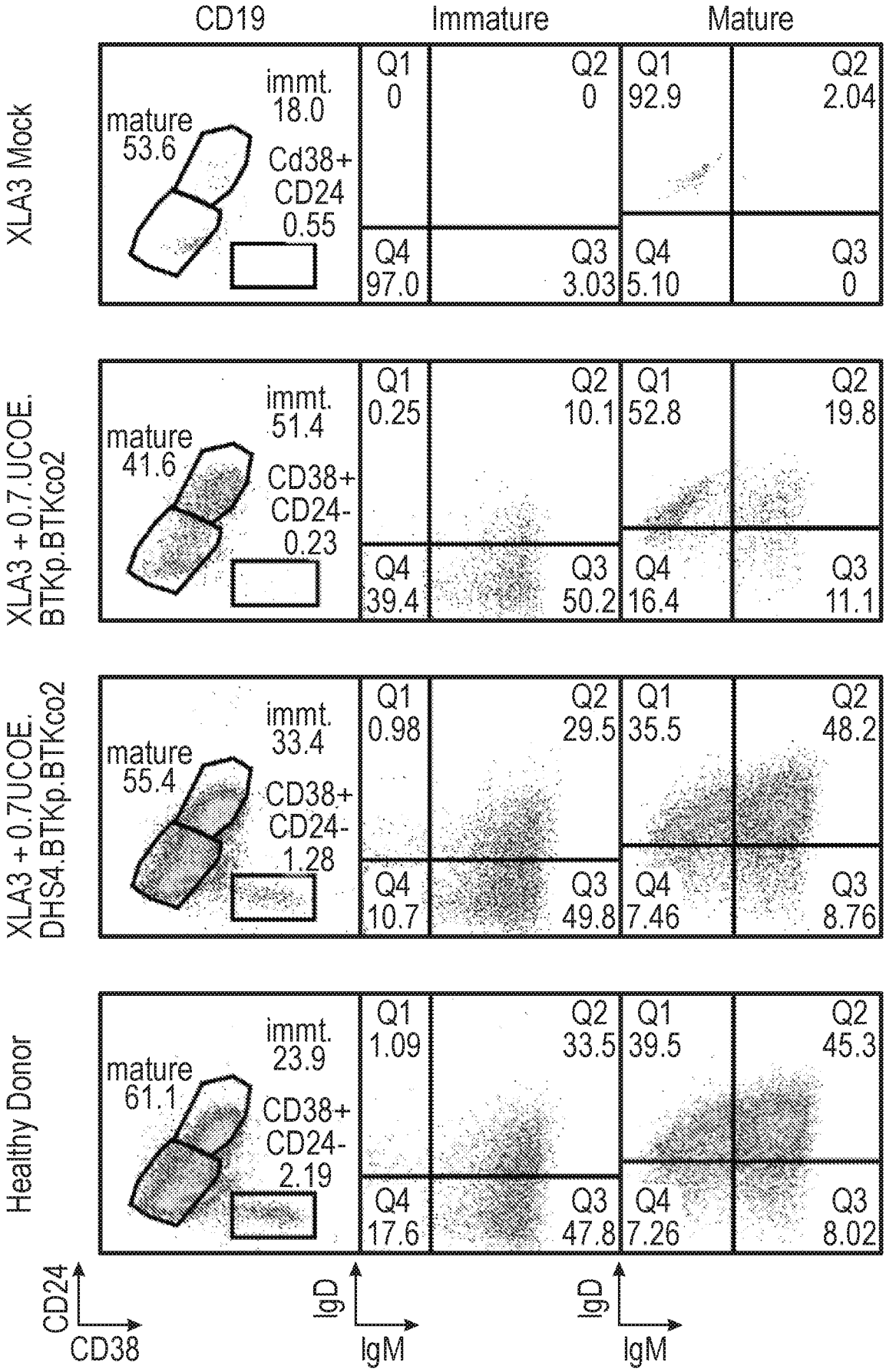


FIG. 101-1

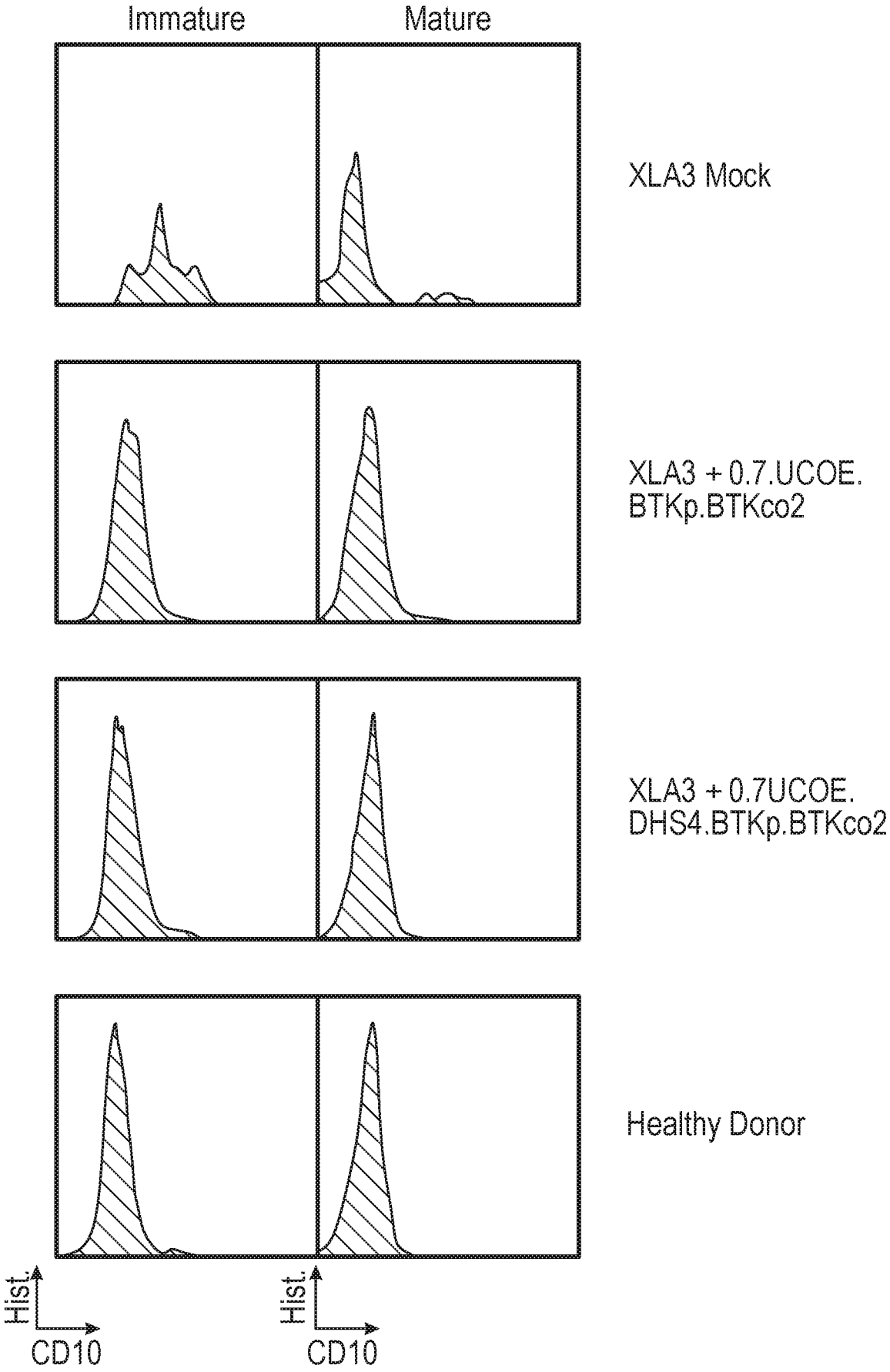
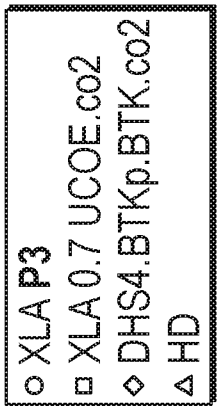

Immature
Mature
XLA3 Mock
XLA3 + 0.7.UCOE.
BTKp.BTKco2
XLA3 + 0.7UCOE.
DHS4.BTKp.BTKco2
Healthy Donor
Hist.
CD10
Hist.
CD10

FIG. 101-2



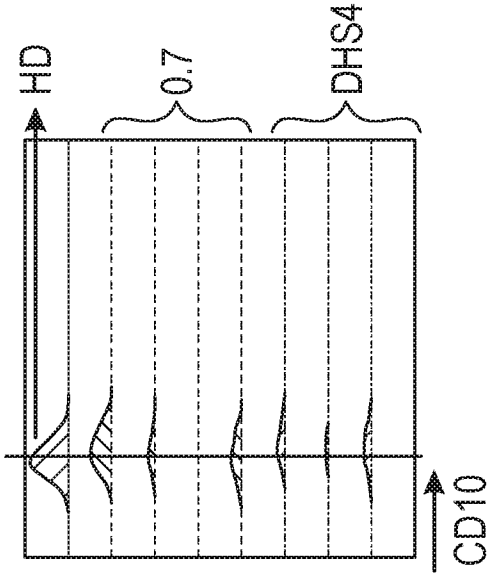


FIG. 102E

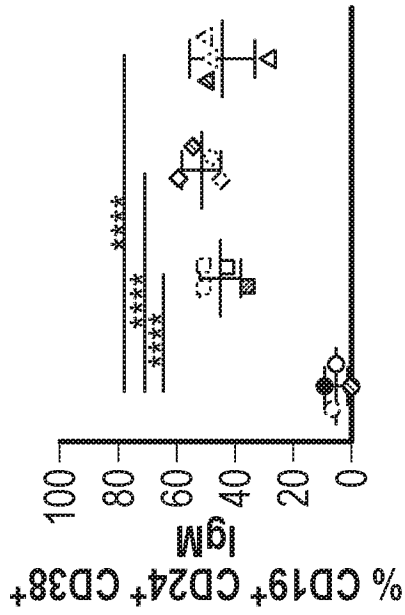


FIG. 102B

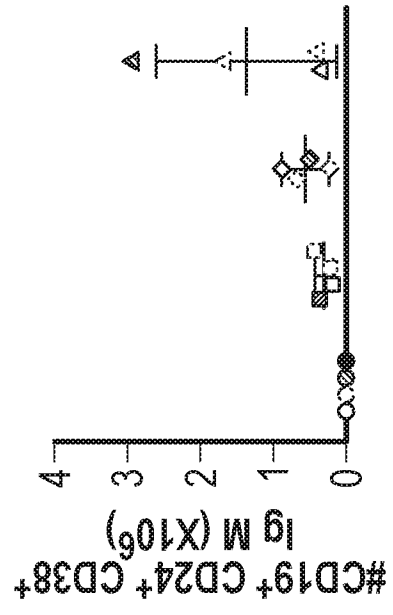


FIG. 102D

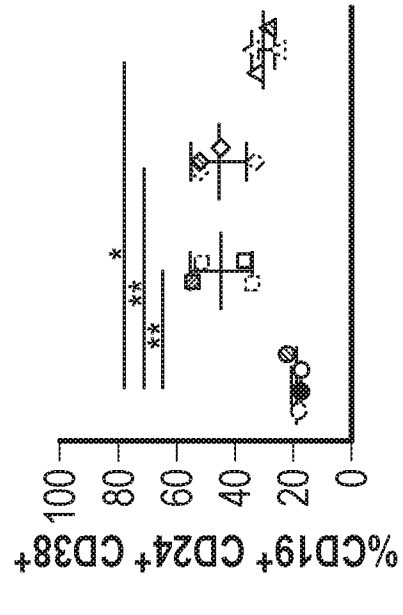


FIG. 102A

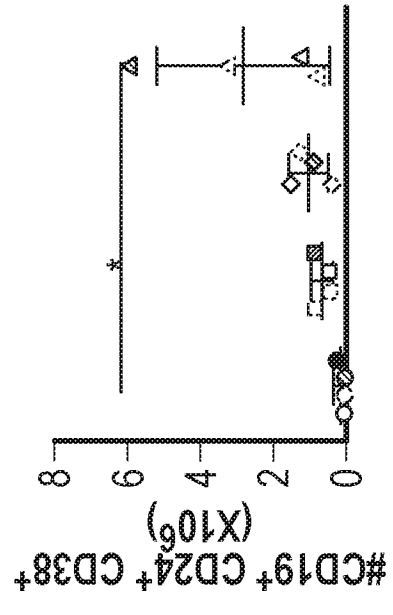
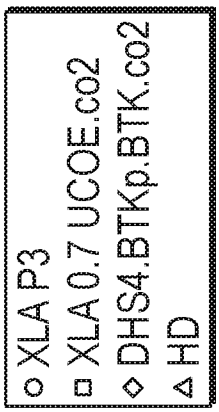


FIG. 102C



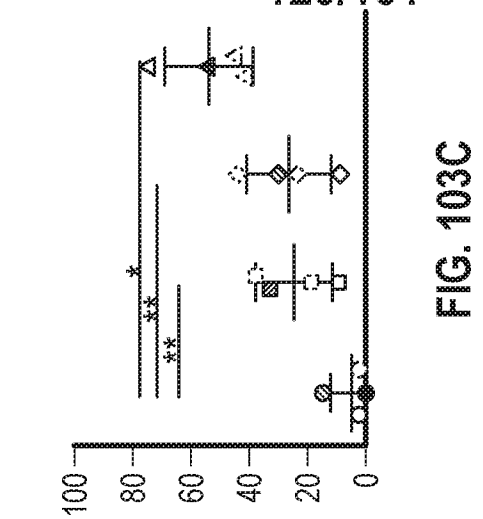


FIG. 103C

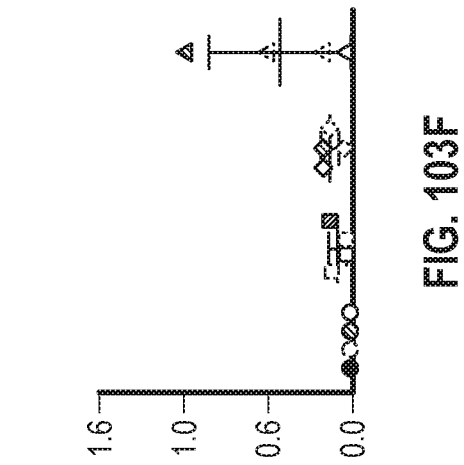


FIG. 103F

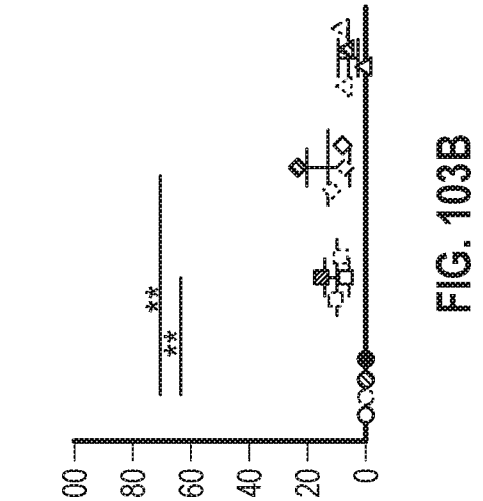


FIG. 103B

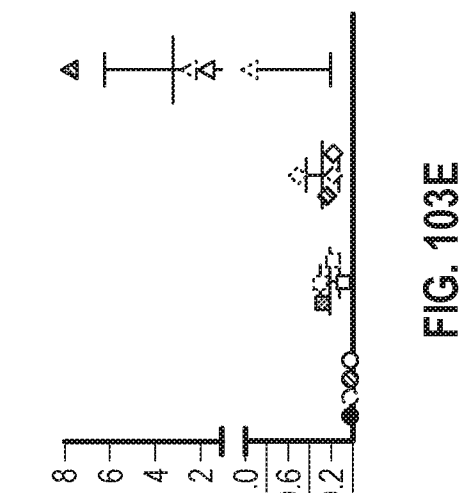


FIG. 103E

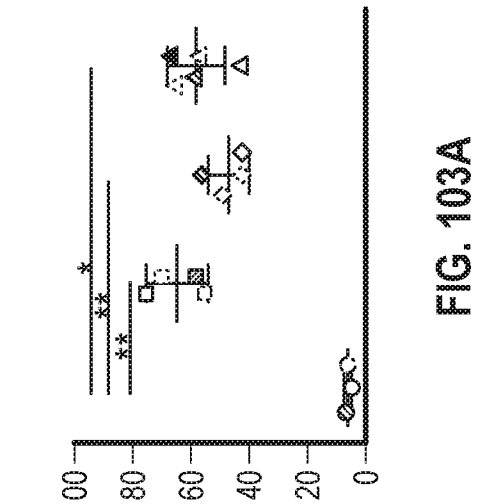


FIG. 103A

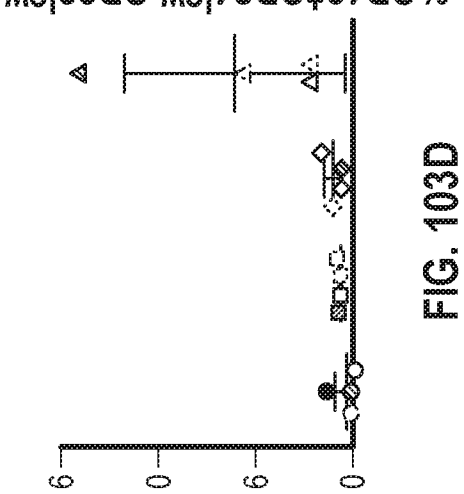


FIG. 103D

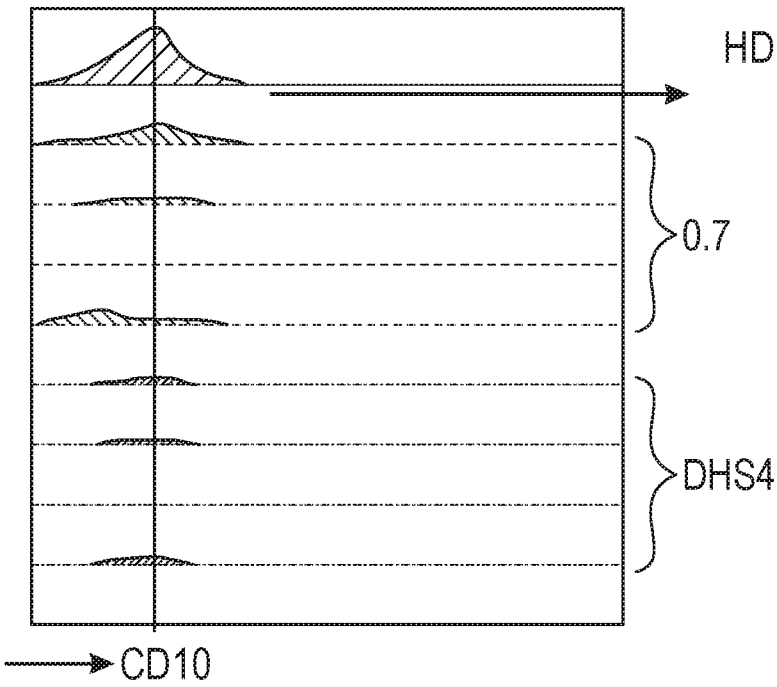


FIG. 103G

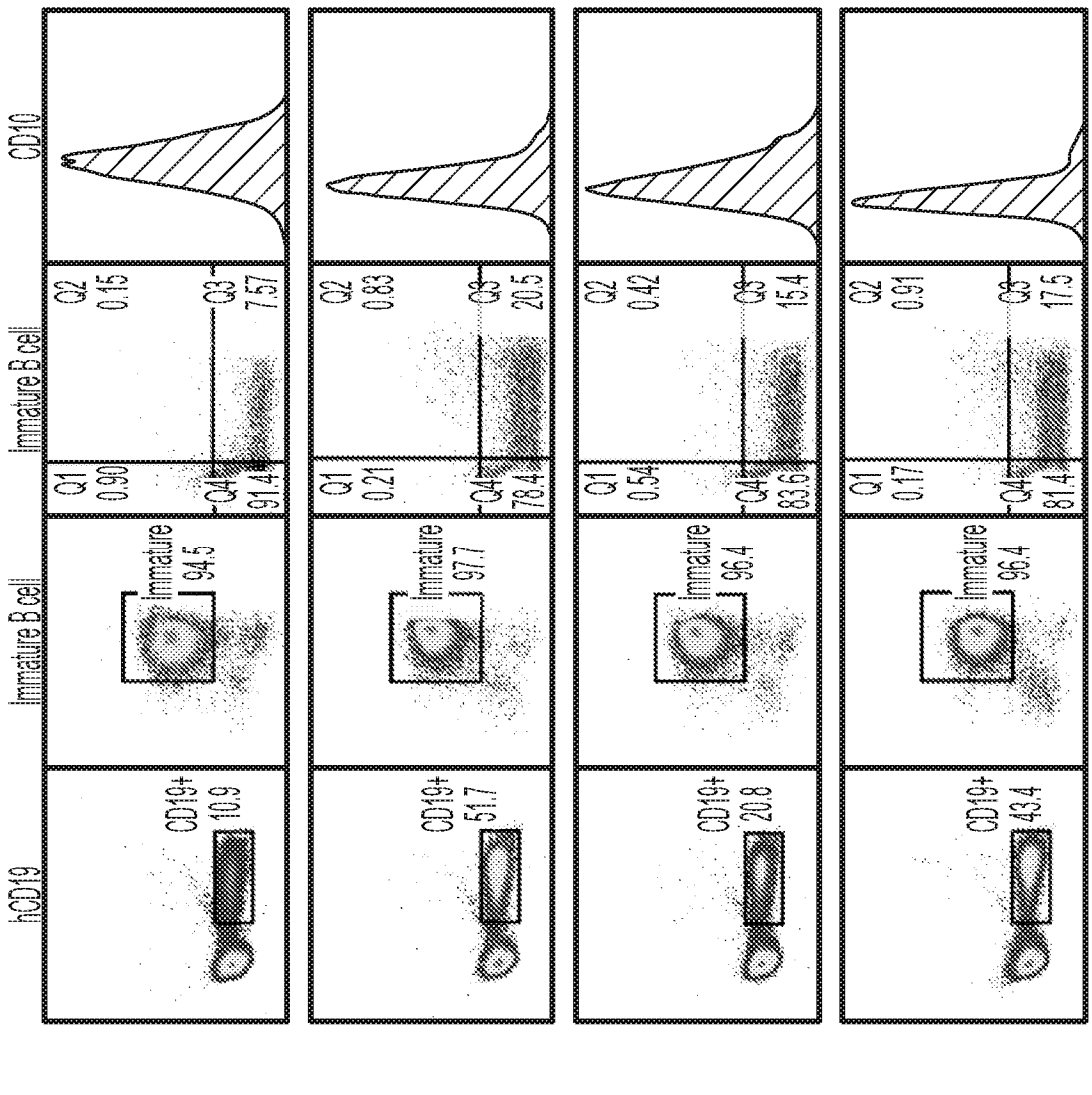
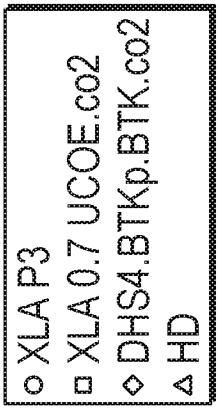

XLA3 Mock
XLA3+0.7.UCOE BTKp.BTKco2
XLA3+0.7.UCOE DHS4.BTKp.BTKco2
Healthy Donor
hCD19
Immature B cell
CD10
CD19+ 10.9
Immature 94.5
Q1 0.90
Q2 0.15
Q3 7.57
Q4 91.4
CD19+ 51.7
Immature 97.7
Q1 0.21
Q2 0.83
Q3 20.5
Q4 78.4
CD19+ 20.8
Immature 96.4
Q1 0.54
Q2 0.42
Q3 15.4
Q4 83.6
CD19+ 43.4
Immature 96.4
Q1 0.17
Q2 0.91
Q3 17.5
Q4 81.4
SSC-A
hCD19
CD24
CD38
IgD
hCD19M
Mat
CD10

FIG. 104



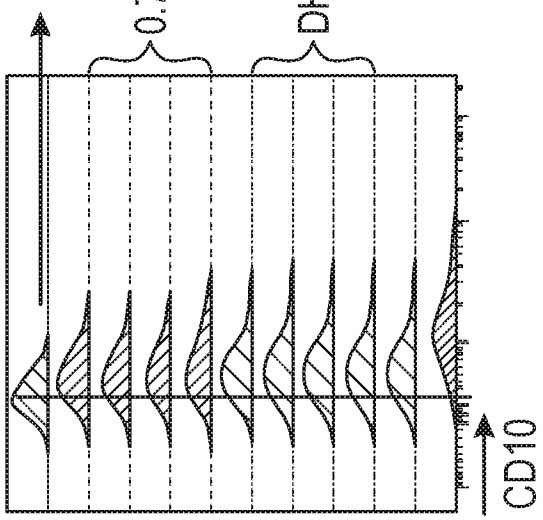


FIG. 105E

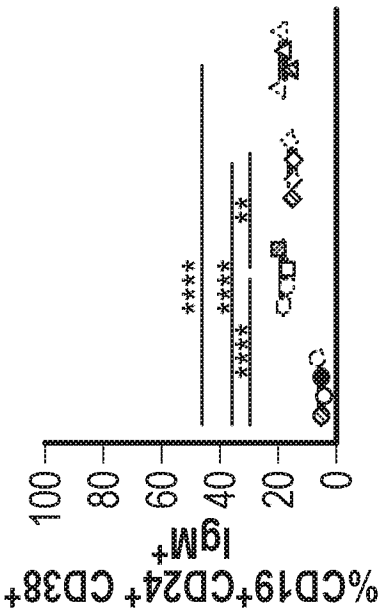


FIG. 105B

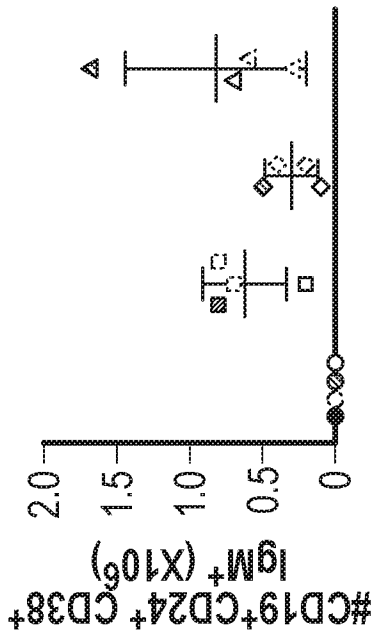


FIG. 105D

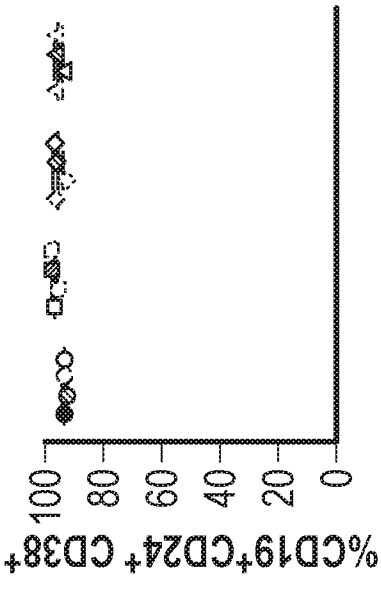


FIG. 105A

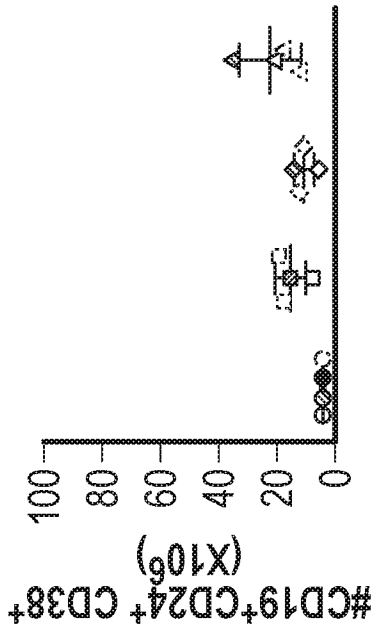


FIG. 105C

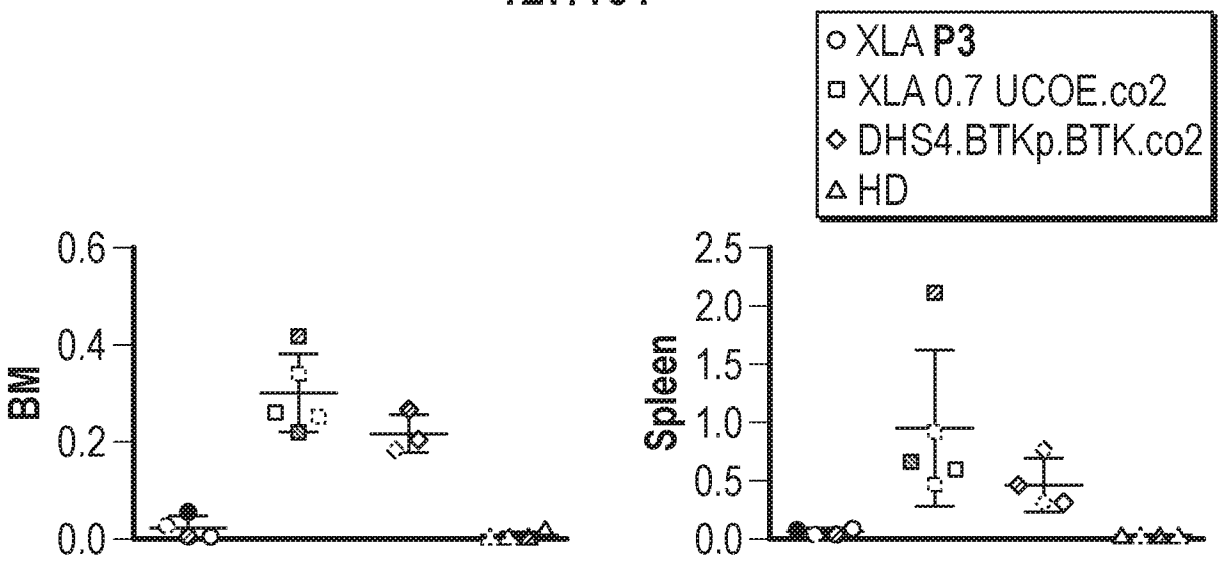


FIG. 106A FIG. 106B

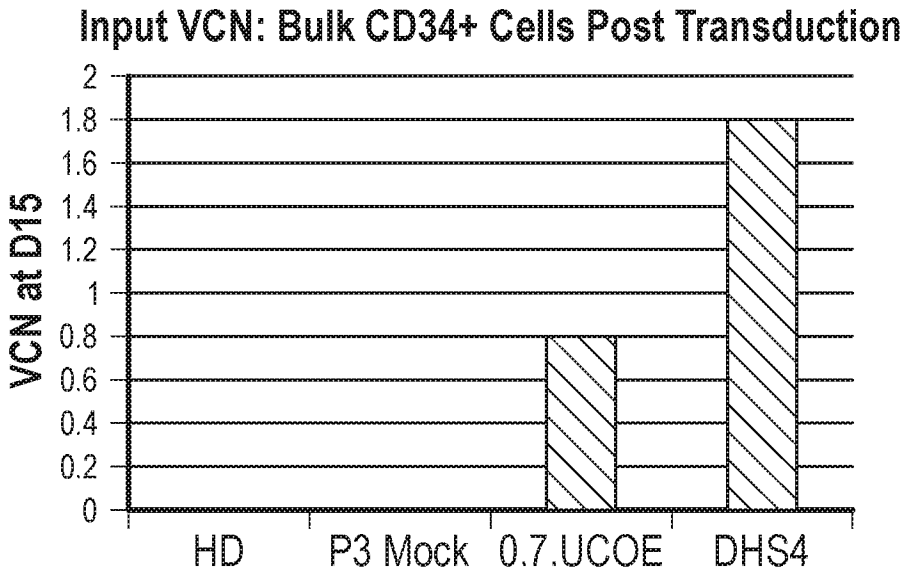


FIG. 106C

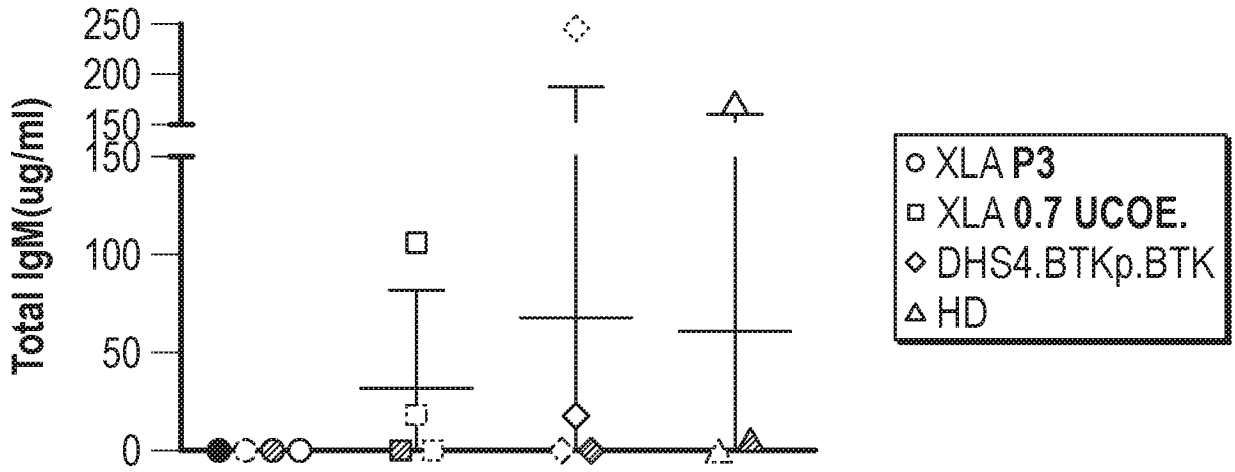


FIG. 107

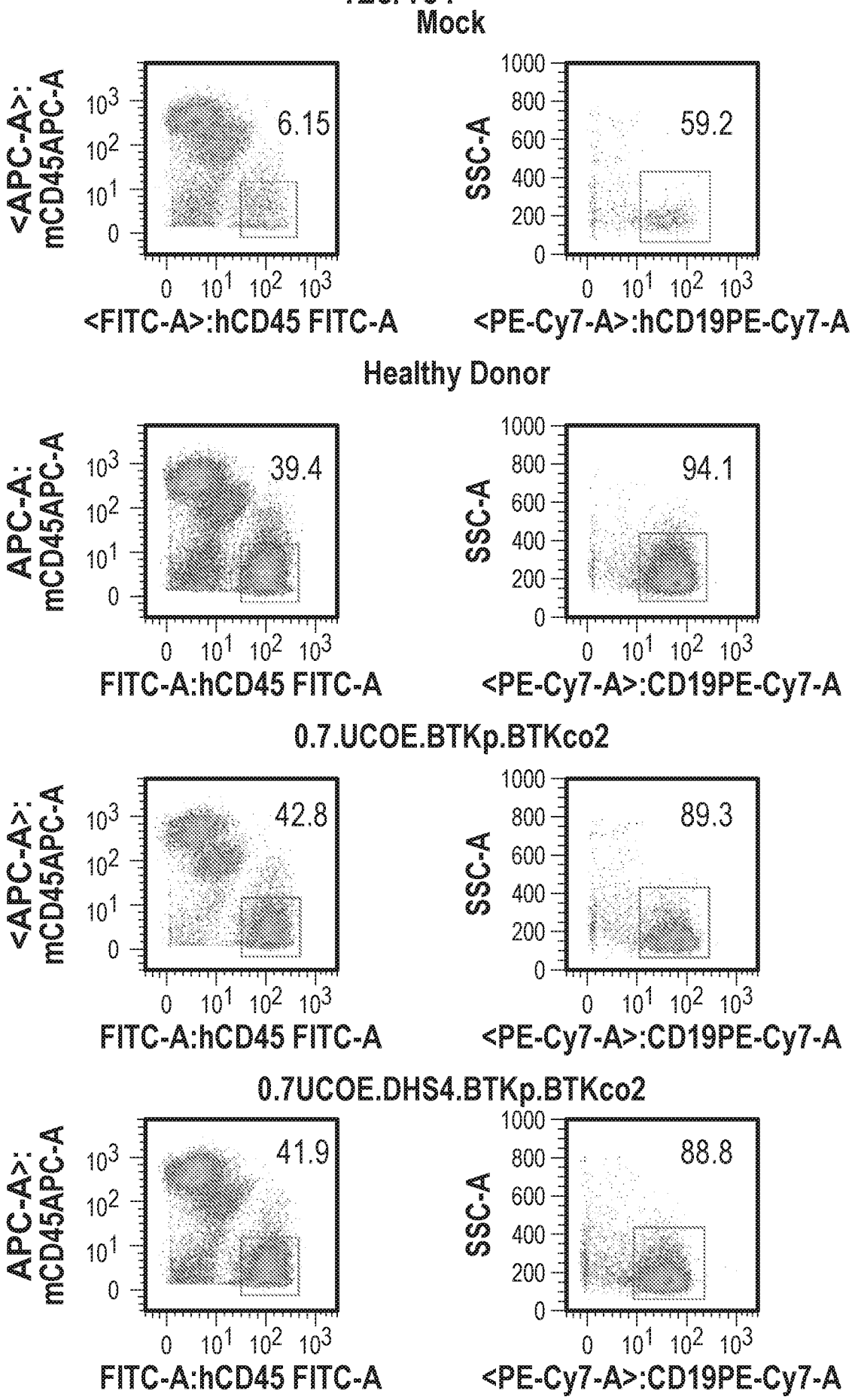

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FIG. 108A

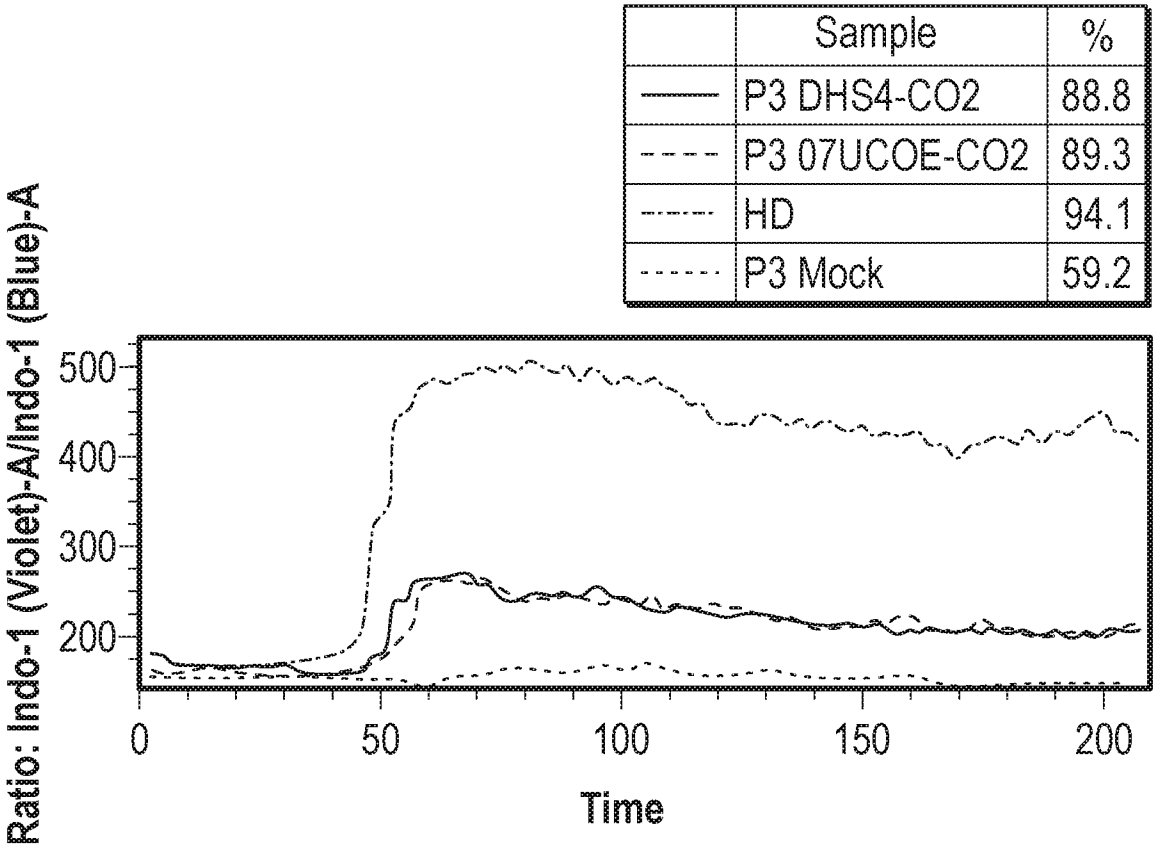

FIG. 108B

Methods: B Cell differentiation Protocol

3 .- Step plasma cell differentiation culture system:

Starting cells: 0.5 x 10^6 cells from NSG recipient spleen

Basic culture media throughout: IMDM + 10% FBS + BME-and cytokines listed below:

(Phase I; 7 days) MegaCD40L(100 ng/mL) + CpG ODN 2006 (1μg/mL) + IL-2 (50 ng/mL) + IL-10 (50 ng/ml) + IL-15 (10 ng/mL)

(Phase II; 3 days) IL-2 (50 ng/mL) + IL-6 (50 ng/mL) + IL-10 (50 ng/ml) + IL-15 (10 ng/mL)

Phase III; 4 days) IL-6 (50 ng/mL) + IL-15 (10 ng/mL) + IFN-α 2B (100 U/mL)

Notes: Double the culture volume after Day 1 and maintain cell density at 1 x 10^6 cells/mL thereafter (or double culture volume every two days); PBS wash before switching cytokines (especially between steps I and II).

FIG. 109

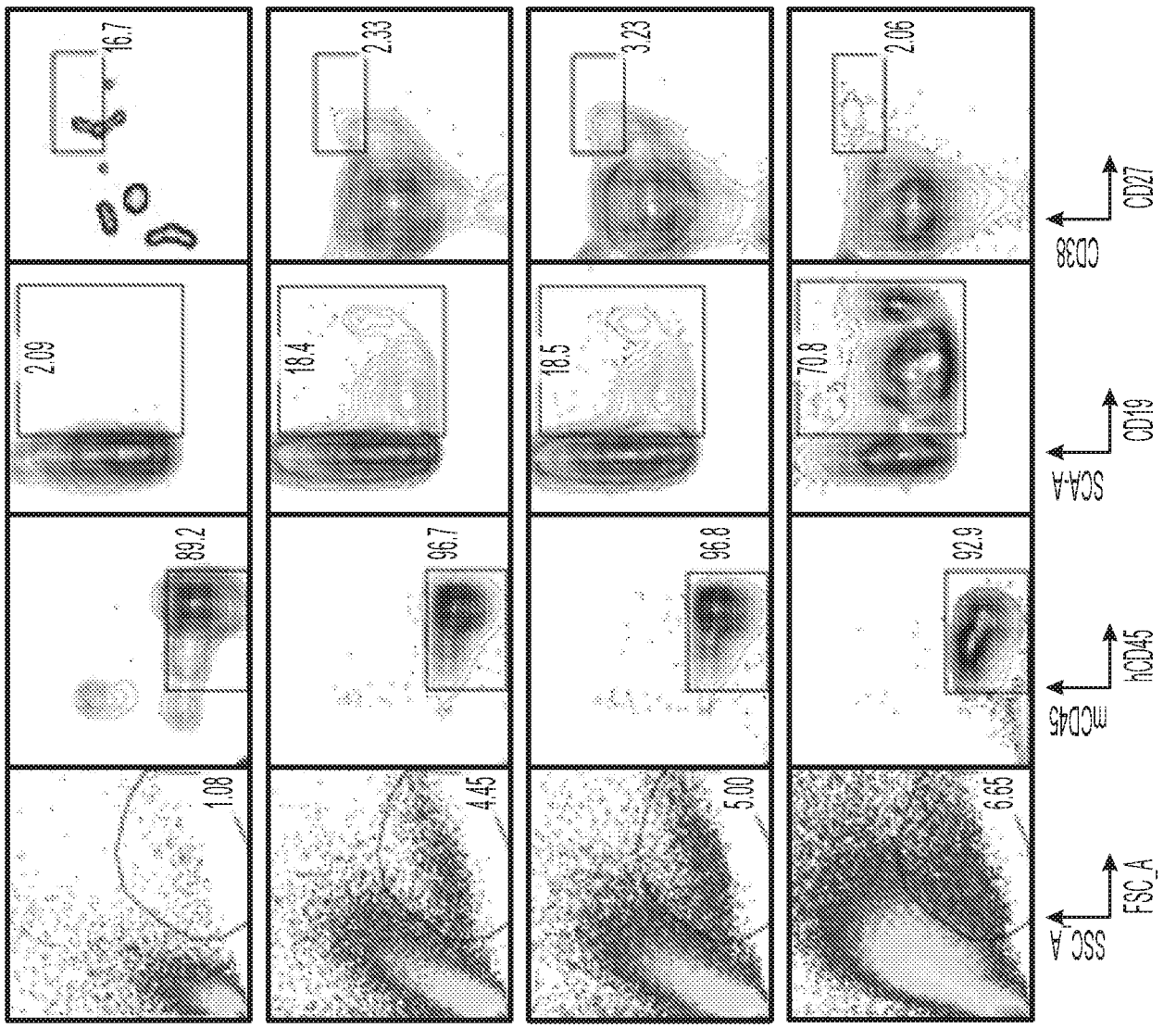
XLA3 Mock
XLA3 + LV 0.7UCOE. BTKp.BTKco2
XLA3 + LV 0.7UCOE. DHS4.BTKp.BTKco2
Healthy Donor
1.08
89.2
2.09
16.7
4.45
96.7
18.4
2.33
5.00
96.8
18.5
3.23
6.55
92.9
70.8
2.06
SSC_A
FSC_A
mCD45
hCD45
SCA-A
CD19
CD38
CD27

FIG. 110

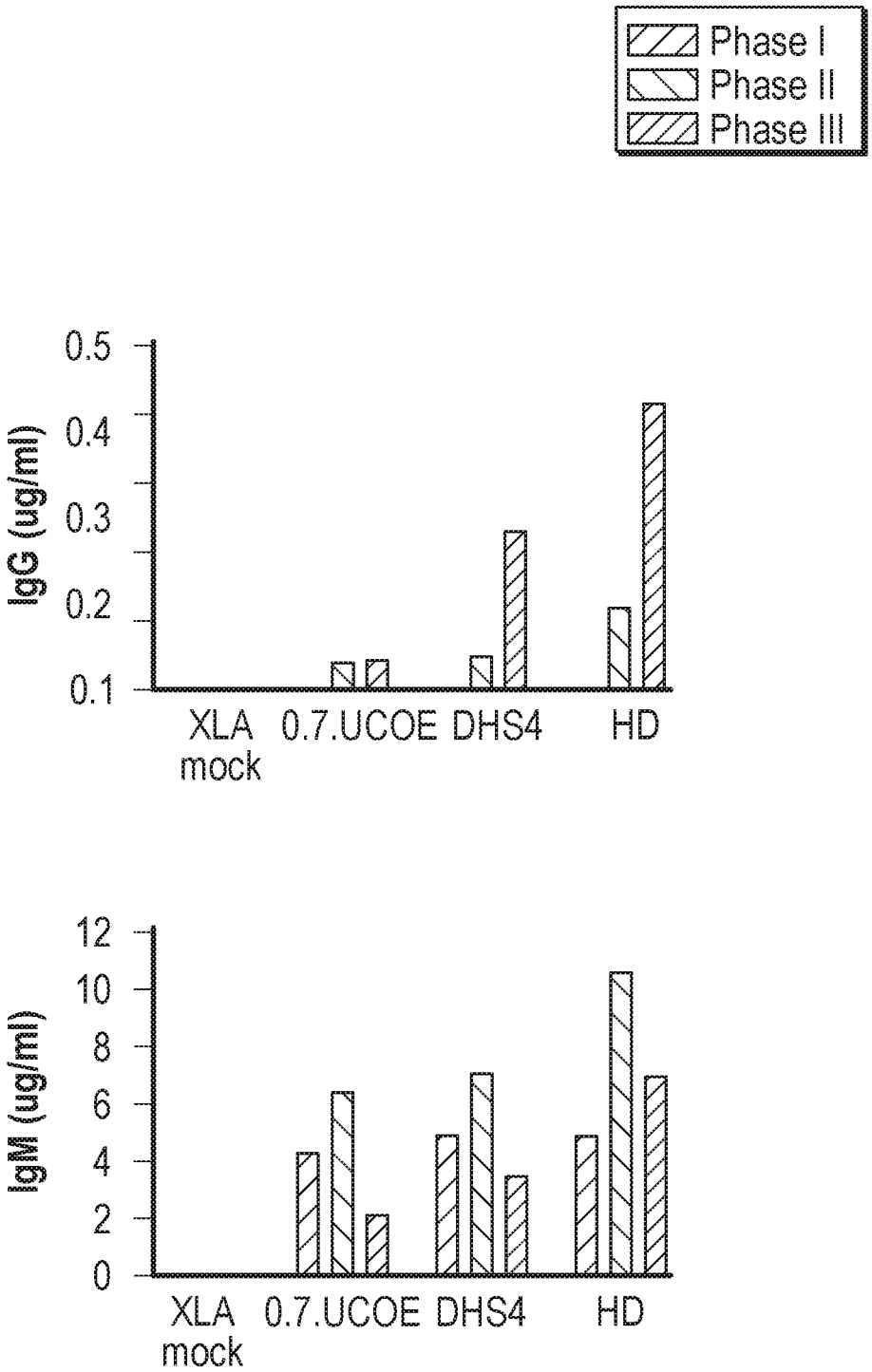
Phase I
Phase II
Phase III
IgG (ug/ml)
0.5
0.4
0.3
0.2
0.1
XLA mock
0.7.UCOE
DHS4
HD
IgM (ug/ml)
12
10
8
6
4
2
0
XLA mock
0.7.UCOE
DHS4
HD

FIG. 111

SEQUENCE LISTING

<110> Rawlings, David J.
Sommer, Karen

<120> OPTIMIZED LENTIVIRAL VECTOR FOR XLA GENE THERAPY

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<150> 62/488523
<151> 2017-04-21

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<211> 2282
<212> DNA
<213> Artificial Sequence

<220>
<223> >ABCD

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<212> DNA
<213> Artificial Sequence

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<213> Artificial Sequence

<220>
<223> >AB

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<212> DNA
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<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> >B

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<210> 21
<211> 1645
<212> DNA
<213> Artificial Sequence

<220>
<223> >BTKe

<400> 21
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<212> DNA
<213> Artificial Sequence

<220>
<223> >BTKe?Myc

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<210> 23
<211> 1565
<212> DNA
<213> Artificial Sequence

<220>
<223> >BTKp.GFP

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<210> 24
<211> 2798
<212> DNA
<213> Artificial Sequence

<220>
<223> INT4.BTKp.GFP

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<210> 25
<211> 2735
<212> DNA
<213> Artificial Sequence

<220>
<223> INT5.BTKp.GFP

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