



(51) International Patent Classification:

A61K 47/64 (2017.01)

(21) International Application Number:

PCT/US2019/038264

(22) International Filing Date:

20 June 2019 (20.06.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/688,468 22 June 2018 (22.06.2018) US

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(81) Designated States (unless otherwise indicated, for every

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

(84) Designated States (unless otherwise indicated, for every

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

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: ANTIBODY LINKED PEPTIDE BASED IMMUNOTHERAPY FOR TYPE 1 DIABETES

(57) Abstract: Embodiments of the disclosure include methods and compositions related to preventing or delaying onset of an autoimmune disease, including at least Type I Diabetes. In specific embodiments, methods and compositions are related to (a) an antibody that targets dendritic cells and/or Foxp3⁺ cells; linked to (b) a peptide or fusion of peptides, wherein the peptides are pancreatic beta cell antigens or is an autoimmune antigen-derived peptide.



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Antibody Linked Peptide Based Immunotherapy for Type 1 Diabetes**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 62/688468, filed June 22, 2018, which is incorporated by reference herein in its entirety.

**STATEMENT REGARDING FEDERALLY SPONSORED
RESEARCH OR DEVELOPMENT**

[0002] This invention was made with government support under K22 AI104761-02 awarded by National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[0003] Embodiments of the disclosure include at least the fields of molecular biology, cell biology, immunology, and medicine.

BACKGROUND

[0004] Both central and peripheral tolerance mechanisms are crucial in preventing the onset of autoimmunity. Normally, tissue-specific antigens (TSAs) are presented by autoimmune regulator (Aire) and Fezf2 expressing thymic medullary epithelial cells (mTECs) to aide in the deletion of self-reactive thymocytes (1, 2). These mTECs can also cross present antigens, including insulin peptides, to thymic resident dendritic cells (DCs) to help delete self-reactive T cells and establish central tolerance (3). Dendritic cells and Aire expressing mTECs are also essential in generating thymically derived Foxp3+ regulatory T cells (Tregs) and promoting self-tolerance (4, 5). Indeed, there appears to be a correlation between a reduction in dendritic cell (DC) numbers and residual β cell function in Type 1 diabetic (T1D) subjects (6), while in the NOD mouse there is an overall reduction in dendritic cells (7, 8), suggesting a relationship between self-tolerance and the absolute number of DCs present in the thymus and periphery.

[0005] Importantly, studies have shown that the generation of thymic regulatory T cells by antigen presenting mTECs and DCs early in life (neonatal) is critical in maintaining tolerance to self-antigens (5, 9). However, not all peripheral antigens are expressed by mTECs and therefore negative selection must also rely on peripheral antigen retrieval and delivery to the thymus by DCs. Besides insulin, Chromogranin A (ChgA) is the only other currently known β

cell antigen necessary for the initiation of autoimmune diabetes in the NOD mice; however, expression within mTECs has not yet been detected (10). Therefore, tolerance to ChgA may be due in part to peripheral dendritic cells presenting ChgA to developing and naive T cells. The recent revelation of post-translationally modified peptides (PTMs) such as insulin-chromogranin fusion peptide, allows exciting new approaches to study the development of β cell antigens in vivo using the NOD model.

[0006] Neo-antigen expression in β cells: The mechanisms behind the break in tolerance to self, allowing for the development of autoimmune diseases, appear to be multifaceted and poorly understood (10-12). Because of the demand on insulin producing β cells, oxidative and ER stress appear to be contributing factors in the initiation of T1D (13, 14). A consequence of cellular stress is the altered processing of proteins, such as changes in post-translational modifications (PTMs) by deamidation or proteolytic transpeptidation, which can lead to generation of tissue specific neo-antigens (15-18). Pathogenic T cells that are specific for neo-antigens uniquely expressed in the pancreas may escape thymic selection by a process known as ignorance (19).

[0007] Interestingly, Emil Unanue's group showed that insulin containing granules are highly immunogenic compared to artificially synthesized protein, suggesting that insulin-specific PTM takes place within the islet granules (20). For the dominant insulin epitope targeted in the NOD mice (B:9-23), the modification likely affects the MHC binding register of the peptide, resulting in stable binding of peptide in a register (register 3) that is normally unstable and very likely presented at low levels in the thymus (21). In support of this concept, John Kappler's group showed that a mimotope of the InsB₉₋₂₃ insulin peptide with a change in the MHC anchor residue (R22E) was highly stimulatory for insulin reactive T cells and was used to generate MHC:peptide tetramers to track this cells in vivo (22). Very recently, Kathryn Haskins' group demonstrated that PTMs allow for the formation of neo-antigens by fusion of the pro-insulin peptide with other peptides within β cells granules (23). Finally, Dr. Eddie James has shown that T cells specific for deamidated PTM β cell antigens are present at higher frequencies in T1D patients (17, 24). Deamidation can occur when tissue transglutaminase 2 (Tgase2) is activated during ER stress from the release of high Ca^{2+} levels. The activation of Tgase2 allows for it to translocate to secretory granules and modify peptides (25). However, it is still unknown to what extent PTM peptide bearing APCs can influence the development of autoreactive T cells and

protective T regulatory cells. To date there are no proven vaccine strategies that will halt the initiation and development of autoimmune Type 1 diabetes.

[0008] Since the success of exogenous insulin delivery, which can now provide close to normal life expectancy for T1D patients, it is understood that any improved treatments for T1D should have minimal risk to benefit ratio. Although immunotherapeutic interventions will inevitably be a part of any such treatment, most immunotherapeutic agents available to date are broad-spectrum, and as a result exhibit potentially risky side effects. Therefore, safe and efficacious immunotherapeutic interventions for T1D should be based on antigen-specific treatments or at least have a significant component that will direct the therapy specifically to self-antigen reactive cells. Many clinical trials are currently using whole proteins, peptides or tolerogenic dendritic cell strategies. Thus, there is a clear need in the art to design targeted and safe immunotherapies for autoimmune disease, and with the hope of halting and even preventing β islet cell destruction before it happens. The present disclosure satisfies such a need.

BRIEF SUMMARY

[0009] The present disclosure is directed to compositions, systems, and methods that prevent or delay the onset of one or more autoimmune diseases in an individual having, or at risk of having, an autoimmune disease. The individual may have, or be at risk of having, Type 1 diabetes, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, celiac sprue disease, pernicious anemia, vitiligo, scleroderma, psoriasis, Inflammatory bowel diseases, Addison's Disease, Graves' Disease, Sjögren's syndrome, or any other autoimmune disease, or a combination thereof. The individual may be of any age, such as an individual *in utero*, a neonatal individual, a pre-pubescent individual, a pubescent individual, or an adult. Some embodiments of the disclosure concern methods that are suitable for ameliorating one of more symptoms arising from the autoimmune disease, the cause of the autoimmune disease, or both. Some embodiments concern one or more compositions that may include (1) cellular therapies, such as native or modified cells; and/or (2) immunotherapies, such as antibodies or peptide-linked antibodies, for example. The compositions may target immune cells, such as dendritic cells and/or FoxP3⁺ cells, for example.

[0010] Many autoimmune diseases arise from T cells lacking the ability to recognize "self" antigens. These T cells then attack and destroy "self" cells in an individual, such as the individual having, or at risk of having, an autoimmune disease. At least some methods of the

present disclosure may decrease the T cells that lack “self” recognition. Decreasing these cells may ameliorate one or more symptoms and/or one or more causes of autoimmune diseases. The methods may also increase certain types of cells, including regulatory T (T_{reg}) cells, that regulate autoimmunity. Increasing T_{reg} cells may ameliorate one or more symptoms and/or one or more causes of one or more autoimmune diseases.

[0011] In some embodiments of the present disclosure, one or more compositions are administered to an individual having, or at risk of having, an autoimmune disease. The composition may comprise one or more types of cells, such as dendritic cells or FoxP3⁺ cells, and/or one or more types of compositions that can target immune cells in the individual. The composition may comprise an antibody or a conjugated antibody. The antibody, either alone or conjugated, may target any antigen or cell, such as an antigen or cell that is involved in autoimmunity, including directly or indirectly related to autoimmunity. The conjugated antibody may comprise an antibody that is conjugated to another molecule, such as a peptide, lipid, nucleic acid, small molecule, or any other molecule. The molecule conjugated to the antibody may be useful for T cell antigen recognition, including modifying T cell “self” antigen recognition. The antibody and molecule conjugated to the antibody may be linked in any manner, including a non-covalent assembly system such as a dockerin/ cohesin system.

[0012] In some embodiments of the disclosure, the composition that is administered to the individual may comprise one or more cells, including one or more types of cells. The cell may be of any cell type, including an immune cell and/or antigen presenting cells, such as a dendritic cell. The cell may be manipulated or cultured in a manner to improve the ability of the cell to present an antigen. The cell may present any antigen, including “self” antigens that are pathologically recognized in autoimmune diseases. The presentation of the antigen by the cell of the composition may lead to a decrease in pathogenic immune cells. The presentation of the antigen by the cell of the composition may lead to an increase in T_{reg} cells.

[0013] Embodiments of the disclosure include compositions comprising: (a) an antibody, wherein said antibody targets dendritic cells and/or Foxp3⁺ cells; linked to (b) a peptide or fusion of peptides, wherein said peptide(s) is (are) a pancreatic beta cell antigen(s) or is an autoimmune antigen-derived peptide(s). In specific embodiments, the antibody targets Langerin, DEC-205, Interleukin 2 (IL2) Receptor, CD25, CD122, or CLEC9A. In specific embodiments, the peptide or fusion of peptides comprise one or more peptides derived from insulin, IL2,

chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein (MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62,sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, or a combination thereof. The peptide may be a hybrid insulin/chromogranin A fusion peptide, such as a hybrid insulin/chromogranin A fusion peptide being 2.5HIP. In some cases, the peptide comprises Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14). In specific cases, the autoimmune antigen-derived peptide is Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), Chromogranin A (WE14), or functional variants having at least 80, 85, 90, 95, 96, 97, 98, or 99% identity thereof. The composition may comprise a mixture of non-identical compositions. For example, in some cases the mixture comprises (a) a first composition comprising an antibody that targets Langerin linked to a hybrid insulin/chromogranin A fusion peptide, and (b) a second composition comprising an antibody that targets Langerin linked to an IL2 peptide. In some cases, the mixture comprises (a) a first composition comprising an antibody that targets Langerin linked to a hybrid insulin/chromogranin A fusion peptide, and (b) an antibody that targets IL-2 receptor linked to an IL2 peptide. In some cases, the mixture comprises (a) a first composition comprising an antibody that targets Langerin linked to a hybrid insulin/chromogranin A fusion peptide, and (b) an antibody that targets CD25 linked to IL2 peptide and (c) an antibody that targets CD122 linked to IL2 peptide. In specific embodiments, the antibody and the peptide(s) are linked by a non-covalent assembly system, such as dockerin/ cohesin.

[0014] In specific embodiments, there is a composition comprising an immune cell, wherein the immune cell presents at least one antigen, wherein the immune cell is modified to present the one or more antigens, wherein the one or more antigens comprise an antigen derived from IL2, chromogranin A, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62,sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, or a combination thereof. The antigen presented may comprise Insulin B:9-23,

Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14). The antigen presented may comprise Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14) or functional variants having at least 80, 85, 90, 95, 96, 97, 98, or 99% identity thereof.

[0015] In some embodiments, there is a method of preventing or delaying onset of an autoimmune disease in an individual, comprising the step of providing to the individual an effective amount of one or more of the compositions encompassed by the disclosure. The individual may be *in utero*, is a newborn, is an infant, is a child, is an adolescent, or is an adult. The composition may be administered topically, intravenously, or intraperitoneally, including by injection. In some cases, the autoimmune disease is Type 1 Diabetes, rheumatoid arthritis, systemic lupus erythematosus, celiac sprue disease, pernicious anemia, vitiligo, scleroderma, psoriasis, inflammatory bowel diseases, Addison's Disease, Graves' Disease, or Sjögren's syndrome. The autoimmune disease may comprise the recognition of one or more antigens, wherein the one or more antigens comprise an antigen derived from insulin, IL2, chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein (MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62, sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, or a combination thereof. In some cases, the autoimmune disease comprises the recognition of one or more antigens, wherein the one or more antigens comprise Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), Chromogranin A (WE14), or a combination thereof. The autoimmune disease may comprise the recognition of one or more antigens, wherein the one or more antigens comprise a functional variant comprising 80, 85, 90, 95, 96, 97, 98, or 99% identity to Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), Chromogranin A (WE14), or a combination thereof. In particular cases, the antibody targets Langerin, DEC-205, Interleukin 2 (IL2) Receptor, CD25, CD122, or CLEC9A. In particular cases, the peptide comprises Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14). The individual may be a neonate, and

the cell may comprise an antigen derived from insulin. In specific cases, the antigen comprises Insulin B:9-23, Insulin B:9-23 (R22E), or both.

[0016] The foregoing has outlined rather broadly the features and technical advantages of the present disclosure in order that the detailed description that follows may be better understood. Additional features and advantages will be described hereinafter which form the subject of the claims herein. It should be appreciated by those skilled in the art that the conception and specific embodiments disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present designs. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope as set forth in the appended claims. The novel features which are believed to be characteristic of the designs disclosed herein, both as to the organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] For a more complete understanding of the present disclosure, reference is now made to the following descriptions taken in conjunction with the accompanying drawing, in which:

[0018] FIG. 1 shows targeting of thymic antigen presenting cells to enhance tolerance to AIRE-independent antigens. Adult NOD WT mice were intraperitoneal injected once with 3.0ug of anti-Langerin APC. At indicated time points, thymus was harvested and co-stained with anti-langerin PE to determine binding efficiency and persistence within the thymus over time.

[0019] FIG. 2 demonstrates that α -Langerin-2.5HIP treatment induces thymic Treg development and deletion in Adult BDC2.5 TCR Tg Mice. Adult TCR transgenic BDC2.5 NOD (T Cell Receptor is specific for 2.5HIP) mice were intraperitoneal injected once with 10.0 μ g of α -Langerin-2.5HIP. After 48 hours, thymus was harvested and thymocyte cellularity and maturation markers were analyzed. Administration of 2.5HIP, depletes immature CD4+CD8+ Double positive (DP) thymocytes, however, there is no change in the more mature CD4+ single positive (SP) population.

[0020] FIG. 3 shows that α -Langerin-2.5HIP treatment induces thymic Treg development and deletion in Adult BDC2.5 TCR Tg Mice. Adult TCR transgenic BDC2.5 NOD were intraperitoneal injected once with 10.0 μ g of α -Langerin-2.5HIP. After 48 hours, thymus was harvested and the Foxp3+ T Regulatory cell (Tregs) population was assessed. Of the CD4+ SP thymocytes, there was a significant increase in Foxp3+ Tregs after α -Langerin-2.5HIP treatment, indicating antigen specific generation of 2.5HIP reactive Tregs.

[0021] FIGS. 4A-4B provide that α -Langerin-2.5HIP treatment induces neonatal thymic Treg development. Day 1-3 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with 5 μ g anti-langerin alone, 2.5ug α -Langerin-2.5HIP or 5 μ g anti-langerin/2.5HIP . (bottom left) It appears 5 μ g of α -Langerin-2.5HIP does not induce dramatic CD4+CD8+ DP reduction like adult mice with 10 μ g. (right side) After 48 hours, CD4 SP Foxp3+ Treg development was assessed and significant increase is observed.

[0022] FIG. 5 demonstrates that α -Langerin-2.5HIP treatment induces differential CD25 expression on thymic Tregs. Day 1-3 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with 2.5 μ g α -Langerin-2.5HIP. “New” Foxp3 Tregs are not CD25+. Thymic Tregs are typically 50-60% CD25+ and peripheral Foxp3+ Tregs are near 90% positive in the periphery.

[0023] FIG. 6 shows α -Langerin-2.5HIP treatment induces differential CD25 expression on thymic Tregs. Day 1-3 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with 2.5 μ g α -Langerin-2.5HIP. “New” Foxp3 Tregs are not CD25+, however normal levels of Helios (top right), a thymically derived Treg marker, but low for Nr1p1 (bottom right), a peripheral marker for non-gut derived Tregs.

[0024] FIG. 7 illustrates CD122 and CD25 expression on Foxp3+ cells. Day 1-3 Neonatal BDC2.5 TCR Transgenic mice were intraperitoneal injected once with 2.5 μ g α -Langerin-2.5HIP. “New” Foxp3 Tregs are express intermediate levels of CD122 (green shaded box and histogram), which is part of the low affinity IL-2 receptor.

[0025] FIG. 8 illustrates selective T cell subset potentiation with IL-2 antibodies. One can determine whether exogenous IL-2 cytokine can help upregulate CD25 that is the high affinity IL-2 receptor. CD25 is highly expressed on mature, functional Tregs.

[0026] FIG. 9 demonstrates an effect of Anti-Langerin-2.5HIP IL-2 combination on Foxp3+ thymocyte development. HI and LO IL-2 complexes are antibodies targeting IL-2. The JES6-IA12 antibody (HI) recognizes the high affinity IL-2 receptor chain CD25, while JES6-IA12 antibody (LO) recognized the low affinity IL-2 receptor chain CD122. By linking active IL-2 to either JES6-IA12 or JES6-IA12 antibody, IL-2 can be targeted to CD25+ and/or CD122+ expressing Foxp+ Tregs. Two-day old neonatal mice were given either Anti-langerin-2.5HIP or a combination of Anti-langerin and IL-2 (HI) or a 1:1 ratio of HI and LO-IL-2 complex.

[0027] FIG. 10 provides that α -Langerin-2.5HIP with IL-2 complex promotes thymocyte survival. Day 2 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with anti-langerin alone, 2.5ug α -Langerin-2.5HIP, or with anti-Langerin bound to active human IL-2 (middle), or co-injected with mouse IL-2 bound to anti-CD25 (second from right) or anti-CD122 and anti-CD25 (far right). IL-2 treatment with α -Langerin-2.5HIP treatment stabilizes CD4+CD8+ thymocyte development.

[0028] FIG. 11 shows that α -Langerin-2.5HIP with IL-2 complex promotes Treg development. Day 2 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with anti-langerin alone, 2.5 μ g α -Langerin-2.5HIP, or with anti-Langerin bound to active human IL-2 (middle), or co-injected with mouse IL-2 bound to anti-CD25 (second from right) or anti-CD122 and anti-CD25 (far right). IL-2 treatment with α -Langerin-2.5HIP treatment dramatically increases Tregs development.

[0029] FIG. 12 demonstrates that α -Langerin-2.5HIP with IL-2 complex does not lead to CD25 expression. Day 2 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with anti-langerin alone, 2.5 μ g α -Langerin-2.5HIP, or with anti-Langerin bound to active human IL-2 (middle), or co-injected with mouse IL-2 bound to anti-CD25 (second from right) or anti-CD122 and anti-CD25 (far right). IL-2 treatment with α -Langerin-2.5HIP DOES NOT rescue CD25 expression on “new” Foxp3+ Tregs.

[0030] FIG. 13 demonstrates indication of protection/delay in developing Type I Diabetes. 1-2 day old NOD WT female pups were injected with anti-langerin alone or α -Langerin-2.5HIP. Diabetes incidence were monitored weekly by Diastix and confirmed by blood glucose level. Diabetes is defined as blood glucose level of >300 mg/dl for 2 consecutive days or >400 mg/dl at the first reading.

[0031] FIG. 14 shows that Foxp3+ Tregs are not killed by antibody treatment as indicated by cleaved (active) Caspase3 staining. Day 2 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with 2.5 µg anti-langerin alone, 2.5 µg α-Langerin-2.5HIP, or DPBS. α-Langerin-2.5HIP or anti-langerin alone does not kill “new” Foxp3+ Tregs.

[0032] FIG. 15 shows Ab-2.5HIP-generated Foxp3+ cells are almost entirely CD73- (thymically derived). Day 2 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with 2.5 µg anti-langerin alone, 2.5 µg α-Langerin-2.5HIP, or DPBS. Lack of CD73 expression indicates thymically derived Tregs. Peripheral Tregs that circulate back to the thymus are CD73+.

DETAILED DESCRIPTION

I. **[0033] Examples of Definitions**

[0034] In keeping with long-standing patent law convention, the words "a" and "an" when used in the present specification in concert with the word comprising, including the claims, denote "one or more." Some embodiments of the disclosure may consist of or consist essentially of one or more elements, method steps, and/or methods of the disclosure. It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein.

[0035] As used herein, the term "about" or "approximately" refers to a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 % to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length. In particular embodiments, the terms "about" or "approximately" when preceding a numerical value indicates the value plus or minus a range of 15%, 10%, 5%, or 1 %. With respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Unless otherwise stated, the term 'about' means within an acceptable error range for the particular value.

[0036] The term "administered" or "administering", as used herein, refers to any method of providing a composition to an individual such that the composition has its intended effect on the patient. For example, one method of administering is by an indirect mechanism using a medical device such as, but not limited to a catheter, applicator gun, syringe etc. A second

exemplary method of administering is by a direct mechanism such as, local tissue administration, oral ingestion, transdermal patch, topical, inhalation, suppository etc.

[0037] As used herein, the term “antigen” describes any molecule that is recognized by immune cells or immune molecules, such as an antibody. The term may refer to any small molecule or macromolecule, such as a nucleic acid of any length, a peptide of any length, a lipid of any length, or a combination thereof. The term may include peptides derived from proteins that are present in an individual. The antigen may be any peptide derived from any protein described in the disclosure, or any natural or functionally equivalent variant of any protein described in the disclosure, including variants differing by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more amino acids. The natural or functional variants may also have conservative mutations at any site. Conservative mutations may be a change of one amino acid to any other amino acid in the group consisting of Gly, Ala, Val, Leu, Ile; or the group consisting of Ser, Cys, Selenomethionine, Thr, Met; or the group consisting of Phe, Tyr, Trp; or the group consisting of His, Lys, Arg; or the group consisting of Asp, Glu, Asn, Gln. The antigens may have insertions or deletions from the naturally occurring antigen, such as insertions or deletions of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more amino acids. The antigen may be a fusion of two or more proteins, or any fragment of the fusion of two or more proteins. The antigen may be recognized by compositions of the disclosure. The antigen may comprise part or all of the compositions of the disclosure. In specific cases, the antigen is an autoantigen (an antigen that is a normal constituent of an individual and against which the immune system produces autoantibodies).

[0038] The term "individual", as used herein, refers to a human or animal that may or may not be housed in a medical facility and may be treated as an outpatient of a medical facility. The individual may be receiving one or more medical compositions via the internet. An individual may comprise any age of a human or non-human animal and therefore includes both adult and juveniles (*i.e.*, children) and infants. It is not intended that the term "individual" connote a need for medical treatment, therefore, an individual may voluntarily or involuntarily be part of experimentation whether clinical or in support of basic science studies. The term "subject" or "individual" refers to any organism or animal subject that is an object of a method or material, including mammals, *e.g.*, humans, laboratory animals (*e.g.*, primates, rats, mice, rabbits), livestock (*e.g.*, cows, sheep, goats, pigs, turkeys, and chickens), household pets (*e.g.*, dogs, cats, and rodents), horses, and transgenic non-human animals.

[0039] Reference throughout this specification to "one embodiment," "an embodiment," "a particular embodiment," "a related embodiment," "a certain embodiment," "an additional embodiment," or "a further embodiment" or combinations thereof means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Thus, the appearances of the foregoing phrases in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0040] As used herein, the term "peptide" refers to a polypeptide chain of amino acids. In certain embodiments, the peptide is between 9-21 amino acids in length, in some cases between 10-20 amino acids in length, in some cases between 11-20 amino acids in length. In some embodiments, the peptide is derived from a protein. The peptide may be any polypeptide chain from the protein. Some embodiments of the present disclosure concern multiple peptides, including multiple peptides derived from the same protein. In such embodiments, a peptide may overlap with a different peptide derived from the same protein. In certain embodiments, the overlapping peptides have one or more amino acids that overlap, such as 1-10, 1-9, 1-8, 10-7, 1-6, 1-5, 1-4, 1-3, or 1-2 amino acids that overlap.

[0041] As used herein, the term "self" in the context of protein, antigens, cells, or the like; "self-cell"; or "self-antigen" refer to proteins, antigens, cells, or the like that originate from an individual that has, or is at risk of having, an autoimmune disease. These "self" molecules are endogenous to the individual and may be pathologically recognized by immune cells of the individual.

[0042] As used herein, the term "therapeutically effective amount" is synonymous with "effective amount", "therapeutically effective dose", and/or "effective dose" and refers to the amount of compound that will elicit the biological, cosmetic or clinical response being sought by the practitioner in an individual in need thereof. As one example, an effective amount is the amount sufficient to reduce immunogenicity of a group of cells. As a non-limiting example, an effective amount is an amount sufficient to promote formation of a blood supply sufficient to support the transplanted tissue. As another non-limiting example, an effective amount is an amount sufficient to promote formation of new blood vessels and associated vasculature (angiogenesis) and/or an amount sufficient to promote repair or remodeling of existing blood

vessels and associated vasculature. The appropriate effective amount to be administered for a particular application of the disclosed methods can be determined by those skilled in the art, using the guidance provided herein. For example, an effective amount can be extrapolated from in vitro and in vivo assays as described in the present specification. One skilled in the art will recognize that the condition of the individual can be monitored throughout the course of therapy and that the effective amount of a compound or composition disclosed herein that is administered can be adjusted accordingly.

[0043] "Treatment," "treat," or "treating" means a method of reducing the effects of a disease or condition. Treatment can also refer to a method of reducing the disease or condition itself rather than just the symptoms. The treatment can be any reduction from pre-treatment levels and can be but is not limited to the complete ablation of the disease, condition, or the symptoms of the disease or condition. Therefore, in the disclosed methods, treatment" can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of an established disease or the disease progression, including reduction in the severity of at least one symptom of the disease. For example, a disclosed method for reducing the immunogenicity of cells is considered to be a treatment if there is a detectable reduction in the immunogenicity of cells when compared to pre-treatment levels in the same subject or control subjects. Thus, the reduction can be a 10, 20, 30, 40, 50, 60, 70, 80, 90, 100%, or any amount of reduction in between as compared to native or control levels. It is understood and herein contemplated that "treatment" does not necessarily refer to a cure of the disease or condition, but an improvement in the outlook of a disease or condition. In specific embodiments, treatment refers to the lessening in severity or extent of at least one symptom.

II. [0044] Autoimmune Diseases

[0045] Autoimmune diseases are thought to arise from immune cells in an individual pathologically recognizing self-antigens as foreign antigens, thus triggering an immune response against self-cells. In an individual that does not have an autoimmune disease, there are mechanisms and immune cells, such as dendritic cells and regulatory T (T_{reg}) cells that allow for self-tolerance. In autoimmune diseases these mechanisms and immune cells may malfunction. There are many different self-antigens that are recognized, leading to different autoimmune diseases. As a non-limiting example, Type 1 diabetes arises from the pathological recognition of self-antigens present on β cells of the pancreas. Pathogenic T cells, which recognize the self-antigens on β cells, trigger immune mechanisms that lead to the destruction of β cells, limiting

the functionality of the pancreas. Other examples of autoimmune diseases include, but are not limited to, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, celiac sprue disease, pernicious anemia, vitiligo, scleroderma, psoriasis, inflammatory bowel diseases, Addison's Disease, Graves' Disease, or Sjögren's syndrome.

[0046] Embodiments of the disclosure concern methods of reducing the immune system pathological recognition of self-antigens. The self-antigen may be any antigen, including those that may trigger autoimmune reactions. The self-antigen may be expressed on any self-cell in an individual having, or at risk of having, an autoimmune disease.

[0047] Embodiments of the methods of the disclosure decrease the recognition of self-antigens by pathogenic immune cells, including pathogenic T cells. The methods in specific aspects increase the recognition of self-antigens by regulatory and/or anti-inflammatory immune cells. The self-antigens may be derived from one or more of the following: insulin, IL2, chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein (MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62, sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, or a combination thereof. Decreasing pathogenic immune cells, including those that recognize self-antigens, and increasing regulatory immune cells, including those that recognize self-antigens, may alter the pathogenesis of certain autoimmune diseases. Altering the pathogenesis of one or more autoimmune diseases may lead to an increase of the self-cells that were targeted by pathogenic immune cells. Increasing the number of self-cells that were targeted by immune cells may restore function that was lost due to the autoimmune disease.

III. [0048] Compositions

[0049] Embodiments of the disclosure concern compositions, such as a cell and/or a molecule (including bipartite molecules comprising an antibody linked to a peptide), that regulate autoimmunity. In some embodiments, the composition comprises at least one cell, such as an immune cell or antigen presenting cell. The cell may present one or more antigens that are

involved in the pathogenesis of an autoimmune disease. The cell may present the antigen endogenously or may be manipulated to present the antigen. In some embodiments, the cell may be incubated with a single peptide or a mixture different pulsed with peptides from the antigen involved in autoimmunity. The cell may also be manipulated to exogenously express and present the antigen. Any method known in the art for manipulating a cell to present a specific antigen may be used. In some embodiments, the antigen is a fragment from the protein and/or peptide selected from the group consisting of insulin, IL2, chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein (MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62, sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, and a combination thereof. The antigen may be any fragment of the listed proteins and/or peptides, or a fragment of any functional and/or natural variant of the listed proteins and/or peptides. The functional variant may have at least 80, 85, 90, 95, 96, 97, 98, or 99% identity thereof. The antigen may be a fusion of peptides derived from two or more proteins, including the proteins disclosed herein.

[0050] Cells of the present disclosure can be isolated from any source, including allogeneic and autologous sources. In some embodiments, antigen presenting cells, such as dendritic cells, are isolated from a source. Dendritic cells may be isolated from blood or other leukocytes using known methods in the art. In some embodiments, antigen presenting cells, including dendritic cells for example, are generated from other cell types, such as monocytes for example. The cells may be cultured using any known culture methods known in the art. In some embodiments, the cells are manipulated to increase the presentation of one or more antigens that are involved in autoimmune diseases. Any known method may be used to increase the presentation of one or more antigens disclosed herein. The antigen presented by the cell may be at least one of the antigens selected from the group consisting of insulin, IL2, chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein

(MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62,sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, and a combination thereof. The antigen presented by the cell may be any peptide fragment from insulin, including insulin B:9-23, insulin B:9-23 (R22E). The antigen presented by the cell may be any peptide fragment of chromogranin A, including WE14. The antigen presented by the cell may be any fragment of a fusion between two or more proteins, such as the peptide 2.5HIP. The antigen presented by the cell may be any functional or natural variant of the antigens described herein. The functional variant may have at least 80, 85, 90, 95, 96, 97, 98, or 99% identity thereof.

[0051] In some embodiments of the disclosure, the composition comprises at least one molecule, such as an antibody. In some embodiments, the molecule comprises an antibody. The antibody may recognize any antigen on one or more self-cells, such as a self-cell that is involved in one or more autoimmune diseases. The antibody may recognize antigens present on immune cells such as dendritic cells. In some embodiments, the antibody may bind to dendritic cells located in the thymus of an individual. The antibody may recognize any antigen derived from langerin, DEC-205, IL-2 receptor, CD25, CD122, CLEC9A or a combination thereof.

[0052] In some embodiments of the disclosure, the compositions comprises one or more antibodies fused with another molecule. The antibody may be any antibody described herein, including an antibody that recognizes dendritic cells or markers of dendritic cells. The antibody may be fused to any molecule, including a peptide of any length, a lipid of any length, a nucleic acid of any length, a small molecule, or a combination thereof. The molecule fused to the antibody may comprise an antigen, including any antigen involved in an autoimmune disease. The antigen may be represented by a peptide as a fragment of the antigen. The molecule fused to the antibody may comprise an antigen derived from any protein including insulin, IL2, chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein (MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62,sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB,

UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, or a combination thereof. The molecule fused to the antibody may comprise any antigen from insulin, including insulin B:9-23, insulin B:9-23 (R22E). The molecule fused to the antibody may comprise any antigen from chromogranin A, including WE14. The molecule fused to the antibody may comprise any antigen from any fragment of a fusion between two or more proteins, such as the peptide 2.5HIP. The molecule fused to the antibody may be any functional or natural variant of the antigens described herein. The functional variant may have at least 80, 85, 90, 95, 96, 97, 98, or 99% identity thereof. In some embodiments the composition may comprise a mixture of antibodies described herein. In some embodiments the composition may comprise a mixture of antibodies fused with another molecule, including any of the antibodies fused with another molecule described herein.

[0053] Examples of specific peptide sequences that may be employed are as follows:

[0054] Sequences

Peptide	Amino Acid Sequence
Insulin B:9-23	SHLVEALYLVCGERG (SEQ ID NO:1)
Insulin B:9-23 (R22E)	SHLVEALYLVCGEEG (SEQ ID NO:2)
2.5HIP	DLQTLALWSRMDQLC (SEQ ID NO:3)
WE14	WSRMDQLAKELTAEC (SEQ ID NO:4)

[0055] The antibody may be fused to the molecule in any manner known in the art. The antibody may be fused to the molecule using one or more covalent linkers, noncovalent linkers, cleavable linkers, or a combination thereof. The noncovalent linker system may be the dockerin/cohesin system. A dockerin molecule may be linked to the antibody or the peptide. A cohesin molecule may be linked to the antibody or the peptide. In some embodiments, an antibody is linked to a dockerin molecule and a peptide is linked to a cohesin molecule.

[0056] In some embodiments, the composition according to the disclosure may be formulated for delivery *via* any route of administration. "Route of administration" may refer to any systemic or local administration pathway known in the art, including but not limited to aerosol, nasal, oral, intravenous, intramuscular, intraperitoneal, inhalation, transmucosal,

transdermal, parenteral, implantable pump, continuous infusion, topical application, capsules and/or injections.

[0057] The compositions according to the disclosure can also comprise any pharmaceutically acceptable carrier. "Pharmaceutically acceptable carrier" as used herein refers to a pharmaceutically acceptable material, composition, or vehicle that is involved in carrying or transporting a composition of interest from one tissue, organ, or portion of the body to another tissue, organ, or portion of the body. For example, the carrier may be a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, or a combination thereof. Each component of the carrier must be "pharmaceutically acceptable" in that it must be compatible with the other ingredients of the formulation. It must also be suitable for use in contact with any tissues or organs with which it may come in contact, meaning that it must not carry a risk of toxicity, irritation, allergic response, immunogenicity, or any other complication that excessively outweighs its therapeutic benefits.

[0058] The compositions according to the disclosure can also be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. They can be encased in a syringe for injection. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

[0059] The compositions may be made following the conventional techniques of pharmacy involving milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule.

IV. [0060] Administration

[0061] Embodiments of the disclosure concern methods for administering one or more compositions described herein to an individual having, or at risk of having, an autoimmune

disease. The individual may have, or be at risk of having, Type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, celiac sprue disease, pernicious anemia, vitiligo, scleroderma, psoriasis, Inflammatory bowel diseases, Addison's Disease, Graves' Disease, Sjögren's syndrome, or any other autoimmune disease, or a combination thereof. The individual may be any age such as an individual *in utero*, a neonatal individual, a pre-pubescent individual, a pubescent individual, or an adult. A neonatal individual may be less than 1 month old, less than 2 months old, less than 3 months old, less than 4 months old, less than 5 months old, or less than 6 months old. Some embodiments of the disclosure concern a method that may be suitable for ameliorating symptoms arising from the autoimmune disease, the cause of the autoimmune disease, or both.

[0062] The composition may be delivered using any acceptable route of administration either systemically or locally, including but not limited to aerosol administration, nasal administration, oral administration, intravenous administration, intramuscular administration, intraperitoneal administration, inhalation administration, transmucosal administration, transdermal administration, parenteral administration, implantable pump, continuous infusion, topical application, capsules and/or injections.

[0063] The individual described herein may be of any age, including an individual *in utero*, a neonatal individual, a pre-pubescent individual, a pubescent individual, or an adult. The individual may receive one administration of at least one of the compositions described herein, or the individual may receive more than one administration of at least one of the compositions described herein. The compositions may be administered to the individual at any frequency including, but not limited to, daily, weekly, monthly, annually, or any other prescribed frequency. The composition may administered to the individual at various times not set by a specific frequency.

[0064] The compositions according to the disclosure may be administered in a therapeutically effective amount. The precise therapeutically effective amount is that amount of the composition that will yield the most effective results in terms of efficacy of treatment in a given subject. This amount will vary depending upon a variety of factors, including but not limited to the characteristics of the therapeutic compound (including activity, pharmacokinetics, pharmacodynamics, and bioavailability), the physiological condition of the subject (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage,

and type of medication), the nature of the pharmaceutically acceptable carrier or carriers in the formulation, and the route of administration. One skilled in the clinical and pharmacological arts will be able to determine a therapeutically effective amount through routine experimentation, for instance, by monitoring a subject's response to administration of a compound and adjusting the dosage accordingly. For additional guidance, see Remington: The Science and Practice of Pharmacy (Gennaro ed. 20th edition, Williams & Wilkins PA, USA) (2000).

[0065] In some embodiments, the composition is administered in combination with one or more compositions effective for ameliorating symptoms or causes of one or more autoimmune diseases. The compositions effective for ameliorating symptoms or causes of one or more autoimmune diseases may comprise, for example, a steroid (including corticosteroids), a non-steroid anti-inflammatory drug, insulin (or derivatives of insulin), an immune suppressing composition, a pain-killer, an anti-histamine, a biologic, or a combination thereof.

V. [0066] Kits

[0067] Any of the cellular and/or non-cellular compositions described herein or similar thereto may be comprised in a kit. In a non-limiting example, one or more reagents for use in methods for preparing cellular or antibody therapies may be comprised in a kit. Such reagents may include cells, such as dendritic cells and/or cells capable of producing antibodies, antigens, linkers, or a combination thereof, including the antibodies, antigens, and linkers disclosed herein; vectors encoding one or more antibodies, antigens, linkers, or a combination thereof, including antibodies, antigens, and linkers disclosed herein; nucleic acid or polypeptide components that allow production of one or more antibodies, antigens, linkers, or a combination thereof or a region thereof, including antibodies and antigens disclosed herein; one or more growth factors; one or more costimulatory factors; media; enzymes; buffers; nucleotides; salts; primers; and so forth. The kit components are provided in suitable container means.

[0068] Some components of the kits may be packaged either in aqueous media or in lyophilized form. The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which a component may be placed, and preferably, suitably aliquoted. Where there are more than one component in the kit, the kit also will generally contain a second, third or other additional container into which the additional components may be separately placed. However, various combinations of components may be comprised in a vial. The kits of the present disclosure also will typically include a means for

containing the components in close confinement for commercial sale. Such containers may include injection or blow molded plastic containers into which the desired vials are retained.

[0069] When the components of the kit are provided in one and/or more liquid solutions, the liquid solution is an aqueous solution, with a sterile aqueous solution being particularly useful. In some cases, the container means may itself be a syringe, pipette, and/or other such like apparatus, or may be a substrate with multiple compartments for a desired reaction.

[0070] Some components of the kit may be provided as dried powder(s). When reagents and/or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means. The kits may also comprise a second container means for containing a sterile acceptable buffer and/or other diluent.

[0071] In specific embodiments, reagents and materials include primers for amplifying desired sequences, nucleotides, suitable buffers or buffer reagents, salt, and so forth, and in some cases the reagents include apparatus or reagents for isolation of a particular desired cell(s).

[0072] In particular embodiments, there are one or more apparatuses in the kit suitable for extracting one or more samples from an individual. The apparatus may be a syringe, fine needles, scalpel, and so forth.

EXAMPLES

[0073] The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

NEONATAL ADMINISTRATION OF ANTIGEN FUSED ANTIBODIES TO PREVENT
TYPE 1 DIABETES

[0074] As a non-limiting example, the targeted delivery (skin administration, intraperitoneal or intravenous) of peptides, including post-translationally modified (PTM) peptides may alter the development and function of pathogenic T cells or protective T regulatory cells during neonatal development and halt the initiation of autoimmune Type 1 Diabetes.

[0075] An example method for targeted deliver of peptides for altering the development and function of pathogenic T cells is therapeutically targeting dendritic cells by injecting anti-DEC-205 or anti-Langerin antibodies linked to pancreatic beta cell peptides such as, insulin B:9-23 (partial agonist) peptide, insulin mimetope (R22E-agonist) (26), WE14 or 2.5HIP to target the deletion of pathogenic T cells or the development of protective T regulatory cells. One could therapeutically utilize modified β cell peptides to favor anti-inflammatory Tregs and delete β cell-destructive T effector cells.

[0076] This particular approach calls for the use of specific antibodies targeting dendritic cells (anti-Langerin and/or anti-DEC205) throughout neonatal/perinatal period of life. The antibodies could be linked to various peptides specific for the pancreatic beta cell antigens targeted during autoimmune destruction. The antibody-peptide product will be delivered on the skin or by intraperitoneal injection throughout the perinatal period of development as a vaccine.

[0077] *Preventing Type 1 diabetes in murine models*

[0078] Antigen availability drives central tolerance and antigen specific T regulatory (Treg) cell development in the thymus. Insulin 2 $-/-$ mice do not express insulin antigen in the thymus, which allows for escape of pathogenic auto reactive T cells and destruction of insulin producing beta cells, initiating Type 1 Diabetes. Data using ectopically expressed insulin B:9-23 peptide and the agonist peptide B:9-23(R22E), in all MHCII antigen presenting cells, shows that increasing antigen availability and peptide MHC stability (R22E) drives the development of Foxp3 Treg development or negative selection of insulin specific T cells, respectively. Dendritic Cell (DC) transfer of B:9-23 or B:9-23(R22E) peptide pulsed cells into adult TCR transgenic (Insulin Specific), significantly increases the number and ratio of thymic Tregs. DC transfer of

B:9-23(R22E) peptide pulsed cells into neonatal mice (wild type and TCR transgenic) significantly increased thymic Treg numbers and ratios.

[0079] Chromogranin A is the only other beta cell protein (antigen) known to be implicated in the onset of T cell specific T1D autoimmunity. The antigenic peptide was found to be a fusion of insulin and chromogranin A, called hybrid insulin peptide (2.5HIP, Thomas Delong, Science 2016). The fusion occurs from posttranslational modifications to Chromogranin A in beta cell granules. The role of this peptide in the development of 2.5HIP specific T cells is unknown. DC transfer of 2.5HIP into neonatal mice (wild type and TCR transgenic) significantly increased thymic Treg number and ratios.

[0080] *Peptide fusion antibodies*

[0081] One could study the described peptides in the setting of peptide fusion antibodies specific to DCs. The advantages of this method would be that the antibody-peptide will reach more DCs that are located in the thymus than the number of peptide pulsed DCs that one can transfer and migrate to the thymus. One can treat neonatal mice to study Treg development and long term tolerance in the NOD, T1D mouse model. One can treat pre-diabetic mice and study the development of peripheral and thymic Tregs (and deletion) of insulin/chromogranin specific T cells using TCR transgenic as well as insulin and chromogranin tetramer specific T cells.

[0082] Examples of Peptides:

[0083] Insulin B:9-23

[0084] Insulin B:9-23(R22E)

[0085] Chromogranin A (2.5HIP)

[0086] Chromogranin A (WE14)

[0087] *Broader Use*

[0088] The use of anti-langerin conjugated to autoimmune antigen derived peptides would allow potential therapeutic treatment for many autoimmune diseases. By targeting a known tolerogenic DC population (Langerin+ cells), the antibody-peptide could be given to autoimmune susceptible individuals to boost central and peripheral tolerance to self-antigens targeted in autoimmunity to prevent the initiation/progression of these diseases.

[0089] *Auto-antigen recognition in Type 1 diabetes*

[0090] Type 1 Diabetes (T1D) is a T cell-mediated autoimmune disease that involves the destruction of insulin producing β cells found within the pancreatic islets of Langerhans. Recent attention to neonatal thymocyte development has revealed a window during which central tolerance is established in an Autoimmune Regulator (Aire) dependent manner. However, expression of Chromogranin A (ChgA) within the thymus has not been detected; therefore, tolerance to ChgA may be due in part to peripheral dendritic cells (DCs) presenting ChgA to developing thymocytes. The relative contribution of thymically and peripherally derived antigens in the generation of neonatal β cell antigen specific CD4⁺ regulatory T cells (Tregs) is not well understood. For example, post-translational modification (PTM) of ChgA by fusion with an insulin peptide increases epitope immunogenicity by forming neo-antigens. Pathogenic T cells that are specific for neo-antigens uniquely expressed in the pancreas may escape thymic selection. Therefore, one can utilize two experimental designs to test the role of peripheral antigen exposure on neonatal development of β cell specific Tregs. Firstly, one can adoptively transfer dendritic cells pulsed with ChgA peptides into BDC2.5 TCR Tg mice and WT NOD mice to study the role of migratory DCs on neonatal development of ChgA Tregs. Secondly, one can target thymic Langerin⁺ dendritic cells with anti-Langerin linked to ChgA peptides. In both experimental approaches, a robust increase in the ratio and number of ChgA specific Tregs in the presence of the hybrid insulin/chromogranin A peptide (2.5HIP) while also observing an increase in negative selection was found. The expansion of thymic Tregs was observed in both adult and neonatal mice. Together the data suggests neonatal exposure to PTM peptides enhances thymic development of β cell specific Tregs and may alter T1D pathogenesis.

EXAMPLE 2

ADMINISTRATION OF ANTI-LANGERIN ANTIBODIES FUSED TO THE 2.5HIP
ANTIGEN

[0091] Antibodies fused to antigens are useful for treating autoimmune diseases. One antigen fused antibody system that was shown effective is an antibody that targets anti-Langerin fused to 2.5HIP using the non-covalent dockerin/ cohesin fusion system (referred to as α -Langerin-2.5HIP). One may target thymic antigen presenting cells to enhance tolerance to AIRE-independent antigens. (FIG 1, left side) In one study, adult NOD WT mice were intraperitoneal injected once with 3.0ug of α -Langerin APC. At indicated time points, thymus from the injected

mice were harvested and co-stained with anti-Langerin PE to determine binding efficiency and persistence, *in vivo*, of the injected anti-Langerin antibody within the thymus over time (FIG 1, right side).

[0092] A subsequent study demonstrated that α -Langerin-2.5HIP treatment induces thymic Treg development and deletion in Adult BDC2.5 TCR Tg Mice (FIG 2, upper left side). Adult TCR Transgenic BDC2.5 NOD mice (which express a T Cell Receptor specific for the 2.5HIP antigen derived from chromogranin A) were intraperitoneal injected once with 10.0 μ g of α -Langerin-2.5HIP. After 48 hours, thymi were harvested and thymocyte cellularity and maturation markers were analyzed. Administration of α -Langerin-2.5HIP, depletes immature CD4+CD8+ Double positive (DP) thymocytes, however, there is no change in the more mature CD4+ single positive (SP) population (FIG 2). Foxp3+ T Regulatory cell (Tregs) population were also assessed. Of the CD4+ SP thymocytes, there was a significant increase in Foxp3+ Tregs after α -Langerin-2.5HIP, indicating antigen specific generation of 2.5HIP reactive Tregs (FIG 3).

[0093] Another study provided evidence that α -Langerin-2.5HIP treatment induces neonatal thymic treg development. Day 1-3 Neonatal BDC2.5 TCR Transgenic mice were intraperitoneal injected once with 5 μ g anti-langerin alone, 2.5 μ g α -Langerin-2.5HIP or 5 μ g α -Langerin-2.5HIP (FIG 4, top). (bottom left) It appears 5 μ g of α -Langerin-2.5HIP does not induce dramatic CD4+CD8+ DP reduction like adult mice with 10 μ g. (right side) After 48 hours, CD4 SP Foxp3+ Treg development was assessed and significant increase is observed.

[0094] α -Langerin-2.5HIP treatment induces differential CD25 expression on thymic Tregs. Day 1-3 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with 2.5 μ g α -Langerin-2.5HIP. “New” Foxp3 Tregs that are not CD25+ were seen (FIG 5). Thymic Tregs are typically 50-60% CD25+ and peripheral Foxp3+ Tregs are near 90% positive in the periphery. However, normal levels of Helios (FIG 6, top right), a thymically derived Treg marker, were seen while low levels for Nr1 (FIG 6, bottom right), a peripheral marker for non-gut derived Tregs, were seen. “New” Foxp3 Tregs express intermediate levels of CD122 (FIG 7, green shaded box and histogram), which is part of the low affinity IL-2 receptor (FIG 7, left side). One can determine whether exogenous IL-2 cytokine can help upregulate CD25 that is the high affinity IL-2 receptor. CD25 is highly expressed on mature, functional Tregs (FIG 8).

[0095] One experimental procedure (FIG 9), shows that α -Langerin-2.5HIP with IL-2 complex promotes thymocyte survival. Day 2 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with anti-langerin alone (FIG 10, upper left), 2.5 μ g α -Langerin-2.5HIP, or with anti-Langerin bound to active human IL-2 (FIG 10, upper second from left and upper middle respectively), or co-injected with mouse IL-2 bound to anti-CD25 (FIG 10, upper second from right) or anti-CD122 and anti-CD25 (FIG 10, upper right). IL-2 treatment with α -Langerin-2.5HIP treatment stabilizes CD4+CD8+ thymocyte development, while dramatically increasing Treg development (FIG 11) but does not rescue CD25 expression on “new” Foxp3+ Tregs (FIG 12).

[0096] Another study demonstrated an indication of protection/delay in developing Type I Diabetes using α -Langerin-2.5HIP. 1-2 day old NOD WT female pups were injected with anti-langerin alone or α -Langerin-2.5HIP. Diabetes incidence were monitored weekly by Diastix and confirmed by blood glucose level (FIG 13). Diabetes is defined as blood glucose level of >300 mg/dl for 2 consecutive days or >400 mg/dl at the first reading.

[0097] Foxp3+ Tregs are not killed by antibody treatment as indicate by cleaved (active) Caspase3 staining. Day 2 Neonatal BDC2.5 TCR transgenic mice were intraperitoneal injected once with 2.5 μ g anti-langerin alone, 2.5 μ g α -Langerin-2.5HIP or DPBS. α -Langerin-2.5HIP or anti-langerin alone does not kill “new” Foxp3+ Tregs (FIG 14). α -Langerin-2.5HIP generated Foxp3+ cells are almost entirely CD73- (thymically derived) (FIG 15). Lack of CD73 expression indicates thymically derived Tregs. Peripheral Tregs that circulate back to the thymus are CD73+.

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[0098] All patents and publications cited herein are hereby incorporated by reference in their entirety herein. Full citations for the references cited herein are provided in the following list.

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[0125] Although the present disclosure and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the design as defined by the appended claims. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, machine, manufacture, composition of matter, means, methods and steps described in the specification. As one of ordinary skill in the art will readily appreciate from the present disclosure, processes, machines, manufacture, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve substantially the same result as the corresponding embodiments described herein may be utilized according to the present disclosure. Accordingly, the appended claims are intended to include within their scope such processes, machines, manufacture, compositions of matter, means, methods, or steps.

CLAIMS

What is claimed is:

1. A composition comprising:
 - (a) an antibody, wherein said antibody targets dendritic cells and/or Foxp3+ cells; linked to
 - (b) a peptide or fusion of peptides, wherein said peptide(s) is (are) a pancreatic beta cell antigen(s) or is an autoimmune antigen-derived peptide(s).
2. The composition of claim 1, wherein the antibody targets Langerin, DEC-205, Interleukin 2 (IL2) Receptor, CD25, CD122, or CLEC9A.
3. The composition of claim 1 or 2, wherein the peptide or fusion of peptides comprise one or more peptides derived from insulin, IL2, chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein (MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62, sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFC, ANCA, C1q, or a combination thereof.
4. The composition of claim 3, wherein the peptide is a hybrid insulin/chromogranin A fusion peptide.
5. The composition of claim 4, wherein the hybrid insulin/chromogranin A fusion peptide is 2.5HIP.
6. The composition of claim 1, wherein the peptide comprises Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14).
7. The composition of claim 1, wherein the autoimmune antigen-derived peptide is Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), Chromogranin A (WE14), or functional variants having at least 80, 85, 90, 95, 96, 97, 98, or 99% identity thereof.

8. The composition of any one of claims 1-7, wherein the composition is a mixture of non-identical compositions from any one of claims 1-7.

9. The composition of claim 8, wherein the mixture comprises (a) a first composition comprising an antibody that targets Langerin linked to a hybrid insulin/chromogranin A fusion peptide, and (b) a second composition comprising an antibody that targets Langerin linked to an IL2 peptide.

10. The composition of claim 8, wherein the mixture comprises (a) a first composition comprising an antibody that targets Langerin linked to a hybrid insulin/chromogranin A fusion peptide, and (b) an antibody that targets IL-2 receptor linked to an IL2 peptide.

11. The composition of claim 8, wherein the mixture comprises (a) a first composition comprising an antibody that targets Langerin linked to a hybrid insulin/chromogranin A fusion peptide, and (b) an antibody that targets CD25 linked to IL2 peptide and (c) an antibody that targets CD122 linked to IL2 peptide.

12. The composition of any one of claims 1-11, wherein the antibody and the peptide(s) are linked by a non-covalent assembly system.

13. The composition of claim 12, wherein the non-covalent assembly system comprises dockerin/ cohesin.

14. A composition comprising an immune cell, wherein the immune cell presents at least one antigen, wherein the immune cell is modified to present the one or more antigens, wherein the one or more antigens comprise an antigen derived from IL2, chromogranin A, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62,sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFC, ANCA, C1q, or a combination thereof.

15. The composition of claim 14, wherein the antigen presented comprises Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14).

16. The composition of claim 14, wherein the antigen presented comprises Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14) or functional variants having at least 80, 85, 90, 95, 96, 97, 98, or 99% identity thereof.

17. A method of preventing or delaying onset of an autoimmune disease in an individual, comprising the step of providing to the individual an effective amount of one or more of the compositions of claims 1-16.

18. The method of claim 17, wherein the individual is *in utero*, is a newborn, is an infant, is a child, is an adolescent, or is an adult.

19. The method of any one of claims 17-18, wherein the composition is administered topically, intravenously, or intraperitoneally.

20. The method of any one of claims 17-19, wherein the composition is administered by injection.

21. The method of any one of claims 17-20, wherein the autoimmune disease is Type 1 Diabetes, rheumatoid arthritis, systemic lupus erythematosus, celiac sprue disease, pernicious anemia, vitiligo, scleroderma, psoriasis, inflammatory bowel diseases, Addison's Disease, Graves' Disease, or Sjögren's syndrome.

22. The method of claim 17, wherein the autoimmune disease is Type 1 Diabetes.

23. The method of claim 17, wherein the autoimmune disease comprises the recognition of one or more antigens, wherein the one or more antigens comprise an antigen derived from insulin, IL2, chromogranin A, glutamic acid decarboxylase 65 (GAD-65), IA-2, ZnT8, ICA69, IGRP, myelin oligodendrocyte glycoprotein (MOG), neurofilament NF-M, myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated antigen (MAG), myelin-associated oligodendrocyte basic protein (MOBP), S100 β , CNPase, Transaldolase, collagen basement membrane type IV, ANA, SMA, LKM-1, LKM-2, LKM-3, SLA, p62, sp100, M2, SSA, HLA-DR52a, BP-1, BP-2, IL-2, IFN-gamma, COL7A1, desmoglein-3, NALP-1 RER, PTPN22, LPP, IL2RA, GXMB, UBASH3A, C1QTNF6, HLADR5, CTLA-4, TSHR, ADAMTS13, HPA-1a, HPA-5b, MMP3, vimentin, MCV, IgGFc, ANCA, C1q, or a combination thereof.

24. The method of claim 17, wherein the autoimmune disease comprises the recognition of one or more antigens, wherein the one or more antigens comprise Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), Chromogranin A (WE14), or a combination thereof.
25. The method of claim 17, wherein the autoimmune disease comprises the recognition of one or more antigens, wherein the one or more antigens comprise a functional variant comprising 80, 85, 90, 95, 96, 97, 98, or 99% identity to Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), Chromogranin A (WE14), or a combination thereof.
26. The method of any one of claims 17-25, wherein the antibody targets Langerin, DEC-205, Interleukin 2 (IL2) Receptor, CD25, CD122, or CLEC9A.
27. The method of any one of claims 17-26, wherein the peptide comprises Insulin B:9-23, Insulin B:9-23 (R22E), Chromogranin A (2.5HIP), or Chromogranin A (WE14).
28. The method any one of claims 17-27, wherein the individual is a neonate, wherein the cell of claim 14 comprises an antigen derived from insulin.
29. The method of claim 28, wherein the antigen comprises Insulin B:9-23, Insulin B:9-23 (R22E), or both.

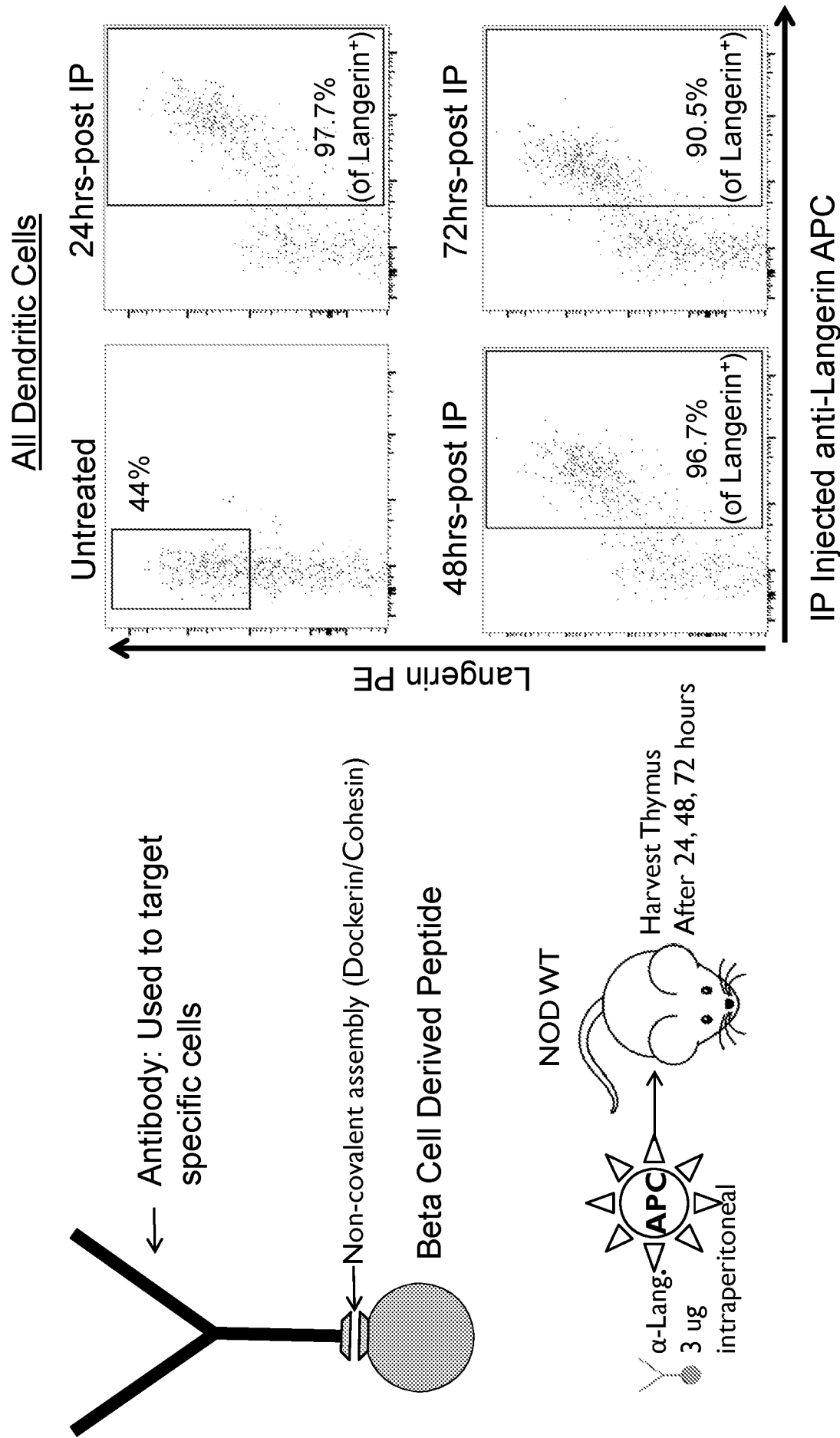


FIG. 1

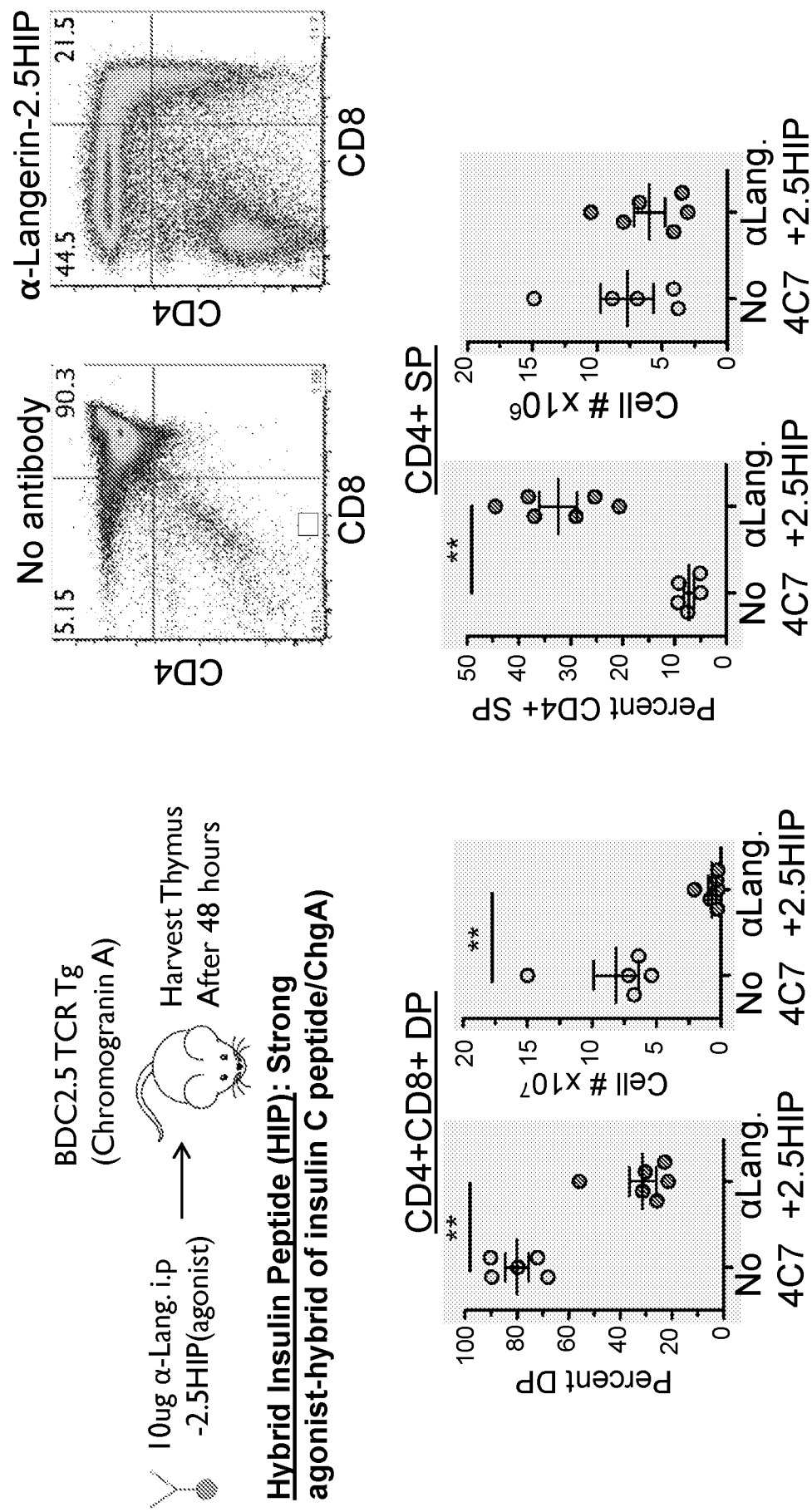


FIG. 2

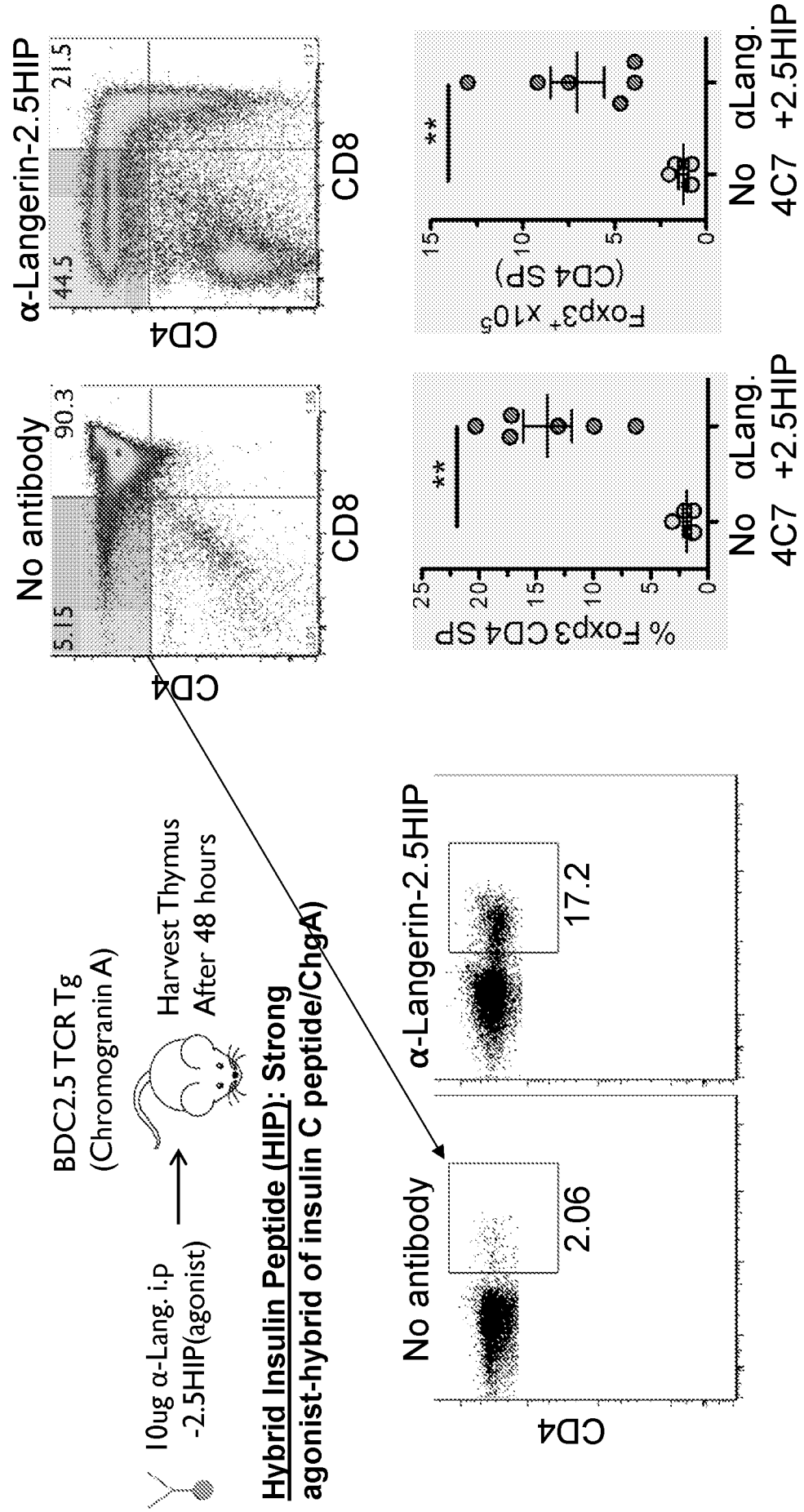
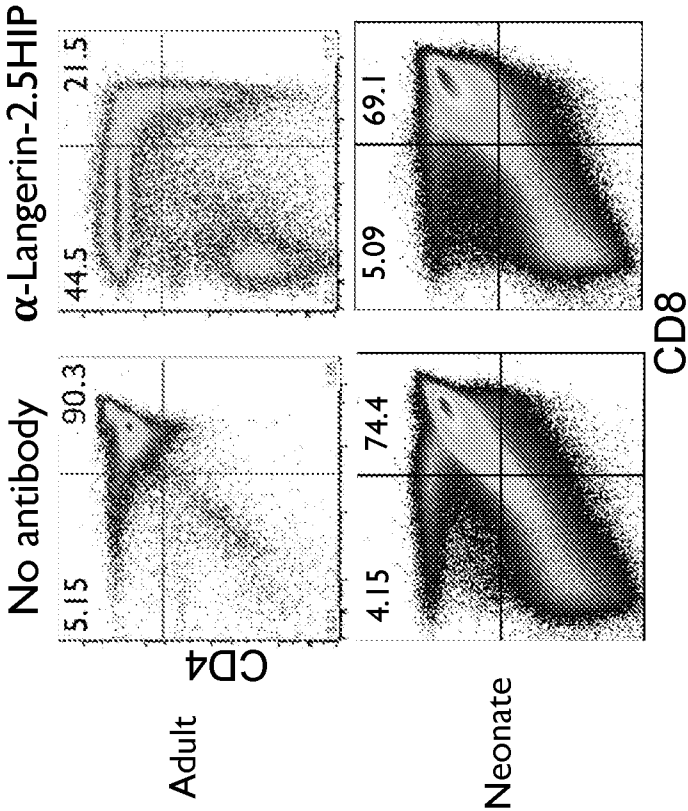
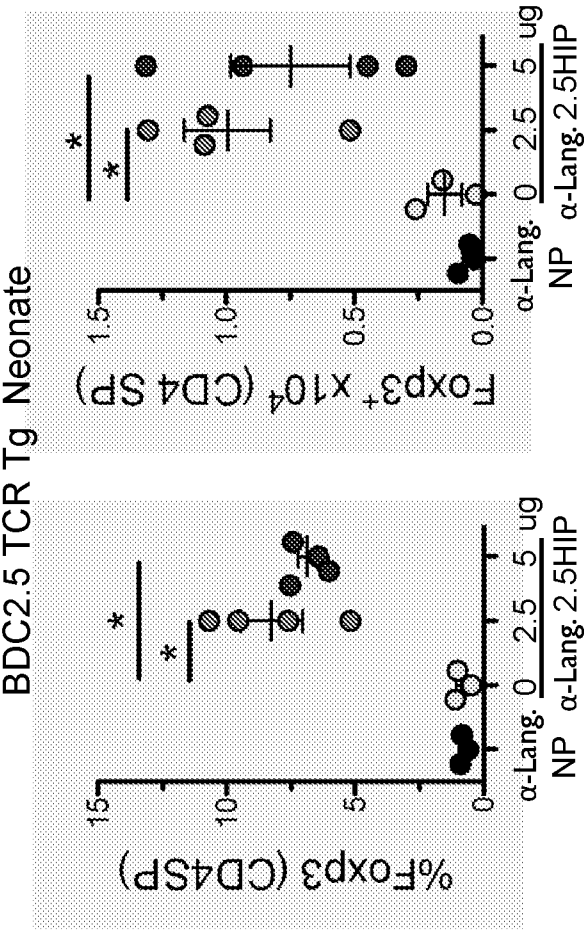
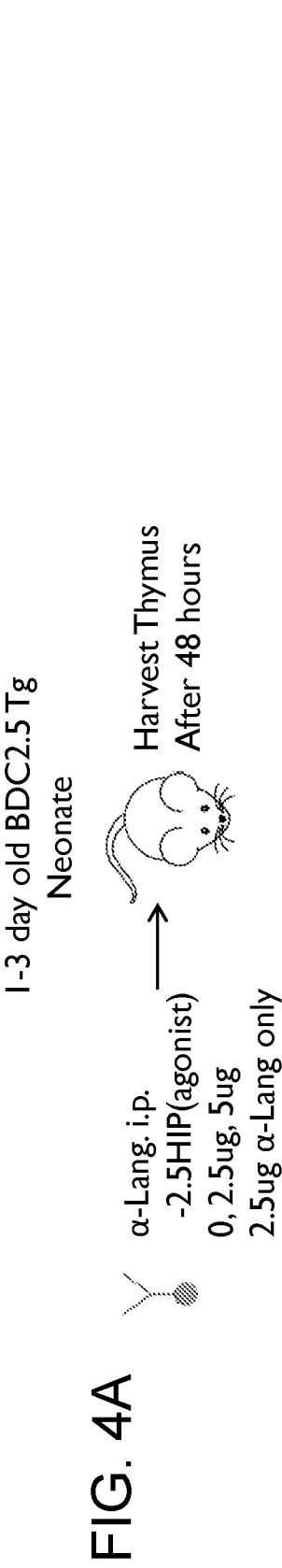
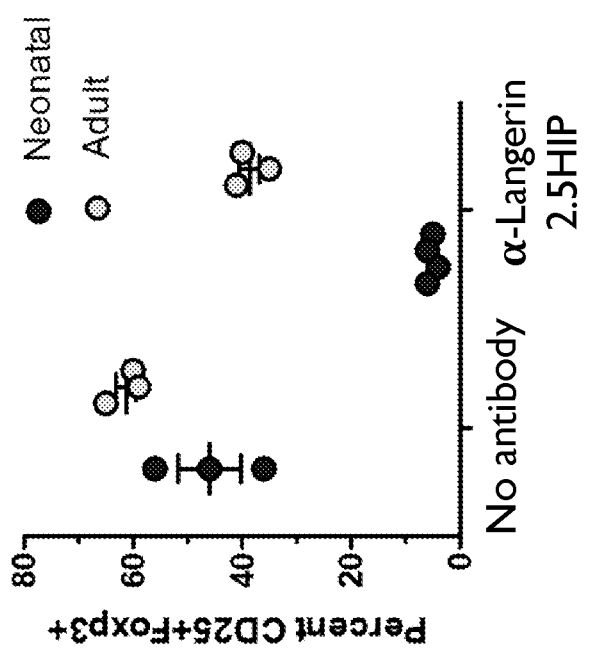
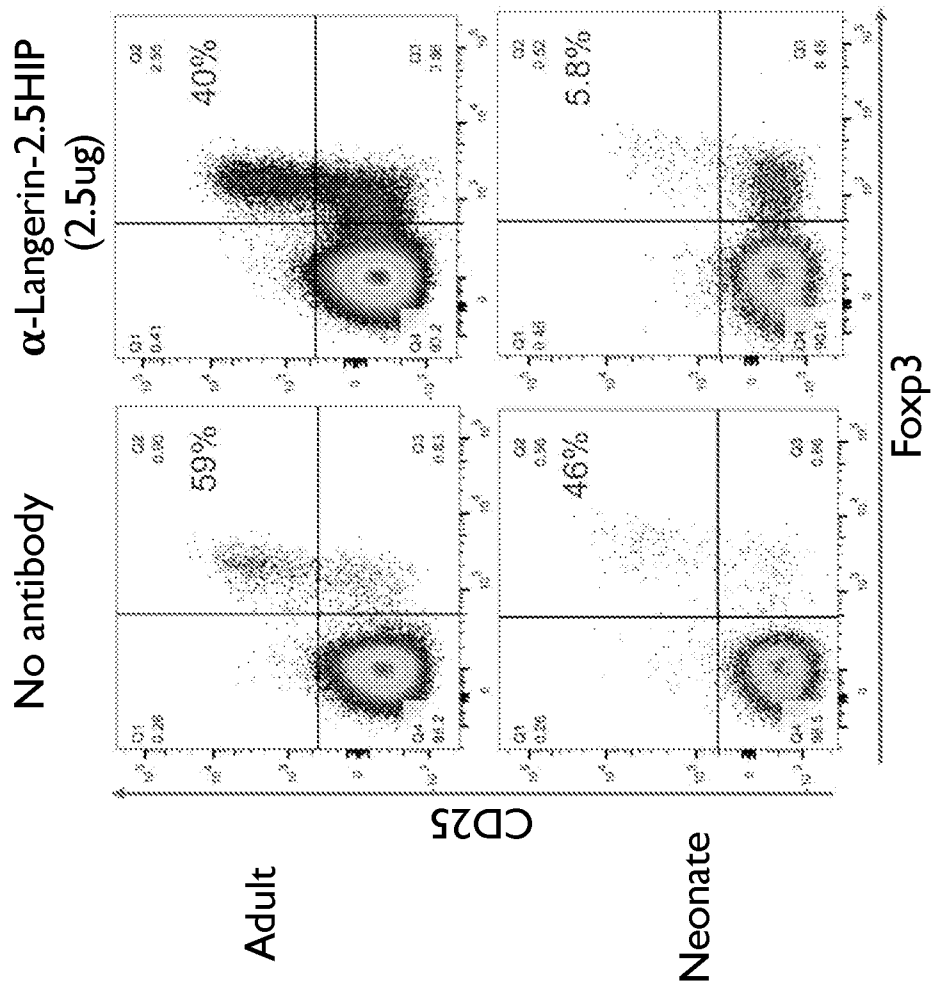


FIG. 3



Neonatal Thymocytes appear to be more resistant to apoptosis than adult thymocytes with anti-Langerin-2.5HIP treatment

BDC2.5TCRTg
Gated on CD4SP
Thymocytes



“New” Foxp3 Tregs are not CD25+
but we don’t know why or if it
matters

FIG. 5

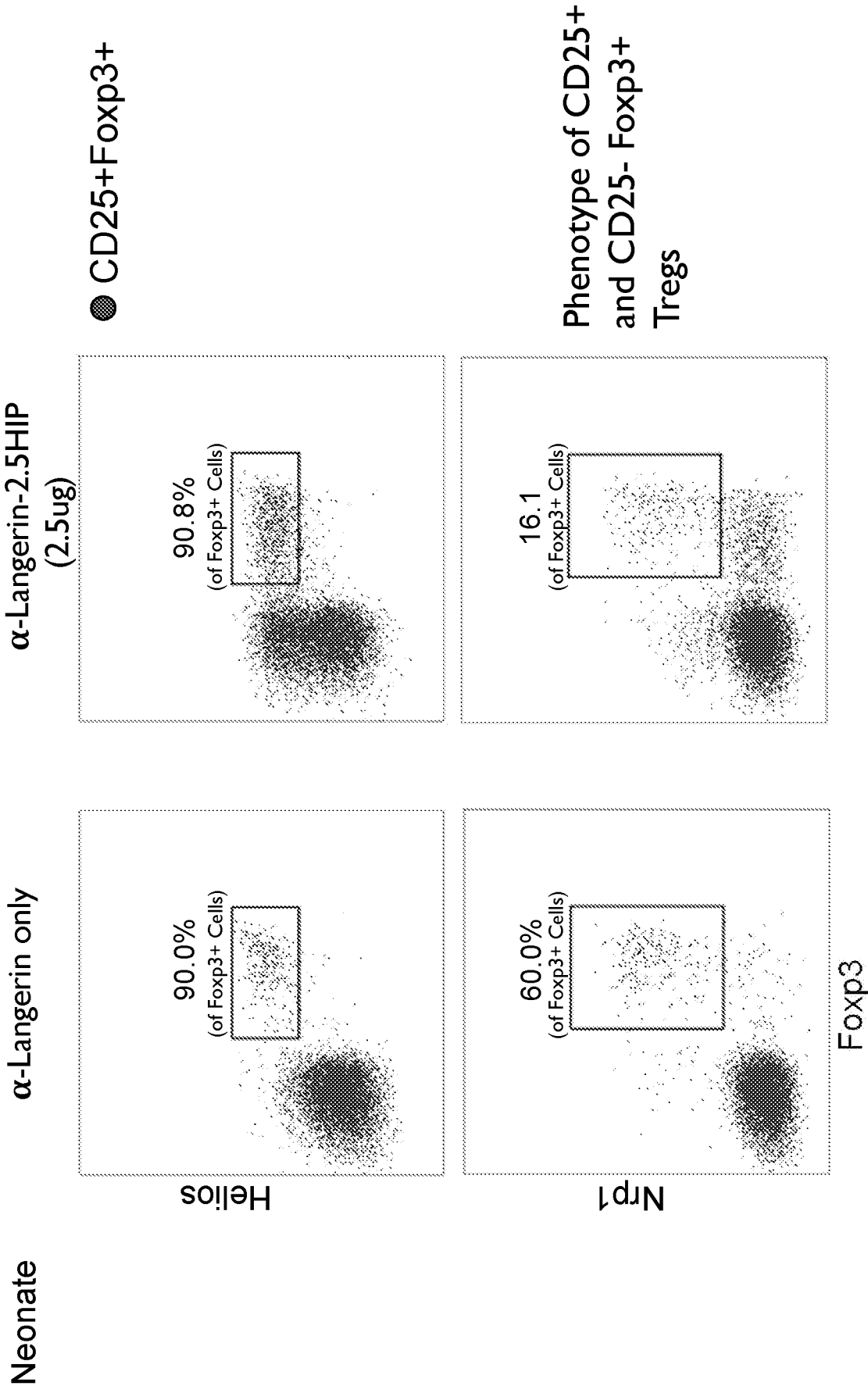


FIG. 6

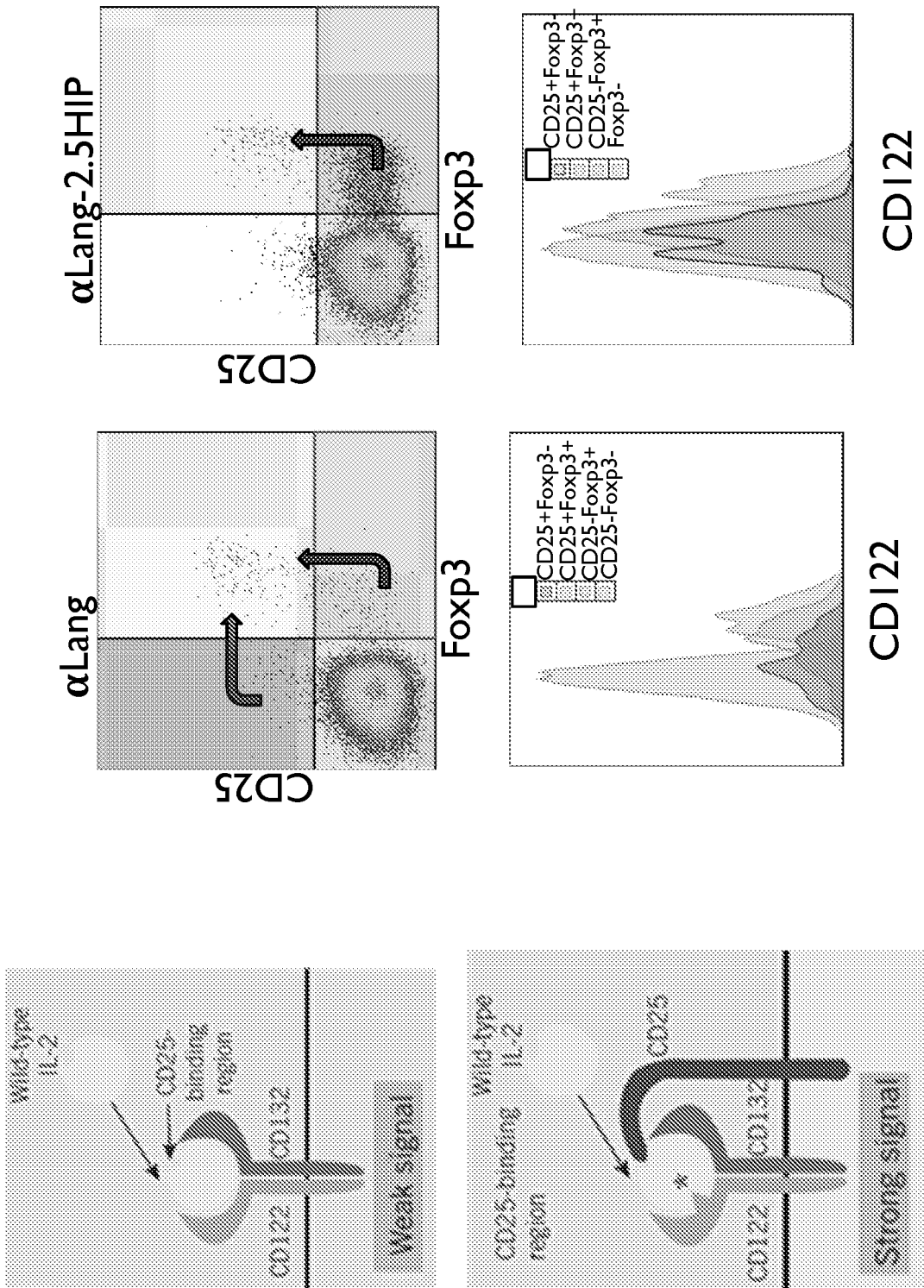


FIG. 7

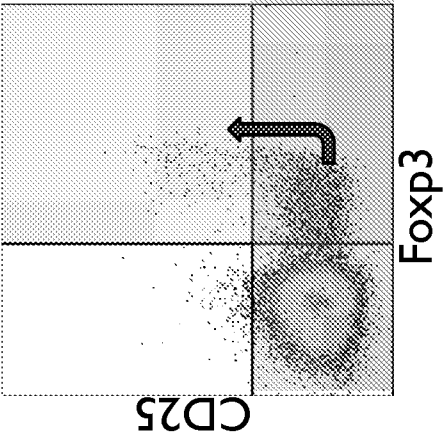
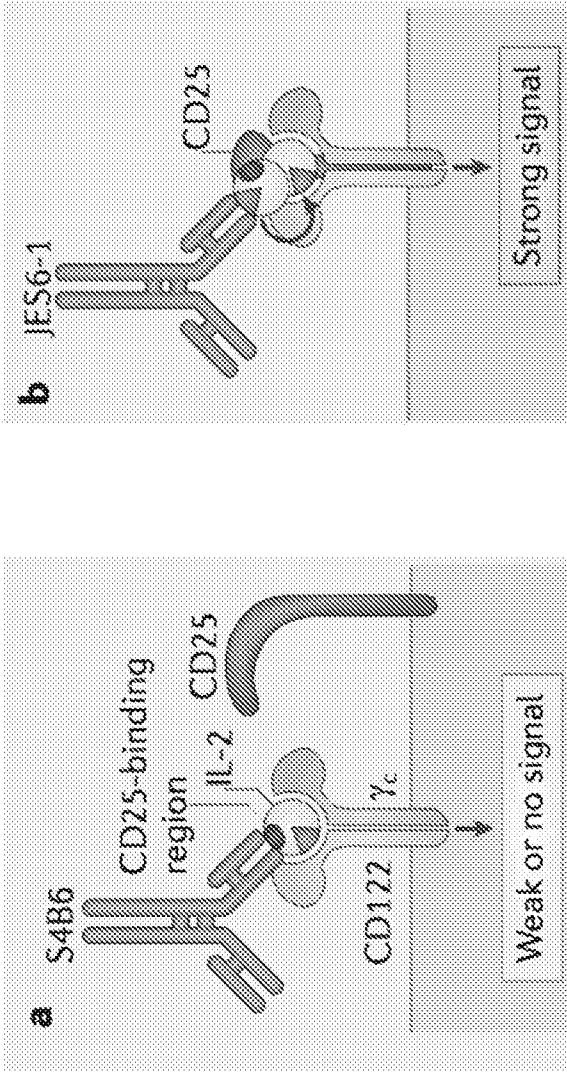
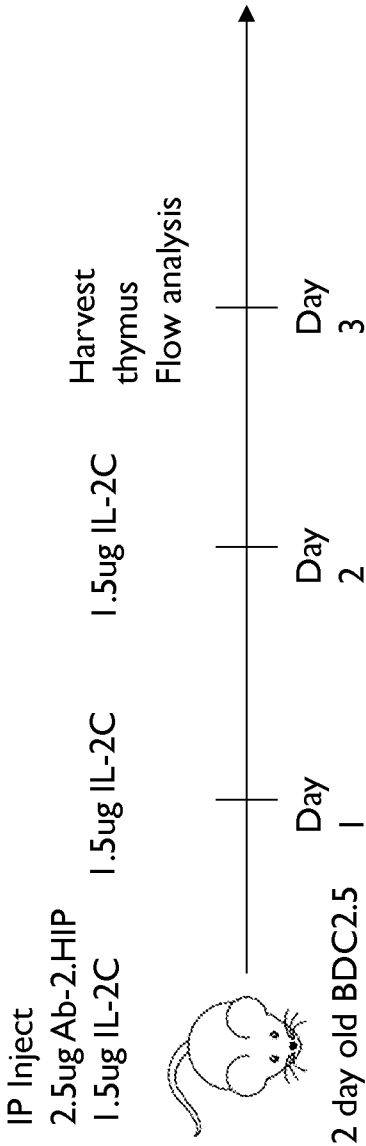


FIG. 8

- 1. α Lang-2.5HIP + HI IL-2Complex (JES6-IA12)
- 2. α Lang-2.5HIP + 1:1 HI:LO IL-2C (JES6-IA12+ JES6-5H4))



3. α Lang-2.5HIP + α Lang-hIL2

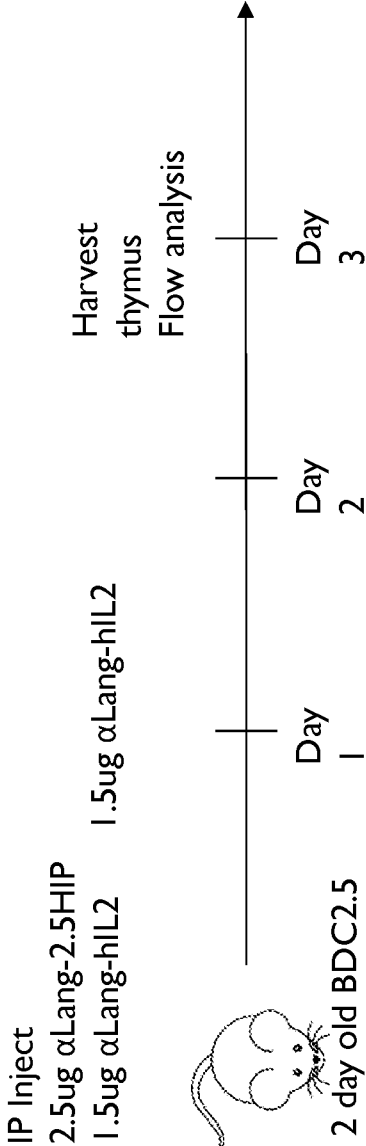


FIG. 9

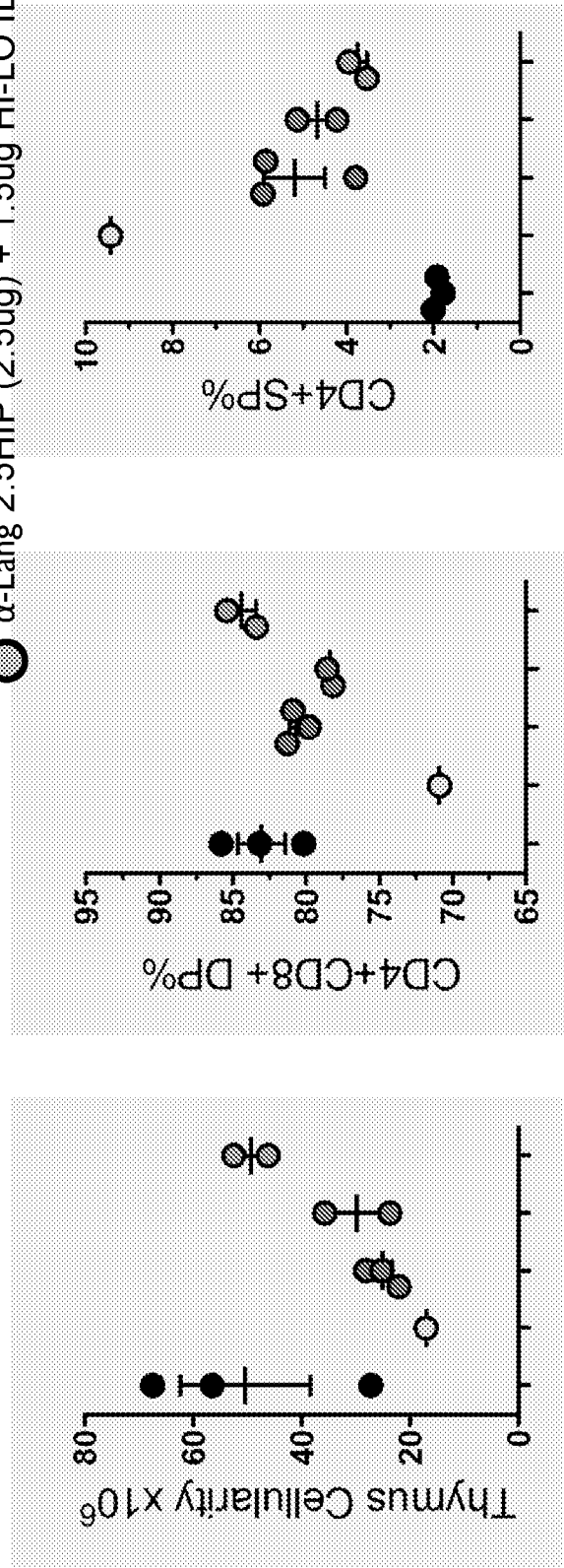
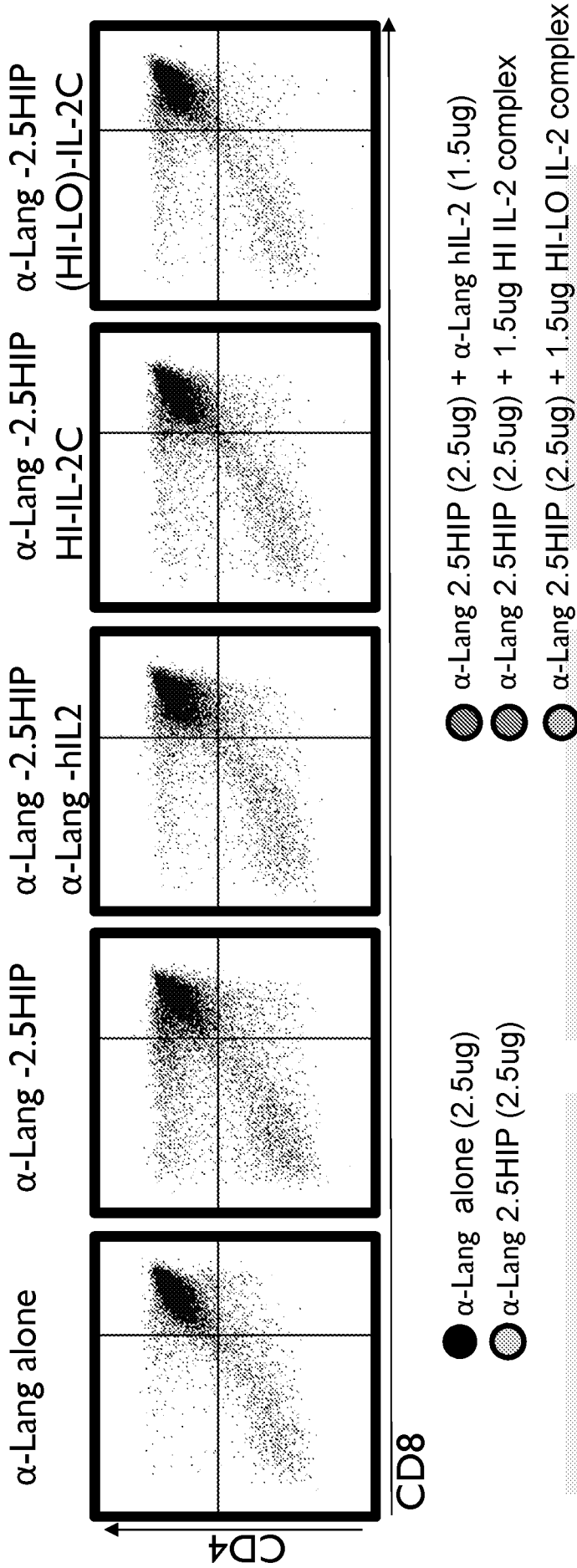


FIG. 10

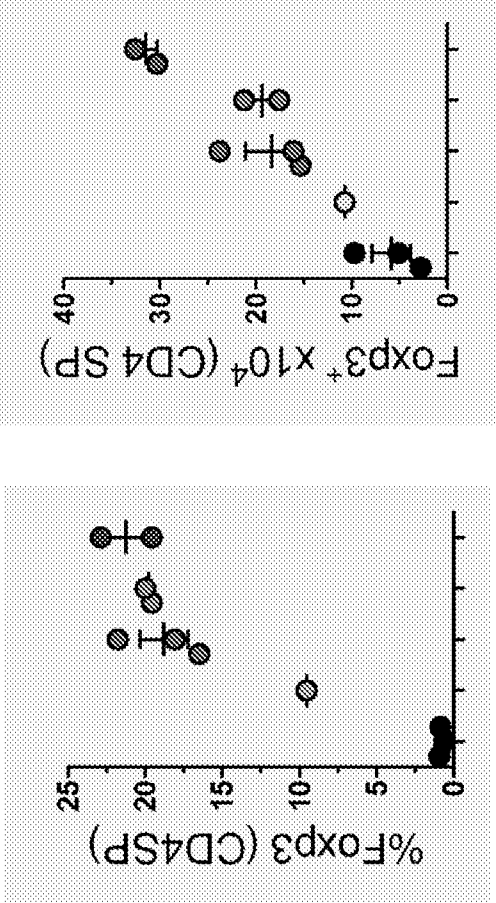
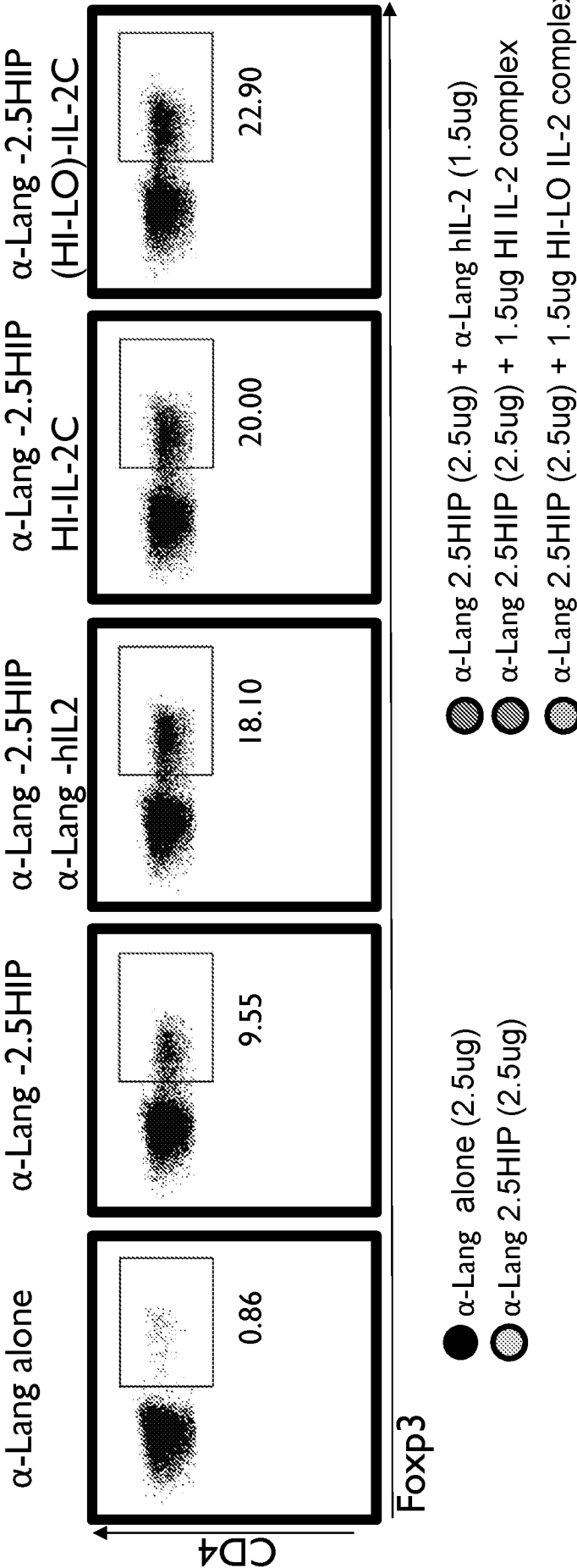


FIG. 11

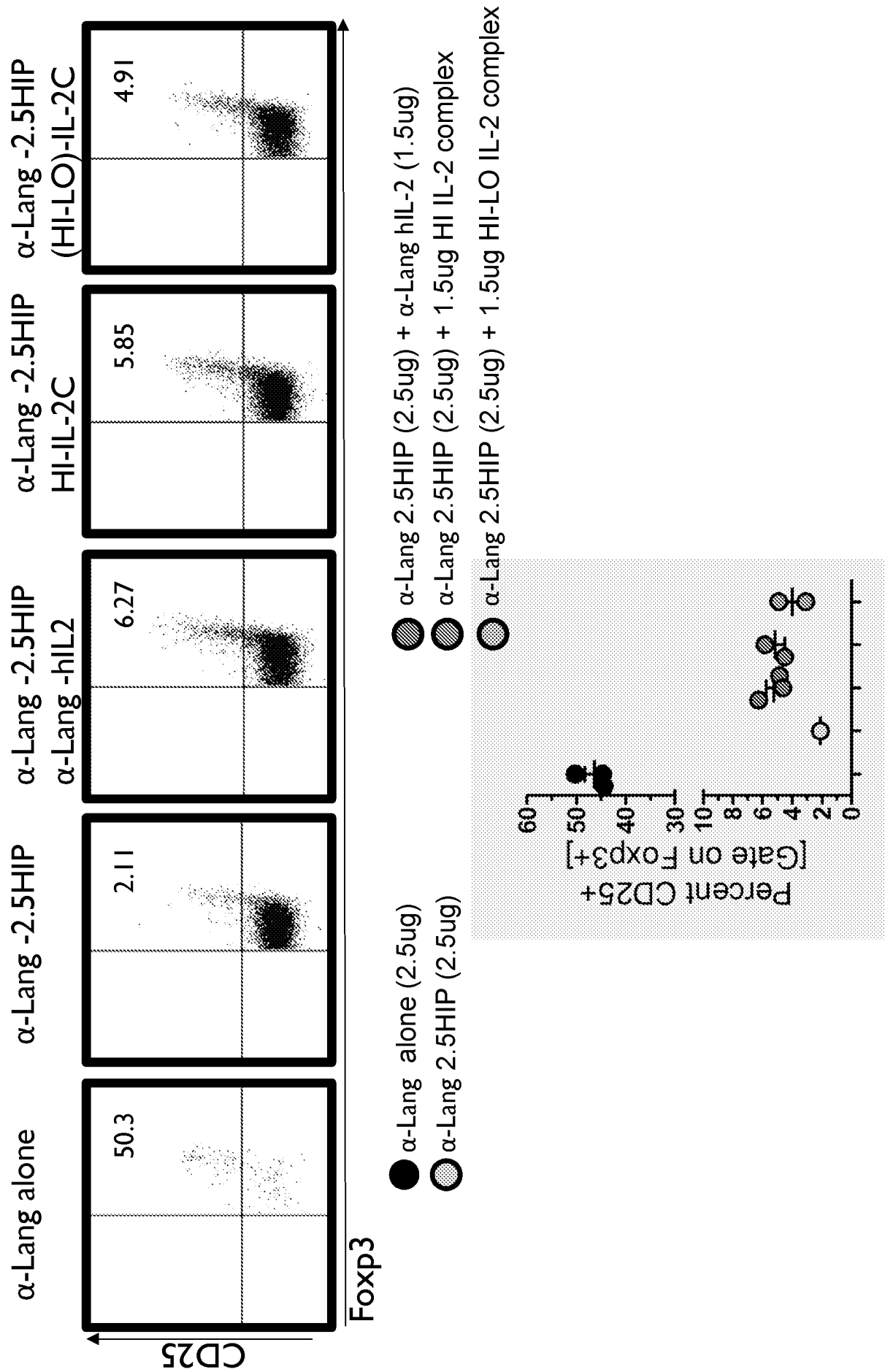


FIG. 12

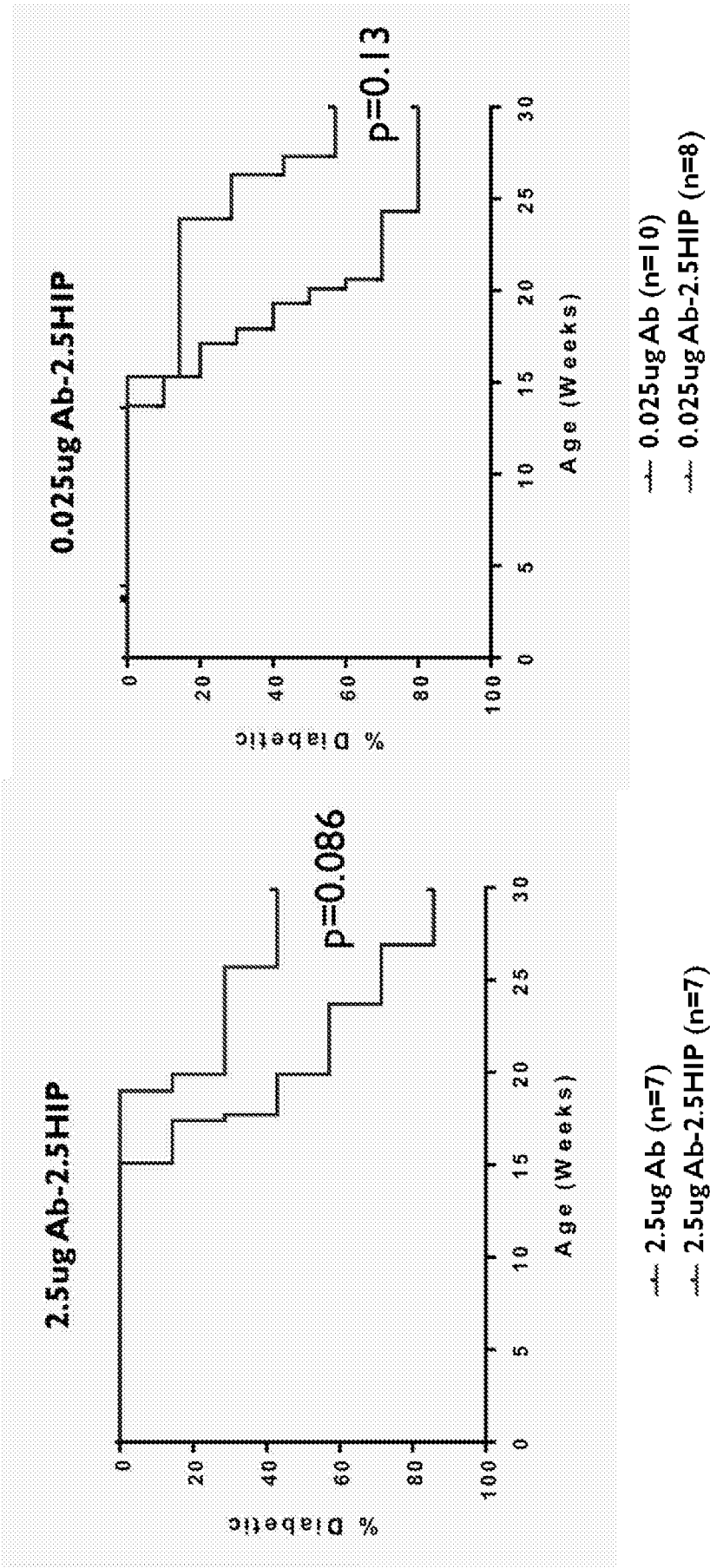


FIG. 13

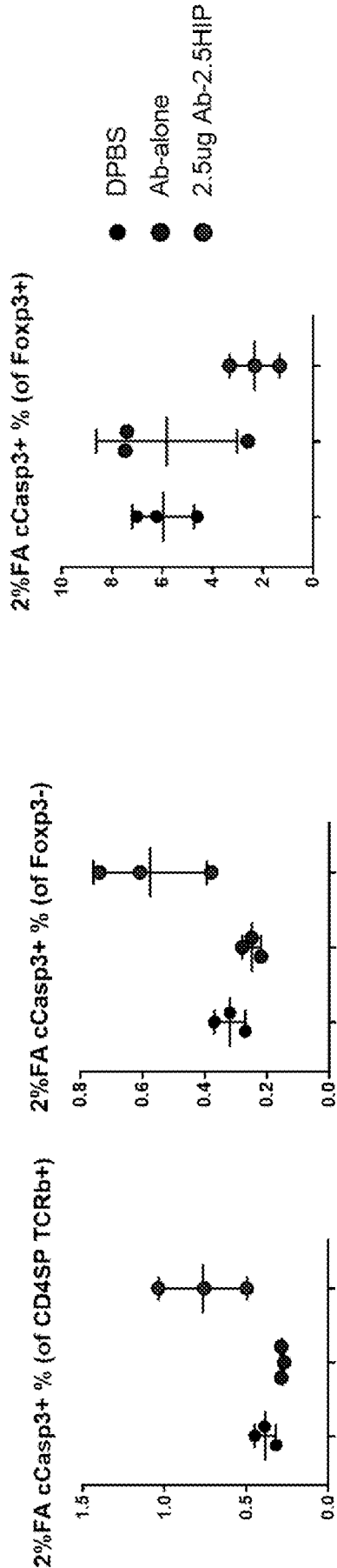
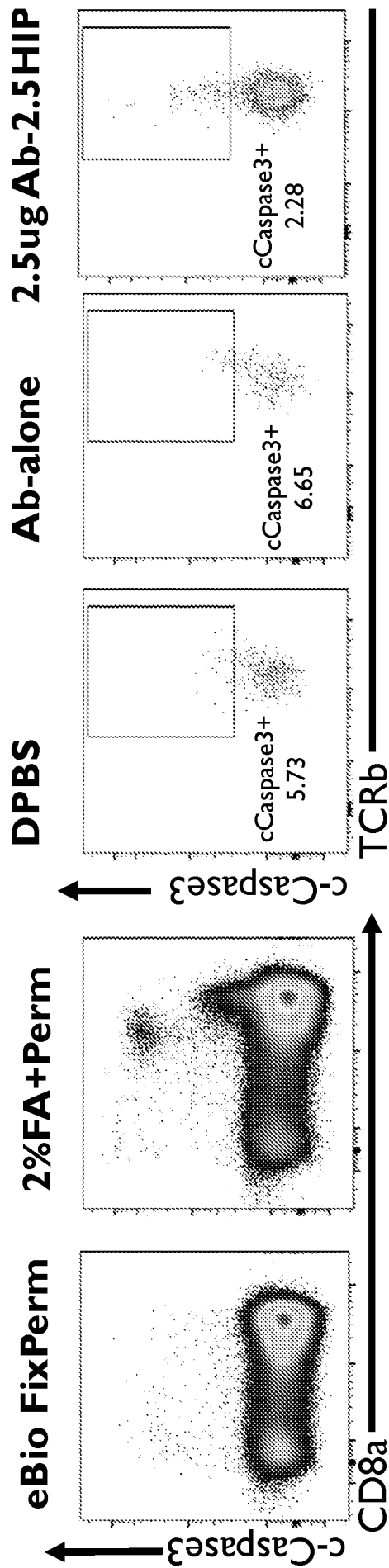
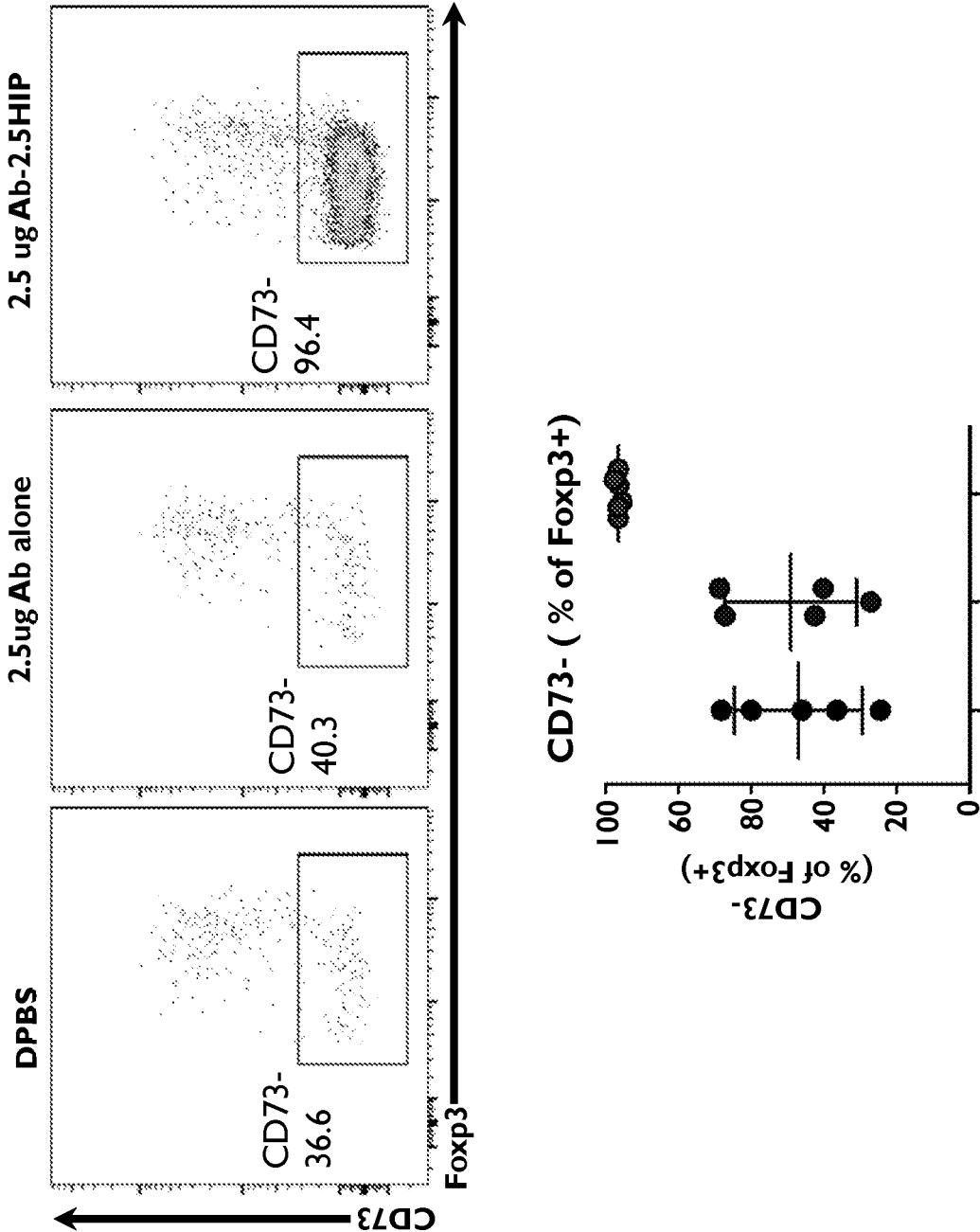


FIG. 14



Gated on CD4SP TCRb+ thymocytes

FIG. 15