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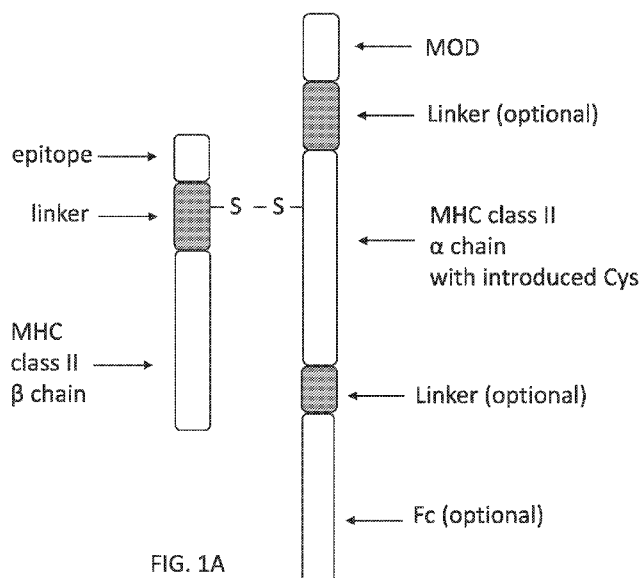


FIG. 1A

(57) Abstract: The present disclosure provides T-cell modulatory multimeric polypeptides (TMMPs) comprising an autoimmune disease-associated peptide epitope, MHC class II polypeptides, and one or more immunomodulatory polypeptides. A TMMP of the present disclosure is useful for modulating activity of a T cell. Thus, the present disclosure provides compositions and methods for modulating the activity of T cells, as well as compositions and methods for treating persons who have an autoimmune disease.

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MHC CLASS II T-CELL MODULATORY MULTIMERIC POLYPEPTIDES AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/076,314, filed September 9, 2020, which application is incorporated herein by reference in its entirety.

INTRODUCTION

[0002] Central to the proper functioning of the mammalian immune system are the coordinated activities and communications between two specialized cell types, antigen-presenting cells (“APCs”) and T cells. APCs serve to capture and break the proteins from foreign organisms, or abnormal proteins (*e.g.*, from genetic mutation in cancer cells), into smaller fragments suitable as signals for scrutiny by the larger immune system, including T cells. In particular, APCs break down proteins into small peptide fragments, which are then paired with proteins of the major histocompatibility complex (“MHC”) and displayed on the cell surface. Cell surface display of an MHC together with a peptide fragment, also known as a T cell epitope, provides the underlying scaffold surveilled by T cells, allowing for specific recognition. The peptide fragments can be pathogen-derived, tumor-derived, or derived from natural host proteins (self-proteins). Moreover, APCs can recognize other foreign components, such as bacterial toxins, viral proteins, viral DNA, viral RNA, etc., whose presence denotes an escalated threat level. The APCs relay this information to T cells through additional costimulatory signals in order to generate a more effective response.

[0003] T cells recognize peptide-major histocompatibility complex (“pMHC”) complexes through a specialized cell surface receptor, the T cell receptor (“TCR”). The TCR is unique to each T cell; as a consequence, each T cell is highly specific for a particular pMHC target. In order to adequately address the universe of potential threats, a very large number (~10,000,000) of distinct T cells with distinct TCRs exist in the human body. Further, any given T cell, specific for a particular T cell peptide, is initially a very small fraction of the total T cell population. Although normally dormant and in limited numbers, T cells bearing specific TCRs can be readily activated and amplified by APCs to generate highly potent T cell responses that involve many millions of T cells. Such activated T cell responses are capable of attacking and clearing viral infections, bacterial infections, and other cellular threats including tumors, as illustrated below. Conversely, the broad, non-specific activation of overly active T cell responses against self or shared antigens can give rise to T cells inappropriately attacking and destroying healthy tissues or cells.

[0004] MHC proteins are referred to as human leukocyte antigens (HLA) in humans. HLA class II gene loci include HLA-DM (HLA-DMA and HLA-DMB that encode HLA-DM α chain and HLA-DM β chain, respectively), HLA-DO (HLA-DOA and HLA-DOB that encode HLA-DO α chain and HLA-DO β chain, respectively), HLA-DP (HLA-DPA and HLA-DPB that encode HLA-DP α chain and HLA-DP β chain, respectively), HLA-DQ (HLA-DQA and HLA-DQB that encode HLA-DQ α chain and HLA-DQ β chain, respectively), and HLA-DR (HLA-DRA and HLA-DRB that encode HLA-DR α chain and HLA-DR β chain, respectively).

SUMMARY

[0005] The present disclosure provides T-cell modulatory multimeric polypeptides (TMMPs) comprising an autoimmune disease-associated peptide epitope, MHC class II polypeptides, and one or more immunomodulatory polypeptides. A TMMP of the present disclosure is useful for modulating activity of a T cell. Thus, the present disclosure provides compositions and methods for modulating the activity of T cells, as well as compositions and methods for treating persons who have an autoimmune disease.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIG. 1A-1E present schematic depictions of TMMPs of the present disclosure, in which the immunomodulatory polypeptide is in Position 1.

[0007] FIG. 2A-2D present schematic depictions of TMMPs of the present disclosure, in which the immunomodulatory polypeptide is in Position 2.

[0008] FIG. 3A-3D present schematic depictions of TMMPs of the present disclosure, in which the immunomodulatory polypeptide is in Position 3.

[0009] FIG. 4A-4D present schematic depictions of TMMPs of the present disclosure, in which the immunomodulatory polypeptide is in Position 5.

[0010] FIG. 5 is a schematic depiction of various possible positions of an immunomodulatory polypeptide in a TMMP of the present disclosure.

[0011] FIG. 6 provides amino acid sequence of an HLA Class II DRA α chain (SEQ ID NO:143).

[0012] FIG. 7 provides amino acid sequences of HLA Class II DRB1 β chains (from top to bottom SEQ ID NOs:144-156).

[0013] FIG. 8 provides amino acid sequences of HLA Class II DRB3 β chains (from to bottom SEQ ID NOs:157-160).

[0014] FIG. 9 provides an amino acid sequence of an HLA Class II DRB4 β chain (SEQ ID NO:161).

[0015] FIG. 10 provides an amino acid sequence of an HLA Class II DRB5 β chain (SEQ ID NO:162).

- [0016] FIG. 11 provides an amino acid sequence of an HLA Class II DMA α chain (SEQ ID NO:163).
- [0017] FIG. 12 provides an amino acid sequence of an HLA Class II DMB β chain (SEQ ID NO:164).
- [0018] FIG. 13 provides an amino acid sequence of an HLA Class II DOA α chain (SEQ ID NO:165).
- [0019] FIG. 14 provides an amino acid sequence of an HLA Class II DOB β chain (SEQ ID NO:166).
- [0020] FIG. 15 provides amino acid sequences of HLA Class II DPA1 α chains (from top to bottom SEQ ID NOs:167, 25).
- [0021] FIG. 16 provides amino acid sequences of HLA Class II DPB1 β chains (from top to bottom SEQ ID NOs:168-176).
- [0022] FIG. 17 provides amino acid sequences of HLA Class II DQA1 α chains (from top to bottom SEQ ID NOs:177-184).
- [0023] FIG. 18 provides an amino acid sequence of an HLA Class II DQA2 α chain (SEQ ID NO:185).
- [0024] FIG. 19A-19C provide amino acid sequences of HLA Class II DQB1 β chains (SEQ ID NOs:186, 187 and 188, respectively).
- [0025] FIG. 20A-20B provide amino acid sequence of HLA Class II DQB2 β chains (SEQ ID NOs:189 and 190, respectively).
- [0026] FIG. 21A-21G provide amino acid sequences of immunoglobulin Fc polypeptides (SEQ ID NOs:191-202, respectively).
- [0027] FIG. 22A-22N provide amino acid sequences of wild-type (FIG. 22A) and variant (FIG. 22B-22N) DRA*0101 α chains.
- [0028] FIG. 22O provides an amino acid sequence of a PD-L1 polypeptide.
- [0029] FIG. 23A-23J provide amino acid sequences of wild-type (FIG. 23A) and variant (FIG. 23B-23J) DRB1*0401 β chains.
- [0030] FIG. 24A-24I provide amino acid sequences of first and second polypeptide chains of TMMPs of the present disclosure.
- [0031] FIG. 25A-25C are schematic depictions of disulfide-linked antigen-presenting polypeptides (APPs) of the present disclosure.
- [0032] FIG. 26A-26W provide amino acid sequences of first and second polypeptide chains of APPs of the present disclosure.

DEFINITIONS

[0033] The terms “polynucleotide” and “nucleic acid,” used interchangeably herein, refer to a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. Thus, this term includes, but is not limited to, single-, double-, or multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, or a polymer comprising purine and pyrimidine bases or other natural, chemically or biochemically modified, non-natural, or derivatized nucleotide bases.

[0034] The terms "peptide," "polypeptide," and "protein" are used interchangeably herein, and refer to a polymeric form of amino acids of any length, which can include coded and non-coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified peptide backbones. Furthermore, as used herein, a "polypeptide" refers to a protein that includes modifications, such as deletions, additions, and substitutions (generally conservative in nature as would be known to a person in the art) to the native sequence, as long as the protein maintains the desired activity. These modifications can be deliberate, as through site-directed mutagenesis, or can be accidental, such as through mutations of hosts that produce the proteins, or errors due to polymerase chain reaction (PCR) amplification or other recombinant DNA methods. References herein to a specific residue or residue number in a known polypeptide, e.g., position 72 or 75 of human DRA MHC class II polypeptide, are understood to refer to the amino acid at that position in the wild-type polypeptide (i.e. I72 or K75). To the extent that the sequence of the wild-type polypeptide is altered, either by addition or deletion of one or more amino acids, one of ordinary skill will understand that a reference to the specific residue or residue number will be correspondingly altered so as to refer to the same specific amino acid in the altered polypeptide, which would be understood to reside at an altered position number. For example, if a human DRA MHC class II polypeptide is altered by the addition of one amino acid at the N-terminus, then a reference to position 72 or 75, or to residue I72 or K75, will be understood to indicate the amino acids that are at positions 73 or 76, or to residues I73 and K76. Likewise, a reference herein to substitution of a specific amino acid as a specific position, e.g., I72C, is understood to refer to a substitution of a cysteine for the amino acid at position 72 in the wild-type polypeptide, i.e., isoleucine. If, e.g., the wild-type polypeptide is altered to change the amino acid at position 72 from isoleucine to an alternate amino acid, then the reference to I72C will be understood to refer to the substitution of a cysteine for the alternate amino acid. If in such case the polypeptide is also altered by the addition or deletion of one or more amino acids, then the reference to I72C will be understood to refer to the substitution of a cysteine for the alternate amino acid at the altered position number. A reference to a "non-naturally occurring Cys residue" in a polypeptide, e.g., a DRA MHC class II polypeptide, means that the polypeptide comprises a Cys residue in a location where there is no Cys in the corresponding wild-type polypeptide. This can be accomplished through routine protein engineering in which a cysteine is substituted for the amino acid that occurs in the wild-type sequence, e.g., at position 72 or 75 of the DRA*0101 polypeptide (see FIG. 22G and 22H) instead of the isoleucine (I) or lysine (K) residues that are present in the wild-type DRA*0101 polypeptide (see FIG. 22A).

[0035] A polynucleotide or polypeptide has a certain percent "sequence identity" to another polynucleotide or polypeptide, meaning that, when aligned, that percentage of bases or amino acids are the same, and in the same relative position, when comparing the two sequences. Sequence identity can be determined in a number of different ways. To determine sequence identity, sequences can be aligned

using various convenient methods and computer programs (e.g., BLAST, T-COFFEE, MUSCLE, MAFFT, etc.), available over the world wide web at sites including ncbi.nlm.nih.gov/BLAST, ebi.ac.uk/Tools/msa/tcoffee/, ebi.ac.uk/Tools/msa/muscle/, mafft.cbrc.jp/alignment/software/. See, e.g., Altschul et al. (1990) *J. Mol. Biol.* 215:403-10. Unless otherwise stated, “sequence identity” as referred to herein is determined by BLAST (Basic Local Alignment Search Tool), as described in Altschul et al. (1990) *J. Mol. Biol.* 215:403.

[0036] As used herein the term “*in vivo*” refers to any process or procedure occurring inside of the body, e.g., of a patient having an autoimmune disease.

[0037] As used herein, “*in vitro*” refers to any process or procedure occurring outside of the body.

[0038] The term “conservative amino acid substitution” refers to the interchangeability in proteins of amino acid residues having similar side chains. For example, a group of amino acids having aliphatic side chains consists of glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains consists of serine and threonine; a group of amino acids having amide containing side chains consisting of asparagine and glutamine; a group of amino acids having aromatic side chains consists of phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains consists of lysine, arginine, and histidine; a group of amino acids having acidic side chains consists of glutamate and aspartate; and a group of amino acids having sulfur containing side chains consists of cysteine and methionine. Exemplary conservative amino acid substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine-glycine, and asparagine-glutamine.

[0039] The term “binding,” as used herein (e.g. with reference to binding of a T-cell modulatory antigen-presenting polypeptide to a polypeptide (e.g., a T-cell receptor) on a T cell), refers to a non-covalent interaction between two molecules. Non-covalent binding refers to a direct association between two molecules, due to, for example, electrostatic, hydrophobic, ionic, and/or hydrogen-bond interactions, including interactions such as salt bridges and water bridges.. “Covalent binding” or “covalent bond,” as used herein, refers to the formation of one or more covalent chemical bonds between two different molecules.

[0040] “T cell” includes all types of immune cells expressing CD3, including T-helper cells (CD4⁺ cells), cytotoxic T-cells (CD8⁺ cells), T-regulatory cells (Treg), and NK-T cells.

[0041] The term “immunomodulatory polypeptide” (also referred to as a “co-stimulatory polypeptide”), as used herein, includes a polypeptide on an antigen presenting cell (APC) (e.g., a dendritic cell, a B cell, and the like), or a portion of the polypeptide on an APC, that specifically binds a cognate co-immunomodulatory polypeptide on a T cell, thereby providing a signal which, in addition to the primary signal provided by, for instance, binding of a TCR/CD3 complex with a major histocompatibility

complex (MHC) polypeptide loaded with peptide, mediates a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like. An immunomodulatory polypeptide can include, but is not limited to, a cytokine (e.g., IL-2; TGF β), CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2, 4-1BBL, OX40L, Fas ligand (FasL), inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM), CD30L, CD40, CD70, CD83, HLA-G, MICA, MICB, HVEM, lymphotoxin beta receptor, 3/TR6, ILT3, ILT4, and HVEM.

[0042] As noted above, an “immunomodulatory polypeptide” (also referred to herein as a “MOD”) specifically binds a cognate co-immunomodulatory polypeptide on a T cell (e.g., a target T cell).

[0043] “Phosphate buffer saline” or “PBS”, as used herein, means a water-based buffer solution, typically available as a concentrated solution. Unless stated otherwise, the PBS solution used in this disclosure contains sodium chloride (500 mM), sodium phosphate dibasic (10 mM), potassium phosphate monobasic (2 mM), potassium chloride (2.7 mM), and the rest water. The pH of the PBS is 7.5 ± 0.15 . The buffer can be prepared in 18.2 megohms DNase, and RNase free water and filtered through 0.22 micron filter.

[0044] “Recombinant,” as used herein, means that a particular nucleic acid (DNA or RNA) is the product of various combinations of cloning, restriction, polymerase chain reaction (PCR) and/or ligation steps resulting in a construct having a structural coding or non-coding sequence distinguishable from endogenous nucleic acids found in natural systems. DNA sequences encoding polypeptides can be assembled from cDNA fragments or from a series of synthetic oligonucleotides, to provide a synthetic nucleic acid which is capable of being expressed from a recombinant transcriptional unit contained in a cell or in a cell-free transcription and translation system.

[0045] The terms “recombinant expression vector,” or “DNA construct” are used interchangeably herein to refer to a DNA molecule comprising a vector and at least one insert. Recombinant expression vectors are usually generated for the purpose of expressing and/or propagating the insert(s), or for the construction of other recombinant nucleotide sequences. The insert(s) may or may not be operably linked to a promoter sequence and may or may not be operably linked to DNA regulatory sequences.

[0046] As used herein, the term “affinity” refers to the equilibrium constant for the reversible binding of two agents (e.g., an antibody and an antigen) and is expressed as a dissociation constant (K_D). As used herein, the term “avidity” refers to the resistance of a complex of two or more agents to dissociation after dilution.

[0047] The term “binding” refers to a direct association between two molecules, due to, for example, covalent, electrostatic, hydrophobic, and ionic and/or hydrogen-bond interactions, including interactions such as salt bridges and water bridges. “

[0048] As used herein the term “*in vivo*” refers to any process or procedure occurring inside of the body, e.g., of a patient having an autoimmune disease.

[0049] As used herein, “*in vitro*” refers to any process or procedure occurring outside of the body.

[0050] The terms “treatment”, “treating” and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. “Treatment” as used herein covers any treatment of a disease or symptom in a mammal, and includes: (a) preventing the disease or symptom from occurring in a subject which may be predisposed to acquiring the disease or symptom but has not yet been diagnosed as having it; (b) inhibiting the disease or symptom, i.e., arresting its development; and/or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy will desirably be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease.

[0051] The terms “individual,” “subject,” “host,” and “patient,” are used interchangeably herein and refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired. Mammals include, e.g., humans, non-human primates, rodents (e.g., rats; mice), lagomorphs (e.g., rabbits), ungulates (e.g., cows, sheep, pigs, horses, goats, and the like), etc.

[0052] Unless indicated otherwise, the term “substantially” is intended to encompass both “wholly” and “largely but not wholly”. For example, an Ig Fc that “substantially does not induce cell lysis” means an Ig Fc that induces no cell lysis at all or that largely but not wholly induces no cell lysis.

[0053] As used herein, the term “about” used in connection with an amount indicates that the amount can vary by 10%. For example, “about 100” means an amount of from 90-110. Where about is used in the context of a range, the “about” used in reference to the lower amount of the range means that the lower amount includes an amount that is 10% lower than the lower amount of the range, and “about” used in reference to the higher amount of the range means that the higher amount includes an amount 10% higher than the higher amount of the range. For example, from about 100 to about 1000 means that the range extends from 90 to 1100.

[0054] It is to be understood that this disclosure is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

[0055] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0056] 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 this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0057] It must be noted that as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an immunomodulatory polypeptide” includes a plurality of such immunomodulatory polypeptides and reference to “the Treg” includes reference to one or more Tregs and equivalents thereof known to those skilled in the art, and so forth. It is further noted that the claims may be drafted to exclude any optional element or any element that is included in a list or other recitation of elements that share a common generic or specific feature, property, or activity. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0058] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the disclosure are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present disclosure and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

[0059] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication

provided may be different from the actual publication dates which may need to be independently confirmed.

DETAILED DESCRIPTION

[0060] The present disclosure provides T-cell modulatory multimeric polypeptides (TMMPs) comprising an autoimmune disease-associated peptide, MHC class II polypeptides, and one or more immunomodulatory polypeptides. A TMMP of the present disclosure is useful for modulating activity of a T cell. Thus, the present disclosure provides compositions and methods for modulating the activity of T cells, as well as compositions and methods for treating individuals who have an autoimmune disease.

T-CELL MODULATORY MULTIMERIC POLYPEPTIDES

[0061] The present disclosure provides TMMPs that comprise a disulfide-linked heterodimer comprising: a) a first polypeptide comprising: i) a peptide that, when present in a TMMP of this disclosure, presents an autoimmune disease-associated epitope capable of being bound by a T-cell receptor (TCR) on the surface of a T cell (hereinafter an “autoimmune disease-associated peptide”), where the autoimmune disease-associated peptide is associated with an autoimmune disease other than Type 1 Diabetes (T1D) or celiac disease, or in addition to, T1D or celiac disease; and ii) a first major histocompatibility complex (MHC) class II polypeptide; and b) a second polypeptide comprising a second MHC class II polypeptide. One or both polypeptides of the heterodimer comprise one or more immunomodulatory polypeptides. The first and the second polypeptides of the heterodimer are covalently linked to one another via at least one disulfide bond. One of the polypeptides of the heterodimer optionally comprises an immunoglobulin (Ig) Fc polypeptide or a non-Ig scaffold. A TMMP of the present disclosure can comprise two disulfide-linked heterodimers. When both heterodimers include Ig Fc polypeptides, disulfide bonds will spontaneously form between the respective Ig Fc polypeptides to covalently link the two heterodimers to one another (depicted schematically in FIG. 1E).

[0062] As noted above, the first polypeptide and the second polypeptide of a heterodimer of a TMMP of the present disclosure are covalently linked to one another via at least one disulfide bond. For example, the at least one disulfide bond is present between: i) a Cys present in the first MHC class II polypeptide and a Cys present in the second MHC class II polypeptide; or ii) a Cys present in a peptide linker in the first polypeptide and a Cys present in an MHC class II polypeptide present in the second polypeptide; or iii) a Cys present in a peptide linker in the second polypeptide and a Cys present in an MHC class II polypeptide present in the first polypeptide. These various embodiments are depicted schematically in FIG. 1A-1E, FIG. 2A-2D, FIG. 3A-3D, and FIG. 4A-4D.

[0063] The at least one disulfide bond formed between the first polypeptide and the second polypeptide of a heterodimer of a TMMP of the present disclosure provides for increased stability and/or expression of the TMMP, compared to a control TMMP lacking the at least one disulfide bond. For example, in

some cases, a TMMP of the present disclosure is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, or more than 100-fold, more stable than a control TMMP lacking the at least one disulfide bond. Stability can be determined by measuring the amount of intact TMMP monomer remaining after incubation of the TMMP for a specific period of time at a specific temperature (e.g., for 1 hour at 37°C; 1 day at 37°C; 5 days at 37°C; 1 hour at 42°C; 1 day at 42°C; 5 days at 42°C; and the like). A disulfide-bonded TMMP of the present disclosure will in some cases exhibit a stability after 3 days at 37°C at TMMP concentrations of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL in the PBS buffer solution containing 500 mM NaCl (described above), as measured by the percent monomer remaining, that is greater than 50%, greater than 60%, greater than 70%, greater than 80%, or greater than 90%. A disulfide-bonded TMMP of the present disclosure will in some cases exhibit a stability after 5 days at 37°C at TMMP concentrations of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL in the PBS buffer solution containing 500 mM NaCl (described above), as measured by the percent monomer remaining, that is greater than 50%, greater than 60%, greater than 70%, or greater than 80%. A disulfide-bonded TMMP of the present disclosure will in some cases exhibit a stability after 3 days at 42°C at TMMP concentrations of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL in the PBS buffer solution containing 500 mM NaCl (described above), as measured by the percent monomer remaining, that is greater than 30%, greater than 40%, greater than 50%, or greater than 60%. A disulfide-bonded TMMP of the present disclosure will in some cases exhibit a stability after 5 days at 42°C at TMMP concentrations of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL in the PBS buffer solution containing 500 mM NaCl (described above), as measured by the percent monomer remaining, that is greater than 30%, greater than 40%, greater than 50%, or greater than 60%. Whether a protein is present in solution as a monomer can be determined using size exclusion chromatography (SEC). Analytical SEC can be performed using a Superdex 200 Increase (3.2x300 mm) column (e.g., from GE Healthcare). For example, for analytical SEC, the running buffer can be PBS containing 500 mM NaCl (described above) and the flow rate can be 0.15 ml/minute.

[0064] As another example, in some cases, a TMMP of the present disclosure is expressed (produced) in a Chinese hamster ovary (CHO) cell *in vitro* at a level that is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, or more than 100-fold, higher than the expression level of a control TMMP lacking the at least one disulfide bond when expressed under the same conditions and in the same CHO cells. Expression levels can be determined by: i) producing the TMMP in a mammalian cell *in vitro* in a CHO cell *in vitro*; and ii) determining the amount of TMMP produced by the mammalian cell. For example, where a TMMP comprises an Ig Fc polypeptide, the TMMP can be isolated from the mammalian cells

and/or from culture medium in which the mammalian cells are cultured, where isolation of the TMMP can be carried out by affinity chromatography, e.g., on a Protein A column, a Protein G column, or the like. An example of a suitable mammalian cell is a CHO cell; e.g., an Expi-CHO-S™ cell (e.g., ThermoFisher Scientific, Catalog #A29127).

[0065] A protein consisting of the desired TMMP is referred to herein as a “monomer.” For example, “monomer” can refer to a single heterodimer that is the desired TMMP when the heterodimer is not covalently bonded to another heterodimer, e.g., when the heterodimer does not include an optional Ig Fc polypeptide. Likewise, a homodimeric TMMP protein comprising 2 heterodimers, each comprising 2 polypeptide chains (for a total of 4 polypeptide chains), where 2 of the four polypeptide chains comprise Ig Fc polypeptides, wherein the Ig Fc polypeptides spontaneously form disulfide bonds that covalently link the heterodimers to each other, also is referred to herein as a “monomer.” The term “monomer” does not include aggregates of monomers. Whether a protein is present in solution as a monomer can be determined using size exclusion chromatography (SEC). Analytical SEC can be performed using a Superdex 200 Increase (3.2x300 mm) column (e.g., from GE Healthcare). For example, for analytical SEC, the running buffer can be PBS containing 500 mM NaCl (described above) and the flow rate can be 0.15 ml/minute.

[0066] In some cases, a TMMP of the present disclosure exhibits at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, or more than 100-fold, greater stability in the PBS buffer solution containing 500 mM NaCl (described above) *in vitro* over a specified period of time and at a specified temperature (e.g., in a solution at a temperature of from 37°C to 42°C for a period of time of from 1 hour to 28 days; e.g., for 1 hour at 37°C; 1 day at 37°C; 5 days at 37°C; 1 hour at 42°C; 1 day at 42°C; 5 days at 42°C; 5 days at 37°C; 10 days at 37°C; 14 days at 37°C; 28 days at 37°C; and the like), compared to a control TMMP lacking the at least one disulfide bond between the first polypeptide and the second polypeptide of the heterodimer. The TMMP can be present in the PBS buffer solution in a concentration of from 0.1 mg/mL to 10 mg/mL, and the buffer solution can be kept at 37°C or 42°C for 1 hour, 5 days, 10 days, 14 days, 21 days, or 28 days. As discussed herein, stability is determined by measuring the percent of monomer (as defined above) remaining in the solution after a specified time in the solution at a specified temperature. Loss of monomer often is characterized by the formation of aggregates, or alternatively by the breakdown of the monomer into one or more separate polypeptide chains or fragments thereof. Thus, for example, “at least 10% greater stability” means that at least 10% more TMMP monomer is present in a test sample than in a control sample comprising the same polypeptide chains but lacking the at least one disulfide bond between the first polypeptide and the second polypeptide of the heterodimer. The percent more monomer in the test sample is calculated based on the amount of monomer in the control

sample. Thus, e.g., after a specified period of time at a specified temperature, at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, or more than 100-fold, more monomer remains of a TMMP of the present disclosure (comprising a disulfide bond between the first and second polypeptide chains) compared to the amount of monomer remaining of a control TMMP lacking a disulfide bond between the first and second polypeptide chains.

[0067] As discussed herein, stability can be expressed as the “% monomer” (as defined above) remaining after incubation of a TMMP of the present disclosure in the PBS buffer described above at a certain temperature for a certain amount of time. In some cases, the % monomers remaining after incubation of a TMMP of the present disclosure in the PBS buffer for a given time at a given temperature (e.g., 37°C for 1 hour; 37°C for 1 day; 37°C for 5 days; 37°C for 10 days; 37°C for 14 days, 37°C for 28 days; 42°C for 1 hour; 42°C for 1 day; 42°C for 5 days; 42°C for 10 days; or the like) is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, or more than 100-fold, higher than the % monomers of a control TMMP lacking at least one disulfide bond between the two polypeptides of the heterodimers.

[0068] A TMMP of the present disclosure can comprise two heterodimers. In some cases, the two heterodimers each include an Ig Fc polypeptide. In some cases, the TMMP comprises two heterodimers that are disulfide linked to one another via Cys residues present in the Ig Fc polypeptides. See, e.g., FIG. 1E for a schematic depiction of an example of such a TMMP.

Immunomodulatory Polypeptides

[0069] A TMMP of the present disclosure comprises one or more immunomodulatory polypeptides. In some cases, a TMMP of the present disclosure comprises a single immunomodulatory polypeptide. In some cases, where a TMMP of the present disclosure comprises a single immunomodulatory polypeptide, the single immunomodulatory polypeptide is on the first polypeptide. In some cases, where a TMMP of the present disclosure comprises a single immunomodulatory polypeptide, the single immunomodulatory polypeptide is on the second polypeptide. In some cases, where a TMMP of the present disclosure comprises a single immunomodulatory polypeptide, the single immunomodulatory polypeptide is on the second polypeptide, and the second polypeptide comprises an MHC class II alpha polypeptide.

[0070] In some cases, a TMMP of the present disclosure comprises two or more immunomodulatory polypeptides (e.g., 2, 3, 4, or 5 immunomodulatory polypeptides). As noted above, a TMMP of the present disclosure comprises a disulfide-linked heterodimer comprising a first polypeptide and a second polypeptide. In some cases, the two or more immunomodulatory polypeptides are present in the first

polypeptide chain only. In some cases, the two or more immunomodulatory polypeptides are present in the second polypeptide chain only. In some cases, where a TMPP of the present disclosure comprises a first polypeptide and a second polypeptide, at least one of the two or more immunomodulatory polypeptides are present in the first polypeptide chain; and at least one of the two or more immunomodulatory polypeptides are present in the second polypeptide chain. In some cases, where a TMPP of the present disclosure comprises two or more immunomodulatory polypeptides, the immunomodulatory polypeptides are on the second polypeptide, and the second polypeptide comprises an MHC class II alpha polypeptide. Where a TMPP of the present disclosure comprises 2 or 3 copies of an immunomodulatory polypeptide, in some cases, the 2 or 3 copies are in tandem. Where a TMPP of the present disclosure comprises 2 or 3 copies of an immunomodulatory polypeptide, in some cases, the 2 or 3 copies are separated from one another by a linker.

[0071] In some cases, where a TMPP of the present disclosure comprises two immunomodulatory polypeptides, the two immunomodulatory polypeptides have the same amino acid sequence, i.e., the TMPP comprises two copies of an immunomodulatory polypeptide. In some cases, where a TMPP of the present disclosure comprises two immunomodulatory polypeptides, the two immunomodulatory polypeptides do not have the same amino acid sequence; e.g., one of the two immunomodulatory polypeptides comprises a first amino acid sequence and the second of the two immunomodulatory polypeptides comprises a second amino acid sequence, where the first and the second amino acid sequences are not identical. In some cases, the first and the second amino acid sequences differ from one another in amino acid sequence by from 1 amino acid to 10 amino acids, from 10 amino acids to 25 amino acids, or more than 25 amino acids. In some cases, the first and the second amino acid sequences share less than 98%, less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, or less than 70%, amino acid sequence identity with one another.

[0072] A TMPP of the present disclosure modulates activity of a T cell. In some cases, a TMPP of the present disclosure reduces activity of an autoreactive T cell and/or an autoreactive B cell, e.g., a T cell reactive with an autoimmune disease-associated epitope or a B cell reactive with an autoimmune disease-associated epitope (e.g., a B cell that produces antibodies that bind to an autoimmune disease-associated epitope). In some cases, a TMPP of the present disclosure increases the number and/or activity of a regulator T cell (Treg), resulting in reduced activity of an autoreactive T cell and/or an autoreactive B cell. Thus, a TMPP of the present disclosure is useful for treating an autoimmune disease in an individual.

[0073] Immunomodulatory polypeptides that are suitable for inclusion in a TMPP of the present disclosure include, but are not limited to, IL-2, transforming growth factor-beta (TGF β), JAG1, CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2, 4-1BBL, OX40L, Fas ligand (FasL), inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM), CD30L, CD40, CD70, CD83,

HLA-G, MICA, MICB, lymphotoxin beta receptor, 3/TR6, ILT3, ILT4, and HVEM. In some cases, a TMMP of the present disclosure comprises one or more immunomodulatory polypeptides selected from the group consisting of an IL-2 polypeptide, a PD-L1 polypeptide, a FasL polypeptide, a TGF- β polypeptide, and combinations thereof. In some cases, a TMMP of the present disclosure comprises one or more immunomodulatory polypeptides, where at least one of the one or more immunomodulatory polypeptides is a PD-L1 polypeptide. In some cases, a TMMP of the present disclosure comprises one or more immunomodulatory polypeptides, where at least one of the one or more immunomodulatory polypeptides is an IL-2 polypeptide. In some cases, a TMMP of the present disclosure comprises one or more immunomodulatory polypeptides, where at least one of the one or more immunomodulatory polypeptides is a TGF- β polypeptide. In some cases, a TMMP of the present disclosure comprises one or more immunomodulatory polypeptides, where at least one of the one or more immunomodulatory polypeptides is a FasL polypeptide.

[0074] In some cases, an immunomodulatory polypeptide suitable for inclusion in a TMPP of the present disclosure comprises a wild-type amino acid sequence. In some cases, an immunomodulatory polypeptide suitable for inclusion in a TMPP of the present disclosure is a variant, e.g., comprising from 1 to 10 amino acid substitutions relative to a wild-type or naturally-occurring immunomodulatory polypeptide. In some cases, an immunomodulatory polypeptide suitable for inclusion in a TMPP of the present disclosure is a variant that exhibits reduced affinity to its cognate co-immunomodulatory polypeptide (e.g., a co-immunomodulatory polypeptide present on the surface of a T cell), compared to the affinity of the wild-type or naturally-occurring immunomodulatory polypeptide for the cognate co-immunomodulatory polypeptide.

Arrangement of TMMP Components

[0075] A TMMP of the present disclosure comprises two disulfide-linked heterodimeric polypeptides comprising the following components: a) an autoimmune disease-associated peptide; b) an MHC class II α polypeptide; c) an MHC class II β polypeptide; and d) one or more immunomodulatory polypeptides; and may also one or more peptide linkers; and may also include Ig Fc polypeptide(s). Although the autoimmune disease-associated peptide can be on same polypeptide with either the MHC class II α polypeptide or MHC class II β polypeptide, the autoimmune disease-associated peptide typically will be on the same polypeptide chain as the MHC class II β polypeptide. These components can be present in a TMMP of the present disclosure in various arrangements. Examples of such arrangements are depicted schematically in FIG. 1A-1E, FIG. 2A-2D, FIG. 3A-3D, and FIG. 4A-4D. In some cases, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) an MHC class II β polypeptide, optionally joined by a linker; and b) a second polypeptide comprising: i) an

immunomodulatory polypeptide; and ii) an MHC class II α polypeptide, optionally joined by a linker, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond. In some cases, a TMPP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) an MHC class II β polypeptide, optionally joined by a linker; and b) a second polypeptide comprising: i) one or more immunomodulatory polypeptides (where two or more immunomodulatory polypeptides are present, they optionally may be joined by one or more linkers); ii) an MHC class II α polypeptide, optionally joined by a linker to the immunomodulatory polypeptide(s); and iii) an Ig Fc polypeptide, optionally joined by a linker to the MHC class II α polypeptide; where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond. The arrangement (N-terminus to C-terminus order) of the immunomodulatory polypeptide, the MHC class II α polypeptide, and the Ig Fc polypeptide, can vary.

[0076] As one example of a possible arrangement, in some cases, a TMPP of the present disclosure comprises a heterodimer comprising two disulfide-linked polypeptides, wherein the heterodimer comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an autoimmune disease-associated peptide; and ii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an immunomodulatory polypeptide; ii) an MHC class II α polypeptide; and iii) an Ig Fc polypeptide. (See FIG. 5, MOD position 1.) As another example of a possible arrangement, in some cases, a TMPP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an autoimmune disease-associated peptide; and ii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including one or more linkers that do not comprise a Cys): i) an MHC class II α polypeptide; ii) one or more immunomodulatory polypeptides; and iii) an Ig Fc polypeptide. (See FIG. 5, MOD position 2.) As another example of a possible arrangement, in some cases, a TMPP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an autoimmune disease-associated peptide; and ii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an MHC class II α polypeptide; ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD position 3.) As another example of a possible arrangement, in some cases, a TMPP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) one or more immunomodulatory polypeptides; ii) an autoimmune disease-associated peptide; and iii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an MHC class II α polypeptide; and ii) an Ig Fc polypeptide. (See FIG.

5, MOD position 4.). As another example of a possible arrangement, in some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an autoimmune disease-associated peptide; ii) an MHC class II β polypeptide; and iii) one or more immunomodulatory polypeptides; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including linkers): i) an MHC class II α polypeptide; and ii) an Ig Fc polypeptide. (See FIG. 5, MOD position 5.) The immunomodulatory polypeptide(s) can be on the same polypeptide chain as the MHC class II α polypeptides.

[0077] Generally speaking, potential locations in the heterodimer for disulfide bonds are where residues in the first and second polypeptides of the heterodimer are separated by a distance of 5 angstroms or less. Such locations represent potential locations where Cys residues, if not naturally present, can be substituted for the residues that exist in the polypeptides. A first polypeptide and a second polypeptide thus can be linked via a disulfide bond between two Cys residues that are generally no more than about 5 angstroms apart from one another in the heterodimer. In some cases, one or both of the Cys residues are non-naturally-occurring. An amino acid in the alpha chain and an amino acid in the beta chain of MHC class II polypeptides that are no more than 5 angstroms from one another in an MHC class II heterodimer, represent amino acids that, when substituted with a Cys, can form a disulfide bond in a TMMP of the present disclosure. Similarly, a disulfide bond can be formed i) between a Cys residue in a linker and a Cys residue in an MHC class II polypeptide, or ii) between a Cys residue in a linker in one polypeptide of the heterodimer and a Cys residue in a linker in the other polypeptide of the heterodimer, where the two Cys residues are no more than about 5 angstroms apart from each other in the heterodimer. Notably, however, not all pairs of residues separated by about 5 angstroms or less will be suitable for formation of a disulfide bond or provide a disulfide bond that stabilizes the resulting heterodimer.

Disulfide Bond Between a Peptide Linker and an MHC class II Polypeptide

[0078] In any of the above embodiments, in some cases the TMMP comprises a peptide linker between the autoimmune disease-associated peptide and the MHC class II polypeptide. Where desired, the linker can comprise a Cys that can be used to form a disulfide bond between the two polypeptides in the heterodimer.

Position 1 MOD(s)

[0079] In some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a peptide linker comprising a Cys; and iii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including one or more linkers that do not comprise a

Cys): i) one or more immunomodulatory polypeptides; ii) an MHC class II α chain; and (optionally) iii) an Ig Fc polypeptide. (See FIG. 5, MOD position 1.) The peptide linker comprising a Cys can comprise an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). In any of the above embodiments, in some cases the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof, and in some cases the immunomodulatory polypeptide is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide. In any of the above embodiments, in some cases, the MHC class II α chain comprises an amino acid substitution of an amino acid (other than a Cys) with a Cys, such that the Cys in the MHC class II α chain forms a disulfide bond with the Cys in the first polypeptide linker.

Position 2 MOD(s)

[0080] In some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a peptide linker comprising a Cys; and iii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including one or more linkers that do not comprise a Cys): i) an MHC class II α chain; ii) one or more immunomodulatory polypeptides; and iii) an Ig Fc polypeptide. (See FIG. 5, MOD position 2.) The peptide linker comprising a Cys can comprise, e.g., an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). Other peptide linkers comprising a Cys may be used. In any of the above embodiments, in some cases the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof, and in some cases, the immunomodulatory polypeptide is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a

multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide. In any of the above embodiments, in some cases, the MHC class II α chain comprises an amino acid substitution of an amino acid (other than a Cys) with a Cys, such that the Cys in the MHC class II α chain forms a disulfide bond with the Cys in the linker.

Position 3 MOD(s)

[0081] In some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a peptide linker comprising a Cys; and iii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus (optionally including one or more linkers that do not comprise a Cys): i) an MHC class II α chain; ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD position 3.) The peptide linker comprising a Cys can comprise, e.g., an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). Other peptide linkers comprising a Cys may be used. In any of the above embodiments, in some cases, the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof. In any of the above embodiments, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof. In any of the above embodiments, in some cases, the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof. In any of the above embodiments, in some cases, the immunomodulatory polypeptide is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide. In any of the above embodiments, in some cases, the MHC class II α chain comprises an amino acid substitution of an amino acid (other than a Cys) with a Cys, such that the Cys in the MHC class II α chain forms a disulfide bond with the Cys in the linker.

Position 4 MOD(s)

[0082] In some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) one or more immunomodulatory polypeptides; ii) an

autoimmune disease-associated peptide; ii) a peptide linker comprising a Cys; and iii) an MHC class II β polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain; and (optionally) ii) an Ig Fc polypeptide, optionally joined by a linker that does not comprise a Cys. (See FIG. 5, MOD position 4.) The peptide linker comprising a Cys can comprise, e.g., an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). Other peptide linkers comprising a Cys may be used. In any of the above embodiments, in some cases the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof, and in some cases the immunomodulatory polypeptide is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide. In any of the above embodiments, in some cases, the MHC class II α chain comprises an amino acid substitution of an amino acid (other than a Cys) with a Cys, such that the Cys in the MHC class II α chain forms a disulfide bond with the Cys in the linker.

Position 5 MOD(s)

[0083] In some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a peptide linker comprising a Cys; iii) an MHC class II β polypeptide; and iv) one or more immunomodulatory polypeptides; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain; and (optionally) ii) an Ig Fc polypeptide, optionally joined by a linker that does not comprise a Cys. (See FIG. 5, MOD position 4.) The peptide linker comprising a Cys can comprise, e.g., an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). Other peptide linkers comprising a Cys may be used. In any of the above embodiments, in some cases the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof, and in some cases the

immunomodulatory polypeptide is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide. In any of the above embodiments, in some cases, the MHC class II α chain comprises an amino acid substitution of an amino acid (other than a Cys) with a Cys, such that the Cys in the MHC class II α chain forms a disulfide bond with the Cys in the linker.

Disulfide Bond Between Peptide Linkers in the First and Second Polypeptides

[0084] In some cases, the TMMP comprises a first Cys-containing peptide linker between the autoimmune disease-associated peptide and the MHC class II polypeptide in the first polypeptide, and a second Cys-containing peptide linker between two of the components in the second polypeptide. In such cases, the Cys residues in the first and second Cys-containing linkers can be used to form a disulfide bond between the two polypeptides in the heterodimer.

Position 1 MOD(s)

[0085] In some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a first peptide linker comprising a Cys; and iii) an MHC class II β polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) one or more immunomodulatory polypeptides; ii) an MHC class II α chain (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% amino acid sequence identity to the amino acid sequence depicted in FIG. 13A); and (optionally) iii) an Ig Fc polypeptide. (See FIG. 5, MOD position 1.) The second polypeptide comprises a second peptide linker that comprises a Cys, where the second peptide linker is positioned either between the immunomodulatory polypeptides and the MHC class II α chain or between the MHC class II α chain and the Ig Fc, if present. The second polypeptide optionally may include one or more linkers that do not comprise a Cys. The peptide linkers comprising a Cys can comprise an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). In any

of the above embodiments, in some cases the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof, and in some cases the immunomodulatory polypeptide is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

Position 3 MOD(s)

[0086] In some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a first peptide linker comprising a Cys; and iii) an MHC class II β polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% amino acid sequence identity to the amino acid sequence depicted in FIG. 22A); ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD position 3.) The second polypeptide comprises a second peptide linker that comprises a Cys, where the second peptide linker is positioned either between the MHC class II α chain and the Ig Fc or between the Ig Fc and the one or more immunomodulatory polypeptides. The second polypeptide optionally may include one or more linkers that do not comprise a Cys. The peptide linkers comprising a Cys can comprise an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). In any of the above embodiments, in some cases the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof, in some cases the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof, and in some cases the immunomodulatory polypeptide is a FasL polypeptide or variant thereof. The peptide linkers comprising a Cys can comprise, e.g., an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer

from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). Other peptide linkers comprising a Cys may be used. In any of the above embodiments, in some cases, the immunomodulatory polypeptide is a PD-L1 polypeptide or variant thereof. In any of the above embodiments, in some cases the immunomodulatory polypeptide is a TGF- β polypeptide or variant thereof. In any of the above embodiments, in some cases, the immunomodulatory polypeptide is an IL-2 polypeptide or variant thereof. In any of the above embodiments, in some cases, the immunomodulatory polypeptide is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

[0087] Alternatively, following the same design of including a Cys-containing linker in the first polypeptide between the autoimmune disease-associated peptide and the MHC class II β polypeptide, and a Cys-containing linker between two of the components in the second polypeptide, a disulfide-linked TMMP can be constructed in which the one or more immunomodulatory polypeptides are at Position 2, 4 or 5 as those positions are described above and depicted schematically in FIG. 5.

Disulfide Bond Between the Two MHC class II Polypeptides

[0088] As noted above, in some cases, the first polypeptide of a heterodimer of a TMMP of the present disclosure comprises a first MHC class II polypeptide comprising an amino acid substitution that results in a Cys (a "first Cys"); and the second polypeptide comprises a second MHC class II polypeptide comprising an amino acid substitution that results in a Cys (a "second Cys"); where the heterodimer comprises a disulfide bond formed between the first Cys and the second Cys. For example, in some cases, the first polypeptide comprises an MHC class II β polypeptide comprising an amino acid substitution that results in a Cys (a "first Cys"); and the second polypeptide comprises an MHC class II α polypeptide comprising an amino acid substitution that results in a Cys (a "second Cys"); where the heterodimer comprises a disulfide bond formed between the first Cys and the second Cys.

Position 1 MOD(s)

[0089] In some cases, for example, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a first MHC class II polypeptide comprising a substitution of an amino acid (other than a Cys) with a Cys (a "first Cys"), the components of the first polypeptide optionally being joined by a linker that does not comprise a Cys; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i)

one or more immunomodulatory polypeptides; ii) a second MHC class II polypeptide comprising a substitution of an amino acid (other than a Cys) with a Cys (a “second Cys”); and iii) optionally an Ig Fc polypeptide, the components of the second polypeptide optionally being joined by one or more linkers that do not comprise a Cys; where the first polypeptide and the second polypeptide are linked via a disulfide bond between the first Cys and the second Cys. (See FIG. 5, MOD position 1.) In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, in some cases the one or more immunomodulatory polypeptides is a TGF- β polypeptide or variant thereof, in some cases the one or more immunomodulatory polypeptides is an IL-2 polypeptide or variant thereof, and in some cases the one or more immunomodulatory polypeptides is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison’s disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren’s syndrome-associated peptide, and a psoriasis-associated peptide. In any of the above embodiments, in some cases, the first MHC class II polypeptide is an MHC class II β chain polypeptide and the second MHC class II polypeptide is an MHC class II α chain polypeptide.

Position 3 MOD(s)

[0090] As another example, in some cases, a TMMP of the present disclosure comprises: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a first MHC class II polypeptide comprising a substitution of an amino acid (other than a Cys) with a Cys (a “first Cys”), the components of the first polypeptide optionally being joined by a linker that does not comprise a Cys; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a second MHC class II polypeptide comprising a substitution of an amino acid (other than a Cys) with a Cys (a “second Cys”); ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides, the components of the second polypeptide optionally being joined by a linker that does not comprise a Cys; where the first polypeptide and the second polypeptide are linked via a disulfide bond between the first Cys and the second Cys. (See FIG. 5, MOD position 3.) In any of the above embodiments, in some cases the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, in some cases the one or more immunomodulatory polypeptides is a TGF- β polypeptide or variant thereof, in some cases the one or more immunomodulatory polypeptides is an IL-2 polypeptide or variant thereof, and in some cases the one or more immunomodulatory polypeptides is a FasL polypeptide or variant thereof. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-

associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide. In any of the above embodiments, in some cases, the first MHC class II polypeptide is an MHC class II β chain polypeptide and the second MHC class II polypeptide is an MHC class II α chain polypeptide.

[0091] Alternatively, following the same design of including a Cys in each of the first and second polypeptides, a disulfide-linked TMMP can be constructed in which the one or more immunomodulatory polypeptides are at Position 2, 4, or 5 as those positions are described above and depicted schematically in FIG. 5.

MHC CLASS II POLYPEPTIDES

[0092] As noted above, a TMMP of the present disclosure comprises MHC class II polypeptides.

[0093] Naturally occurring MHC class II polypeptides comprise an α chain and a β chain. As used herein, the term "MHC class II polypeptides" include human leukocyte antigen (HLA) α - and β -chains. MHC class II polypeptides include MHC class II DP α and β polypeptides, DM α and β polypeptides, DOA α and β polypeptides, DOB α and β polypeptides, DQ α and β polypeptides, and DR α and β polypeptides. As used herein, a "MHC class II polypeptide" can comprise a MHC class II α chain polypeptide, a MHC class II β chain polypeptide, or only a portion of a MHC class II α or β chain polypeptide. For example, a "MHC class II polypeptide" can be a polypeptide that includes: i) only the α 1 domain of a MHC class II α chain polypeptide; ii) only the α 2 domain of a MHC class II α chain; iii) only the α 1 domain and an α 2 domain of a MHC class II α chain; iv) only the β 1 domain of a MHC class II β chain; v) only the β 2 domain of a MHC class II β chain; vi) only the β 1 domain and the β 2 domain of a MHC class II β chain; vii) the α 1 domain of a MHC class II α chain, the β 1 domain of a MHC class II β chain, and the β 2 domain of a MHC class II; and the like.

[0094] MHC class II polypeptides include allelic forms. The HLA locus is highly polymorphic in nature. As disclosed in the Nomenclature for Factors of the HLA System 2000 (Hum. Immunol.; 62(4):419-68, 2001) there are 221 HLA-DRB 1 alleles, 19 DRB3 alleles, 89 DRB4 alleles, 14 DRB5 alleles, 19 DQA1 alleles and 39 DQB1 alleles, with new alleles being discovered continuously. A 2007 update by the WHO nomenclature Committee for Factors of the HLA System (www.anthonynolan.com/HIG/) showed there are 3 DRA alleles, 494 DRB 1 alleles, 1 DRB2 alleles, 44 DRB3 alleles, 13 DRB4 alleles, 18 DRB5 alleles, 3 DRB6 alleles, 2 DRB7 alleles, 10 DRB8 alleles, 1 DRB9 alleles, 34 DQA1 alleles, 83 DQB1 alleles, 23 DPA1, 126 DPB1 alleles, 4 DMA alleles, 7 DMB alleles, 12 DOA alleles and 9 DOB alleles. As used herein, the term "MHC class II polypeptide" includes allelic forms of any known MHC class II polypeptide.

[0095] In some cases, a TMMP of the present disclosure comprises a MHC class II α chain (e.g., a DPA1, DRA1, or DQA1 α chain), without the leader, transmembrane, and intracellular portions (e.g., cytoplasmic tails) that may be present in a naturally-occurring MHC class II α chain. Thus, in some cases, a TMMP of the present disclosure comprises only the $\alpha 1$ and $\alpha 2$ portions of an MHC class II α chain; and does not include the leader, transmembrane, and intracellular portions (e.g., cytoplasmic tails) that may be present in a naturally-occurring MHC class II α chain.

[0096] In some cases, a TMMP of the present disclosure comprises a MHC class II β chain (e.g., a DPB1, DRB1, or DQB1 β chain), without the leader, transmembrane, and intracellular portions (e.g., cytoplasmic tails) that may be present in a naturally-occurring MHC class II β chain. Thus, in some cases, a TMMP of the present disclosure comprises only the $\beta 1$ and $\beta 2$ portions of a MHC class II β chain; and does not include the leader, transmembrane, and intracellular portions (e.g., cytoplasmic tails) that may be present in a naturally-occurring MHC class II β chain.

MHC Class II Alpha Chains

[0097] MHC class II alpha chains comprise an $\alpha 1$ domain and an $\alpha 2$ domain. In some cases, the $\alpha 1$ domain and the $\alpha 2$ domain present in an antigen-presenting cell are from the same MHC class II α chain polypeptide. In some cases, the $\alpha 1$ domain and the $\alpha 2$ domain present in an antigen-presenting cell are from two different MHC class II α chain polypeptides.

[0098] MHC class II alpha chains suitable for inclusion in a TMMP of the present disclosure lack a signal peptide. An MHC class II alpha chain suitable for inclusion in a multimeric polypeptide of the present disclosure can have a length of from about 60 amino acids to about 190 amino acids; for example, an MHC class II alpha chain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 60 amino acids to about 80 amino acids, from about 80 amino acids to about 100 amino acids, from about 100 amino acids to about 120 amino acids, from about 120 amino acids to about 140 amino acids, from about 140 amino acids to about 160 amino acids, from about 160 amino acids to about 180 amino acids, or from about 180 amino acids to about 200 amino acids. An MHC class II $\alpha 1$ domain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 30 amino acids to about 95 amino acids; for example, an MHC class II $\alpha 1$ domain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 30 amino acids to about 40 amino acids, from about 40 amino acids to about 50 amino acids, from about 50 amino acids to about 60 amino acids, from about 60 amino acids to about 70 amino acids, from about 70 amino acids to about 80 amino acids, from about 80 amino acids to about 90 amino acids, or from about 90 amino acids to about 95 amino acids. An MHC class II $\alpha 2$ domain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 30 amino acids to about 95 amino acids; for example, an MHC class II $\alpha 2$ domain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 30 amino acids to about 40 amino acids, from about 40 amino acids to about 50 amino acids, from about 50

amino acids to about 60 amino acids, from about 60 amino acids to about 70 amino acids, from about 70 amino acids to about 80 amino acids, from about 80 amino acids to about 90 amino acids, or from about 90 amino acids to about 95 amino acids.

[0099] In some cases, an MHC class II α chain polypeptide present in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type MHC class II α chain polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys. Such an amino acid substitution can occur between amino acid 55 and 110 of the MHC class II α chain polypeptide. For example, an amino acid substitution that replaces an amino acid other than a Cys with a Cys can be present between amino acids 55 and 60, between amino acids 60 and 65, between amino acids 65 and 70, between amino acids 70 and 75, between amino acids 75 and 80, between amino acids 80 and 85, between amino acids 85 and 90, between amino acids 90 and 95, between amino acids 95 and 100, between amino acids 100 and 105, or between amino acids 105 and 110.

DRA Polypeptides

[00100] In some cases, a suitable MHC class II α chain polypeptide is a DRA polypeptide. A DRA polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 26-203 of the DRA amino acid sequence depicted in FIG. 6. In some cases, the DRA polypeptide has a length of about 178 amino acids (e.g., 175, 176, 177, 178, 179, or 180 amino acids).

[00101] A “DRA polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DRA polypeptide comprises the following amino acid sequence: IKEEH VIIQAEFYLN PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV DKANLEIMTK RSNYTPITNV PPEVTVLTNSPVLEPNVL ICFIDKFTPP VVNVTWLRNG KPVTTGVSET VFLPREDHLF RKFHYLPFLPSTEDVYDCRV EHWGLDEPLL KHW (SEQ ID NO:6, amino acids 26-203 of DRA*01:02:01, see FIG. 6), or an allelic variant thereof. In some cases, the allelic variant is the DRA*01:01:01:01 allelic variant that differs from DRA*01:02:01 by having a valine in place of the leucine at position 242 of the sequence in FIG. 6. In some cases, a DRA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00102] In some cases, a TMMP of the present disclosure comprises a variant DRA polypeptide that comprises a non-naturally occurring Cys residue. For example, in some cases, a TMMP of the present disclosure comprises a variant DRA polypeptide that comprises an amino acid substitution selected from E3C, E4C, F12C, G28C, D29C, I72C, K75C, T80C, P81C, I82C, T93C, N94C, and S95C.

[00103] In some cases, a suitable DRA polypeptide comprises the following amino acid sequence: IKEEH VIIQAEFYLN PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQQALANIAV DKANLE**C**MTK RSNYTPITNV PPEVTVLTNSPVELREPNVL ICFIDKFTPP VVNVTWLRNG KPVTTGVSET VFLPREDHLF RKFHYLPFLPSTEDVYDCRV EHWGLDEPLL KHW (SEQ ID NO:7), where amino acid I72 is substituted with a Cys (shown in bold text). In some cases, a suitable DRA polypeptide comprises the following amino acid sequence: IKEEH VIIQAEFYLN PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQQALANIAV DKANLEIM**T**C RSNYTPITNV PPEVTVLTNSPVELREPNVL ICFIDKFTPP VVNVTWLRNG KPVTTGVSET VFLPREDHLF RKFHYLPFLPSTEDVYDCRV EHWGLDEPLL KHW (SEQ ID NO:8), where amino acid K75 is substituted with a Cys (shown in bold text).

[00104] In some cases, a suitable DRA polypeptide comprises the following amino acid sequence:
IKEEHVIIQAEFYLNPDQSGEFMFD**FDG**DEIFHVDMAKKETVWRLEEFGRFASFEAQQALANIAV DKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTT GVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:9). In some cases, an amino acid between amino acids 55 and 110 is substituted with a Cys. In some cases, an amino acid between amino acids 70 and 85 is substituted with a Cys. In some cases, a suitable DRA polypeptide comprises the following amino acid sequence:

IKEEHVIIQAEFYLNPDQSGEFMFD**FDG****C**EIFHVDMAKKETVWRLEEFGRFASFEAQQALANIAV DKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTT GVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:10), where D29 is substituted with a Cys (shown in bold text). In some cases, a suitable DRA polypeptide comprises the following amino acid sequence:

IKEEHVIIQAEFYLNPDQSGEFMFD**FDG**DEIFHVDMAKKETVWRLEEFGRFASFEAQQALANIAV DKANLE**C**MTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTT GVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:11), where I72 is substituted with a Cys (shown in bold text). In some cases, a suitable DRA polypeptide comprises the following amino acid sequence:

IKEEHVIIQAEFYLNPDQSGEFMFD**FDG**DEIFHVDMAKKETVWRLEEFGRFASFEAQQALANIAV DKANLEIM**T**CRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTT GVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:12), where K75 is substituted with a Cys (shown in bold text). In some cases, a suitable DRA polypeptide comprises the following amino acid sequence:

IKEEHVIIQAEFYLNPDQSGEFMFD**FDG**DEIFHVDMAKKETVWRLEEFGRFASFEAQQALANIAV DKANLEIMTKRSNY**T**CITNVPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTT

GVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:13), where P81 is substituted with a Cys (shown in bold text). In some cases, a suitable DRA polypeptide comprises the following amino acid sequence:

IKEEHVIIQAEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASF EAQGALANIAV
 DKANLEIMTKRSNYTP**C**TNPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTT
 GVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:14), where I82 is substituted with a Cys (shown in bold text).

[00105] A suitable DRA α 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VIIQAEFYLN PDQSGEFMFD

FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV DKANLEIMTK RSNYTPITN (SEQ ID NO:15); and can have a length of about 84 amino acids (e.g., 80, 81, 82, 83, 84, 85, or 86 amino acids). A suitable DRA α 1 domain can comprise the following amino acid sequence:

VIIQAEFYLN PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV
 DKANLEIMTK RSNYTPITN (SEQ ID NO:15), or a naturally-occurring allelic variant. A suitable DRA α 1 domain can comprise the following amino acid sequence: IKEEH VIIQAEFYLN PDQSGEFMFD
 FDG**C**EIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV DKANLEIMTK RSNYTPITN (SEQ ID NO:16), where amino acid D29C is substituted with a Cys (shown in bold text). A suitable

DRA α 1 domain can comprise the following amino acid sequence: IKEEH VIIQAEFYLN
 PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV DKANLE**C**MTK
 RSNYTPITN (SEQ ID NO:17), where amino acid I72 is substituted with a Cys (shown in bold text). A suitable DRA α 1 domain can comprise the following amino acid sequence: IKEEH VIIQAEFYLN
 PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV DKANLEIM**T**C
 RSNYTPITN (SEQ ID NO:18), where amino acid K75 is substituted with a Cys (shown in bold text). A suitable DRA α 1 domain can comprise the following amino acid sequence: IKEEH VIIQAEFYLN
 PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV DKANLEIMTK
 RSNY**T**CITN (SEQ ID NO:19), where amino acid P81 is substituted with a Cys (shown in bold text). A suitable DRA α 1 domain can comprise the following amino acid sequence: IKEEH VIIQAEFYLN
 PDQSGEFMFD FDGDEIFHVD MAKKETVWRL EEFGRFASFE AQGALANIAV DKANLEIMTK
 RSNYTP**C**TN (SEQ ID NO:20), where amino acid I82 is substituted with a Cys (shown in bold text).

[00106] A suitable DRA α 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: V PPEVTVLTNSPVELREPNVL ICFIDKFTPP
 VVNVTWLRNG KPVTTGVSET VFLPREDHLF RKFHYLPFLPSTEDVYDCRV EHWGLDEPLL

KHW (SEQ ID NO:21); and can have a length of about 94 amino acids (e.g., 90, 91, 92, 93, 94, 95, 96, 97, or 98 amino acids).

DMA Polypeptides

[00107] In some cases, a suitable MHC class II α chain polypeptide is a DMA polypeptide. A DMA polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 27-217 of the DMA amino acid sequence depicted in FIG. 11. In some cases, the DMA polypeptide has a length of about 191 amino acids (e.g., 188, 189, 190, 191, 192, or 193 amino acids). In some cases, a DMA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00108] A “DMAA polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DMAA polypeptide comprises the following amino acid sequence: VPEA PTPMWPDDLQ NHTFLHTVYC QDGSPSVGLS EAYDEDQLFF FDFSQNTRVP RLPEFADWAQ EQGDAPAILF DKEFCEWMIQ QIGPKLDGKI PVS RGFPIAE VFTLKPLEFG KPNTLVCFVS NLFPPMLTVN WQHHSVPVEG FGPTFVSAVD GLSFQAFSYL NFTPEPSDIF SCIVTHEIDR YTAIAYW (SEQ ID NO:84; amino acids 27-217 of DMA*01:01:01, see FIG. 11), or an allelic variant thereof. In some cases, a DMA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DMA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00109] A suitable DMA α 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VPEA PTPMWPDDLQ NHTFLHTVYC QDGSPSVGLS EAYDEDQLFF FDFSQNTRVP RLPEFADWAQ EQGDAPAILF DKEFCEWMIQ QIGPKLDGKI PVS R (SEQ ID NO:85); and can have a length of about 98 amino acids (e.g., 94, 95, 96, 97, 98, 99, 100, or 101 amino acids). A suitable DMA α 1 domain can comprise the following amino acid sequence: VPEA PTPMWPDDLQ NHTFLHTVYC QDGSPSVGLS EAYDEDQLFF FDFSQNTRVP RLPEFADWAQ EQGDAPAILF DKEFCEWMIQ QIGPKLDGKI PVS R (SEQ ID NO:85), or a naturally-occurring allelic variant thereof. In some cases, a DMA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DMA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00110] A suitable DMA α 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: GFPIAE VFTLKPLEFG KPNTLVCFVS NLFPPMLTVN WQHHSVPVEG FGPTFVSAVD GLSFQAFSYL NFTPEPSDIF SCIVTHEIDR

YTAIAYW (SEQ ID NO:86); and can have a length of about 93 amino acids (e.g., 90, 91, 92, 93, 94, 95, 96, or 97 amino acids). A suitable DMA $\alpha 2$ domain can comprise the following amino acid sequence: GFPIAE VFTLKPFEFG KPNTLVCFVS NLFPMLTVN WQHHSVPVEG FGPTFVSAVD GLSFQAFSYL NFTPEPSDIF SCIVTHEIDR YTAIAYW (SEQ ID NO:86), or a naturally-occurring allelic variant thereof.

DOA Polypeptides

[00111] In some cases, a suitable MHC class II α chain polypeptide is a DOA polypeptide. A DOA polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 26-204 of the DOA amino acid sequence depicted in FIG. 13. In some cases, the DOA polypeptide has a length of about 179 amino acids (e.g., 175, 176, 177, 178, 179, 180, 181, or 182 amino acids). In some cases, a DOA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DOA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00112] A “DOA polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DOA polypeptide comprises the following amino acid sequence: TKADH MGSYGPAFYQ SYGASGQFTH EFDEEQLFSV DLKKSEAVWR LPEFGDFARF DPQGGLAGIA AIKAHLDILV ERSNRSRAIN VPPRVTVLPK SRVELGQPNI LICIVDNIFP PVINITWLRN GQTVTEGVAQ TSFYSQPDHL FRKFHYLPFV PSAEDVYDCQ VEHWGLDAPL LRHW (SEQ ID NO:87; amino acids 26-204 of DOA*01:01:01:01, see FIG. 13), or an allelic variant thereof. In some cases, the allelic variant may be the DOA*01:02 by having an arginine in place of the cysteine (R80C) at position 80 or the DOA*01:03 variant having a valine in place of the leucine at position 74 (L74V) relative to DOA*01:01:01:01. In some cases, a DOA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DOA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00113] A suitable DOA $\alpha 1$ domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: TKADH MGSYGPAFYQ SYGASGQFTH EFDEEQLFSV DLKKSEAVWR LPEFGDFARF DPQGGLAGIA AIKAHLDILV ERSNRSRAIN (SEQ ID NO:88); and can have a length of about 85 amino acids (e.g., 83, 84, 85, 86, 87, or 88 amino acids). Suitable $\alpha 1$ domain sequence may incorporate the L74V and/or R80C substitutions found in DOA*01:02 and DOA*01:03 (the amino acids corresponding to L74 and R 80 are shown italicized and bolded). A suitable DOA $\alpha 1$ domain can comprise the following amino acid sequence: TKADH MGSYGPAFYQ SYGASGQFTH EFDEEQLFSV DLKKSEAVWR LPEFGDFARF DPQGGLAGIA AIKAHLDILV ERSNRSRAIN (SEQ ID NO:88), or a naturally-occurring allelic variant.

[00114] A suitable DOA $\alpha 2$ domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VPPRVTVLPAK SRVELGQPNL LICIVDNIFP PVINITWLRN GQTVTEGVAQ TSFYSQPDHL FRKFHYLPFV PSAEDVYDCQ VEHWGLDAPL LRHW (SEQ ID NO:89); and can have a length of about 94 amino acids (e.g., 91, 92, 93, 94, 95, 96, or 97 amino acids). A suitable DOA $\alpha 2$ domain can comprise the following amino acid sequence: VPPRVTVLPAK SRVELGQPNL LICIVDNIFP PVINITWLRN GQTVTEGVAQ TSFYSQPDHL FRKFHYLPFV PSAEDVYDCQ VEHWGLDAPL LRHW (SEQ ID NO:89), or a naturally-occurring allelic variant thereof.

DPA1 Polypeptides

[00115] In some cases, a suitable MHC class II α chain polypeptide is a DPA1 polypeptide. A DPA1 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 29-209 of the DPA1 amino acid sequence depicted in FIG. 15. In some cases, the DPA1 polypeptide has a length of about 181 amino acids (e.g., 178, 179, 180, 181, 182, 183, or 184 amino acids). In some cases, a DPA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DPA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00116] A “DPA1 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DPA1 polypeptide comprises the following amino acid sequence: AG AIKADHVSTY AAFVQTHRPT GEFMFEFDED EMFYVDLDKK ETVWHLEEFQ QAFSFEAQGG LANIAILNNN LNTLIQRSNH TQATNDPPEV TVFPKEPVGL GQPNTLICH I DKFFPPVLNV TWLCNGELVT EGVAESLFLP RTDYSFHKFH YLTFVPSAED FYDCRVEHWG LDQPLLKHV (SEQ ID NO:22; amino acids 29-209 of DPA1*01:03:01:01, see FIG. 15), or an allelic variant thereof (e.g., DPA1*02:01; see FIG. 15). In some cases, a DPA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DPA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00117] A suitable DPA1 $\alpha 1$ domain may comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIKADHVSTY AAFVQTHRPT GEFMFEFDED EMFYVDLDKK ETVWHLEEFQ QAFSFEAQGG LANIAILNNN LNTLIQRSNH TQATN (SEQ ID NO:23); and can have a length of about 87 amino acids (e.g., 84, 85, 86, 87, 88, or 89 amino acids). A suitable DPA1 $\alpha 1$ domain can comprise the following amino acid sequence: AIKADHVSTY AAFVQTHRPT GEFMFEFDED EMFYVDLDKK ETVWHLEEFQ QAFSFEAQGG LANIAILNNN LNTLIQRSNH TQATN (SEQ ID NO:23), or a naturally-occurring allelic variant.

[00118] A suitable DPA1 α 2 domain may comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: DPPEV TVFPKEPVEL GQPNTLICHIDKFFPPVLNV TWLCNGELVT EGVAESLFLP RTDYSFHKFH YLTFVPSAED FYDCRVEHWGLDQPLLKHW (SEQ ID NO:24); and can have a length of about 97 amino acids (e.g., 91, 92, 93, 94, 95, 96, or 97 amino acids). A suitable DPA1 α 2 domain can comprise the following amino acid sequence: DPPEV TVFPKEPVEL GQPNTLICHIDKFFPPVLNV TWLCNGELVT EGVAESLFLP RTDYSFHKFH YLTFVPSAED FYDCRVEHWGLDQPLLKHW (SEQ ID NO:24), or a naturally-occurring allelic variant thereof.

[00119] Other DPA1 polypeptides comprise the sequence: MRPEDRMFHIRAVILRALSLAFLLSLRGAGAIKADHVSTYAAFVQTHRPTGEFMFEFDEDEQFYVDLDKKETVWHLEEFGRAFSFEAQGGLANIAILNNLNTLIQRSNHTQAANDPPEVTVFPKEPVELGQPNTLICHIDRFFPPVLNV TWLCNGEPVTEGVAESLFLPRTDYSFHKFH YLTFVPSAEDVYDCRVEHWGLDQPLLKHWEAQEPIQMPETTETVLCALGLVLGLVGIIVGTVLIKSLRSGHDPRAQGPL (SEQ ID NO:25; amino acids 29-209 of DPA1*02:01:01:01, see FIG. 15), or variant thereof having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity.

[00120] A suitable DPA1 α 1 domain may comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acids 29-115 of DPA1*02:01:01:01, SEQ ID NO:25; and can have a length of about 87 amino acids (e.g., 84, 85, 86, 87, 88, or 89 amino acids). A suitable DPA1 α 2 domain may comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to amino acids 116 to 209 of DPA1*02:01:01:01, SEQ ID NO:25; and can have a length of about 97 amino acids (e.g., 91, 92, 93, 94, 95, 96, or 97 amino acids).

DQA1 Polypeptides

[00121] In some cases, a suitable MHC class II α chain polypeptide is a DQA1 polypeptide. A DQA1 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 24-204 of any of the DQA1 amino acid sequences depicted in FIG. 17. In some cases, the DQA1 polypeptide has a length of about 181 amino acids (e.g., 177, 178, 179, 180, 181, 182, or 183 amino acids). In an embodiment, a DQA1 α chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DQA1*01:01 α chain amino acid in FIG. 17, ImMunoGeneTics ("IMGT")/HLA Acc No:HLA00601. In an embodiment, a DQA1 α chain polypeptide can have at least 60%, at least 70%, at least 80%, at least

90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DQA1*01:02 α chain amino acid in FIG. 17, IMGT/HLA Acc No:HLA00603, GenBank NP_002113. In an embodiment, a DQA1 α chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DQA1*02:01 α chain amino acid in FIG. 17, IMGT/HLA Acc No:HLA00607. In an embodiment, a DQA1 α chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DQA1*03:01 α chain amino acid in FIG. 17, IMGT/HLA Acc No:HLA00609. In an embodiment, a DQA1 α chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DQA1*04:01 α chain amino acid in FIG. 17, IMGT/HLA Acc No:HLA00612. In an embodiment, a DQA1 α chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DQA1*05:01 α chain amino acid in FIG. 17, IMGT/HLA Acc No:HLA00613. In an embodiment, a DQA1 α chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DQA1*06:01 α chain amino acid in FIG. 17, IMGT/HLA Acc No:HLA00620. In some cases, a DQA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00122] A “DQA1 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DQA1 polypeptide comprises the following amino acid sequence: EDIVADH VASCGVNLYQ FYGPSGQYTH EFDGDEQFYV DLERKETAWR WPEFSKFGGF DPQGALRNMA VAKHNLNIMI KRYNSTAATN EVPEVTVFSK SPVTLGQPNT LICLVDNIFP PVVNITWLSN GQSVTEGVSE TSFLSKSDHS FFKISYLTFL PSADEIYDCK VEHWGLDQPL LKHW (SEQ ID NO:26), or an allelic variant thereof. In some cases, a DQA polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQA polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00123] A suitable DQA1 α 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: EDIVADH VASCGVNLYQ FYGPSGQYTH EFDGDEQFYV DLERKETAWR WPEFSKFGGF DPQGALRNMA VAKHNLNIMI KRYNSTAATN (SEQ ID NO:27); and can have a length of about 87 amino acids (e.g., 84, 85, 86, 87, 88, or 89 amino acids). A suitable DQA1 α 1 domain can comprise the following amino acid sequence: EDIVADH

VASCGVNLYQ FYGPSGQYTH EFDGDEQFYV DLERKETAWR WPEFSKFGGF DPQGALRNMA VAKHNLNIMI KRYNSTAATN (SEQ ID NO:27), or a naturally-occurring allelic variant.

[00124] A suitable DQA1 α 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: EVPEVTVFSK SPVTLGQPNT LICLVDNIFP PVVNITWLSN GQSVTEGVSE TSFLSKSDHS FFKISYLTFL PSADEIYDCK VEHWGLDQPL LKHW (SEQ ID NO:29); and can have a length of about 94 amino acids (e.g., 91, 92, 93, 94, 95, 96, or 97 amino acids). A suitable DQA1 α 2 domain can comprise the following amino acid sequence: EVPEVTVFSK SPVTLGQPNT LICLVDNIFP PVVNITWLSN GQSVTEGVSE TSFLSKSDHS FFKISYLTFL PSADEIYDCK VEHWGLDQPL LKHW (SEQ ID NO:29), or a naturally-occurring allelic variant thereof.

DQA2 Polypeptides

[00125] In some cases, a suitable MHC class II α chain polypeptide is a DQA2 polypeptide. A DQA2 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 24-204 of the DQA2 amino acid sequence depicted in FIG. 18. In some cases, the DQA2 polypeptide has a length of about 181 amino acids (e.g., 177, 178, 179, 180, 181, 182, or 183 amino acids). In some cases, a DQA2 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQA2 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00126] A “DQA2 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DQA2 polypeptide comprises the following amino acid sequence: EDIVADH VASYGVNFYQ SHGPSGQYTH EFDGDEEFYV DLETKETVWQ LPMFSKFISF DPQSALRNMA VGKHTLEFMM RQSNSTAATN EVPEVTVFSK FVTLGQPNT LICLVDNIFP PVVNITWLSN GHSVTEGVSE TSFLSKSDHS FFKISYLTFL PSADEIYDCK VEHWGLDEPL LKHW (SEQ ID NO:90), or an allelic variant thereof. In some cases, a DQA2 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQA2 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00127] A suitable DQA2 α 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: EDIVADH VASYGVNFYQ SHGPSGQYTH EFDGDEEFYV DLETKETVWQ LPMFSKFISF DPQSALRNMA VGKHTLEFMM RQSNSTAATN (SEQ ID NO:91); and can have a length of about 87 amino acids (e.g., 84, 85, 86, 87, 88, or 89 amino acids). A suitable DQA2 α 1 domain can comprise the following amino acid sequence: EDIVADH

VASYGVNFYQ SHGPSGQYTH EFDGDEEFYV DLETKETVWQ LPMFSKFISF DPQSALRNMA VGKHTLEFMM RQSNSTAATN (SEQ ID NO:91), or a naturally-occurring allelic variant.

[00128] A suitable DQA2 $\alpha 2$ domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: EVPEVTVFSK FPVTLGQPNT LICLVDNIFP PVVNITWLSN GHSVTEGVSE TSFLSKSDHS FFKISYLTFL PSADEIYDCK VEHWGLDEPL LKHW (SEQ ID NO:92); and can have a length of about 94 amino acids (e.g., 91, 92, 93, 94, 95, 96, or 97 amino acids). A suitable DQA2 $\alpha 2$ domain can comprise the following amino acid sequence: EVPEVTVFSK FPVTLGQPNT LICLVDNIFP PVVNITWLSN GHSVTEGVSE TSFLSKSDHS FFKISYLTFL PSADEIYDCK VEHWGLDEPL LKHW (SEQ ID NO:92), or a naturally-occurring allelic variant thereof.

MHC Class II Beta Chains

[00129] MHC class II beta chains comprise a $\beta 1$ domain and a $\beta 2$ domain. In some cases, the $\beta 1$ domain and the $\beta 2$ domain present in an antigen-presenting cell are from the same MHC class II β chain polypeptide. In some cases, the $\beta 1$ domain and the $\beta 2$ domain present in an antigen-presenting cell are from two different MHC class II β chain polypeptides. In some cases, MHC class II β chain polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type MHC class II β chain polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00130] MHC class II beta chains suitable for inclusion in a TMMP of the present disclosure lack a signal peptide. An MHC class II beta chain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 60 amino acids to about 210 amino acids; for example, an MHC class II beta chain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 60 amino acids to about 80 amino acids, from about 80 amino acids to about 100 amino acids, from about 100 amino acids to about 120 amino acids, from about 120 amino acids to about 140 amino acids, from about 140 amino acids to about 160 amino acids, from about 160 amino acids to about 180 amino acids, from about 180 amino acids to about 200 amino acids, or from about 200 amino acids to about 210 amino acids. An MHC class II $\beta 1$ domain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 30 amino acids to about 105 amino acids; for example, an MHC class II $\beta 1$ domain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 30 amino acids to about 40 amino acids, from about 40 amino acids to about 50 amino acids, from about 50 amino acids to about 60 amino acids, from about 60 amino acids to about 70 amino acids, from about 70 amino acids to about 80 amino acids, from about 80 amino acids to about 90 amino acids, from about 90 amino acids to about 95 amino acids, from about 95 amino acids to about 100 amino acids, or from about 100 amino acids to about 105 amino acids. An MHC class II $\beta 2$ domain suitable for inclusion in a

TMMP of the present disclosure can have a length of from about 30 amino acids to about 105 amino acids; for example, an MHC class II β 2 domain suitable for inclusion in a TMMP of the present disclosure can have a length of from about 30 amino acids to about 40 amino acids, from about 40 amino acids to about 50 amino acids, from about 50 amino acids to about 60 amino acids, from about 60 amino acids to about 70 amino acids, from about 70 amino acids to about 80 amino acids, from about 80 amino acids to about 90 amino acids, from about 90 amino acids to about 95 amino acids, from about 95 amino acids to about 100 amino acids, or from about 100 amino acids to about 105 amino acids.

[00131] In some cases, the MHC class II β chain polypeptide is a variant DRB MHC class II polypeptide that comprises a non-naturally occurring Cys residue. For example, in some cases, the MHC class II β chain polypeptide is a variant DRB1 MHC class II polypeptide that comprises an amino acid substitution selected from the group consisting of P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C. In some cases, the MHC class II β chain polypeptide is a variant DRB1 polypeptide comprising an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the following DRB1 amino acid sequence:

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNS
QKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPA
SIEVRWFRNGQEEKTG VVSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSP LTV EWR
ARSESAQSKM (SEQ ID NO:30), and comprising an amino acid substitution selected from the group consisting of P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C. In some cases, the MHC class II β chain polypeptide is a variant DRB3 polypeptide, a variant DRB4 polypeptide, or a variant DRB5 polypeptide comprising an amino acid substitution corresponding to any of the foregoing amino acid substitutions in a variant DRB1 polypeptide. For example, as depicted in FIG. 8: i) an amino acid corresponding to P5 of DRB1 would be P5 of a mature DRB3 polypeptide (lacking the N-terminal signal peptide MVCLKLPGGSSLAALTVTL MVLSSRLAFA (SEQ ID NO:31)); ii) an amino acid corresponding to F7 of DRB1 would be F7 of a mature DRB3 polypeptide; iii) an amino acid corresponding to Q10 of DRB1 would be L10 of a mature DRB3 polypeptide; iv) an amino acid corresponding to N19 of DRB1 would be N19 of a mature DRB3 polypeptide; v) an amino acid corresponding to G20 of DRB1 would be G20 of a mature DRB3 polypeptide; vi) an amino acid corresponding to H33 of DRB1 would be N33 of a mature DRB3 polypeptide; vii) an amino acid corresponding to G151 of DRB1 would be G151 of a mature DRB3 polypeptide; viii) an amino acid corresponding to D152 of DRB1 would be D152 of a mature DRB3 polypeptide; and ix) an amino acid corresponding to W153 of DRB1 would be W153 of a mature DRB3 polypeptide. As another example, as depicted in FIG. 9, i) an amino acid corresponding to P5 of DRB1 would be P15 of a mature DRB4 polypeptide (lacking the N-terminal signal peptide MVCLKLPGGSCMAALTVTL (SEQ ID NO:32)); ii)

an amino acid corresponding to F7 of DRB1 would be F17 of a mature DRB4 polypeptide; iii) an amino acid corresponding to Q10 of DRB1 would be Q20 of a mature DRB4 polypeptide; iv) an amino acid corresponding to N19 of DRB1 would be N29 of a mature DRB4 polypeptide; v) an amino acid corresponding to G20 of DRB1 would be G30 of a mature DRB4 polypeptide; vi) an amino acid corresponding to H33 of DRB1 would be N43 of a mature DRB4 polypeptide; vii) an amino acid corresponding to G151 of DRB1 would be G161 of a mature DRB4 polypeptide; viii) an amino acid corresponding to D152 of DRB1 would be D162 of a mature DRB4 polypeptide; and ix) an amino acid corresponding to W153 of DRB1 would be W153 of a mature DRB4 polypeptide. As another example, as depicted in FIG. 10, i) an amino acid corresponding to P5 of DRB1 would be P15 of a mature DRB5 polypeptide (lacking the N-terminal signal peptide MVCLKLPGGSYMAKLTVT (SEQ ID NO:33)); ii) an amino acid corresponding to F7 of DRB1 would be F17 of a mature DRB5 polypeptide; iii) an amino acid corresponding to Q10 of DRB1 would be Q20 of a mature DRB5 polypeptide; iv) an amino acid corresponding to N19 of DRB1 would be N29 of a mature DRB5 polypeptide; v) an amino acid corresponding to G20 of DRB1 would be G30 of a mature DRB5 polypeptide; vi) an amino acid corresponding to H33 of DRB1 would be N43 of a mature DRB5 polypeptide; vii) an amino acid corresponding to G151 of DRB1 would be G161 of a mature DRB5 polypeptide; viii) an amino acid corresponding to D152 of DRB1 would be D162 of a mature DRB5 polypeptide; and ix) an amino acid corresponding to W153 of DRB1 would be W163 of a mature DRB5 polypeptide.

DRB1 Polypeptides

[00132] In some cases, a suitable MHC class II β chain polypeptide is a DRB1 polypeptide. In an embodiment, a DRB1 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of any DRB1 amino acid sequence depicted in FIG. 7, which displays the DRB1 precursor proteins in which amino acids 1-29 are the signal sequence (underlined), 30-124 form the β 1 region (bolded), 125-227 form the β 2 region (bolded and underlined), and 228-250 form the transmembrane region. In some cases, a DRB1 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRB1 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00133] In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-1 (DRB1*01:01) beta chain amino acid sequence Swiss-Prot/UniProt reference ("sp") P04229.2 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-3 (DRB1*03:01) beta chain amino acid sequence sp P01912.2 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least

60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-4 (DRB1*04:01) beta chain amino acid sequence sp P13760.1 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-7 (DRB1*07:01) beta chain amino acid sequence sp P13761.1 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-8 (DRB1*08:01) beta chain amino acid sequence sp Q30134.2 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-9 (DRB1*09:01) beta chain amino acid sequence sp Q9TQE0.1 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-10 (DRB1*10:01) beta chain amino acid sequence sp Q30167.2 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-11 (DRB1*11:01) beta chain amino acid sequence sp P20039.1 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-12 (DRB1*12:01) beta chain amino acid sequence sp Q95IE3.1 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-13 (DRB1*13:01) beta chain amino acid sequence sp Q5Y7A7.1 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-14 (DRB1*14:01) beta chain amino acid sequence sp Q9GIY3.1 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-15 (DRB1*15:01) beta chain amino acid sequence sp P01911 in FIG. 7. In an embodiment, a DRB1 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-16 (DRB1*16:01) beta chain amino acid sequence sp Q29974.1 in FIG. 7. In some cases, the DRB1 β chain polypeptide has a length of about 198 amino acids (e.g., 195, 196, 197, 198, 199, 200, 201, or 202 amino acids).

[00134] A “DRB1 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DRB1 polypeptide comprises the following amino acid sequence:

DTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNSQ
KDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPGSI
EVRWFRNGQEEKTG VVSTGLIQNGDWFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRA
RSESAQSK (SEQ ID NO: 34) (amino acids 31-227 of DRB1-4, see FIG. 7), or an allelic variant thereof.

[00135] A suitable DRB1 polypeptide can comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNS
QKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPA
SIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWR
ARSESAQSKM (SEQ ID NO:30); and can have a length of from 195 to 205 amino acids, e.g., 199 amino acids.

[00136] A suitable DRB1 polypeptide can comprise the following amino acid sequence:

GDTRCRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNS
QKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPA
SIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWR
ARSESAQSKM (SEQ ID NO:35), where P5 is substituted with a Cys (shown in bold text).

[00137] A suitable DRB1 polypeptide can comprise the following amino acid sequence:

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNS
QKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPA
SIEVRWFRNGQEEKTG VVSTGLIQNC DWFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWR
ARSESAQSKM (SEQ ID NO:36), where G151 is substituted with a Cys (shown in bold text).

[00138] A suitable DRB1 polypeptide can comprise the following amino acid sequence:

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNS
QKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPA
SIEVRWFRNGQEEKTG VVSTGLIQNGDCTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWR
ARSESAQSKM (SEQ ID NO:37), where W153 is substituted with a Cys (shown in bold text).

[00139] A suitable DRB1 β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

DTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNSQ
KDLLEQKRAAVDTYCRHNYGVGESFTVQRRV (SEQ ID NO: 38); and can have a length of about

95 amino acids (e.g., 92, 93, 94, 95, 96, 97, or 98 amino acids). A suitable DRB1 β 1 domain can comprise the following amino acid sequence:

DTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNSQ
KDLLEQKRAAVDTYCRHNYGVGESFTVQRRV (SEQ ID NO:38), or a naturally-occurring allelic variant. A suitable DRB1 β 1 domain can comprise the following amino acid sequence:

GDTRCRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELGRPDAEYWNS
QKDLLEQKRAAVDTYCRHNYGVGESFTVQRRV (SEQ ID NO:39), where P5 is substituted with a Cys (shown in bold text).

[00140] A suitable DRB1 β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

YPEVTVYPAKTQPLQHHNLLVCSVNGFYPGSIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTL
VMLETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSK (SEQ ID NO:40); and can have a length of about 103 amino acids (e.g., 100, 101, 102, 103, 104, 105, or 106 amino acids). A suitable DRB1 β 2 domain can comprise the following amino acid sequence:

YPEVTVYPAKTQPLQHHNLLVCSVNGFYPGSIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTL
VMLETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSK (SEQ ID NO:40), or a naturally-occurring allelic variant thereof. A suitable DRB1 β 2 domain can comprise the following amino acid sequence:

YPEVTVYPAKTQPLQHHNLLVCSVNGFYPA SIEVRWFRNGQEEKTG VVSTGLIQNC DWFQTL
VMLETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:41), where G151 is substituted with a Cys (shown in bold text). A suitable DRB1 β 2 domain can comprise the following amino acid sequence:

YPEVTVYPAKTQPLQHHNLLVCSVNGFYPA SIEVRWFRNGQEEKTG VVSTGLIQNGDCTFQTLV
MLETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:42), where W153 is substituted with a Cys (shown in bold text).

DRB3 Polypeptides

[00141] In some cases, a suitable MHC class II β chain polypeptide is a DRB3 polypeptide. In an embodiment, a DRB3 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of any DRB3 amino acid sequence depicted in FIG. 8, which displays the DRB3 precursor proteins in which amino acids 1-29 are the signal sequence (underlined), 30-124 form the β 1 region (shown bolded), 125-227 for the β 2 region, and 228-250 the transmembrane region. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-3

(DRB3*01:01) beta chain amino acid sequence GenBank NP_072049.1 in FIG. 8. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-3 beta chain amino acid sequence in GenBank accession EAX03632.1 in FIG. 8. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-3 (DRB3*02:01) beta chain amino acid sequence GenBank CAA23781.1 in FIG. 8. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB1-3 (DRB3*03:01) beta chain amino acid sequence GenBank AAN15205.1 in FIG. 8. In some cases, a DRB3 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRB3 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00142] A “DRB3 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DRB3 polypeptide comprises the following amino acid sequence: DTRPRFLELR KSECHFFNGT ERVRYLDRYF HNQEEFLRFD SDVGEYRAVT ELGRPVAESW NSQKDLLEQK RGRVDNYCRH NYGVGESFTV QRRVHPQVTV YPAKTQPLQH HNLLVCSVSG FYPGSIEVRW FRNGQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSVT SALTVEWRAR SESAQSK (SEQ ID NO:43), or an allelic variant thereof. In some cases, a DRB3 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRB3 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys. Thus, e.g., in some cases, the MHC class II β chain polypeptide is a variant DRB3 MHC class II polypeptide that comprises a non-naturally occurring Cys residue; e.g., where the variant DRB3 MHC class II polypeptide comprises an amino acid substitution selected from the group consisting of P5C, F7C, L10C, N19C, G20C, N33C, G151C, D152C, and W153C (of a mature DRB3 polypeptide (lacking the N-terminal signal peptide MVCLKLPGGSSLAALTVTLMVLSSRLAFA (SEQ ID NO:31) depicted in FIG. 8).

[00143] A suitable DRB3 β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: DTRPRFLELR KSECHFFNGT ERVRYLDRYF HNQEEFLRFD SDVGEYRAVT ELGRPVAESW NSQKDLLEQK RGRVDNYCRH NYGVGESFTV QRRV (SEQ ID NO:44); and can have a length of about 95 amino acids (e.g., 93, 94, 95, 96, 97, or 98 amino acids). A suitable DRB3 β 1 domain can comprise the following amino acid sequence: DTRPRFLELR KSECHFFNGT ERVRYLDRYF HNQEEFLRFD SDVGEYRAVT

ELGRPVAESW NSQKDLLEQK RGRVDNYCRH NYGVGESFTV QRRV (SEQ ID NO:44), or a naturally-occurring allelic variant.

[00144] A suitable DRB3 β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: HPQVTV YPAKTQPLQH HNLLVCSVSG FYPGSIEVRW FRNGQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSVT SALTVEWRAR SESAQSK (SEQ ID NO:45); and can have a length of about 103 amino acids (e.g., 100, 101, 102, 103, 104, or 105 amino acids). A suitable DRB3 β 2 domain can comprise the following amino acid sequence: HPQVTV YPAKTQPLQH HNLLVCSVSG FYPGSIEVRW FRNGQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSVT SALTVEWRAR SESAQSK (SEQ ID NO:45), or a naturally-occurring allelic variant thereof.

DRB4 Polypeptides

[00145] In some cases, a suitable MHC class II β chain polypeptide is a DRB4 polypeptide. A DRB4 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB4 amino acid sequence depicted in FIG. 9. In some cases, the DRB4 polypeptide has a length of about 198 amino acids (e.g., 195, 196, 197, 198, 199, 200, 201, or 202 amino acids). In some cases, a DRB4 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRB4 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00146] A “DRB4 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DRB4 polypeptide comprises the following amino acid sequence: T VLSSPLALAG DTQPRFLEQA KCECHFLNGT ERVWNLIRYI YNQEEYARYN SDLGEYQAVT ELGRPDAEYW NSQKDLLERR RAEVDITYCRY NYGVVESFTV QRRVQPKVTV YPSKTQPLQH HNLLVCSVNG FYPGSIEVRW FRNGQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSMM SPLTVQWSAR SESAQSK (SEQ ID NO:46), or an allelic variant thereof. In some cases, a DRB4 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRB4 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys. Thus, e.g., in some cases, the MHC class II β chain polypeptide is a variant DRB4 MHC class II polypeptide that comprises a non-naturally occurring Cys residue; e.g., where the variant DRB4 MHC class II polypeptide comprises an amino acid substitution selected from the group consisting of P15C, F17C, Q20C, N29C, G30C, N43C, G161C, D162C, and W163C (of a mature DRB4 polypeptide (lacking the N-terminal signal peptide MVCLKLPGGSCMAALTVTL (SEQ ID NO:32) depicted in FIG. 9).

[00147] A suitable DRB4 β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: T VLSSPLALAG DTQPRFLEQA KCECHFLNGT ERVWNLIRYI YNQUEEYARYN SDLGEYQAVT ELGRPDAEYW NSQKDLLERR RAEVDITYCRY NYGVVESFTV QRRV (SEQ ID NO:47); and can have a length of about 95 amino acids (e.g., 93, 94, 95, 96, 97, or 98 amino acids). A suitable DRB4 β 1 domain can comprise the following amino acid sequence: T VLSSPLALAG DTQPRFLEQA KCECHFLNGT ERVWNLIRYI YNQUEEYARYN SDLGEYQAVT ELGRPDAEYW NSQKDLLERR RAEVDITYCRY NYGVVESFTV QRRV (SEQ ID NO:47), or a naturally-occurring allelic variant.

[00148] A suitable DRB4 β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: QPKVTV YPSKTQPLQH HNLLVCSVNG FYPGSIEVRW FRNGQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSMM SPLTVQWSAR SESAQSK (SEQ ID NO:48); and can have a length of about 103 amino acids (e.g., 100, 101, 102, 103, 104, or 105 amino acids). A suitable DRB4 β 2 domain can comprise the following amino acid sequence: QPKVTV YPSKTQPLQH HNLLVCSVNG FYPGSIEVRW FRNGQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSMM SPLTVQWSAR SESAQSK (SEQ ID NO:48), or a naturally-occurring allelic variant thereof.

DRB5 Polypeptides

[00149] In some cases, a suitable MHC class II β chain polypeptide is a DRB5 polypeptide. A DRB5 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DRB5 amino acid sequence depicted in FIG. 10. In some cases, the DRB5 polypeptide has a length of about 198 amino acids (e.g., 195, 196, 197, 198, 199, 200, 201, or 202 amino acids). In some cases, a DRB5 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DRB5 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00150] A “DRB5 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DRB5 polypeptide comprises the following amino acid sequence: M VLSSPLALAG DTRPRFLQQD KYECHFFNGT ERVRFLHRDI YNQEEDLRFD SDVGEYRAVT ELGRPDAEYW NSQKDFLEDR RAAVDITYCRH NYGVGESFTV QRRVEPKVTV YPARTQTLQH HNLLVCSVNG FYPGSIEVRW FRNSQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSVT SPLTVEWRAQ SESAQS (SEQ ID NO:49), or an allelic variant thereof. In some cases, a DRB5 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid

substitution, relative to a wild-type DRB5 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00151] Thus, e.g., in some cases, the MHC class II β chain polypeptide is a variant DRB5 MHC class II polypeptide that comprises a non-naturally occurring Cys residue; e.g., where the variant DRB5 MHC class II polypeptide comprises an amino acid substitution selected from the group consisting of P15C, F17C, Q20C, N29C, G30C, N43C, G161C, D162C, and W163C (of a mature DRB5 polypeptide (lacking the N-terminal signal peptide MVCLKLPGGSYMAKLTVT (SEQ ID NO:33) depicted in FIG. 10).

[00152] A suitable DRB5 β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: M VLSSPLALAG DTRPRFLQQD KYECHFFNGT ERVRFLHRDI YNQEEDLRFD SDVGEYRAVT ELGRPDAEYW NSQKDFLEDR RAAVDITYCRH NYGVGESFTV QRRV (SEQ ID NO:50); and can have a length of about 95 amino acids (e.g., 93, 94, 95, 96, 97, or 98 amino acids). A suitable DRB5 β 1 domain can comprise the following amino acid sequence: M VLSSPLALAG DTRPRFLQQD KYECHFFNGT ERVRFLHRDI YNQEEDLRFD SDVGEYRAVT ELGRPDAEYW NSQKDFLEDR RAAVDITYCRH NYGVGESFTV QRRV (SEQ ID NO:50), or a naturally-occurring allelic variant.

[00153] A suitable DRB5 β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: EPKVTY YPARTQTLQH HNLLVCSVNG FYPGSIEVRW FRNSQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSVT SPLTVEWRAQ SESAQS (SEQ ID NO:51); and can have a length of about 103 amino acids (e.g., 100, 101, 102, 103, 104, or 105 amino acids). A suitable DRB5 β 2 domain can comprise the following amino acid sequence: EPKVTY YPARTQTLQH HNLLVCSVNG FYPGSIEVRW FRNSQEEKAG VVSTGLIQNG DWTFQTLVML ETVPRSGEVY TCQVEHPSVT SPLTVEWRAQ SESAQS (SEQ ID NO:51), or a naturally-occurring allelic variant thereof.

DMB Polypeptides

[00154] In some cases, a suitable MHC class II β chain polypeptide is a DMB polypeptide. A DMB polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 19-207 of the DMB amino acid sequence depicted in FIG. 12. In some cases, the DMB polypeptide has a length of about 189 amino acids (e.g., 187, 188, 189, 190, or 191 amino acids). In some cases, a DMB polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DMB polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00155] A “DMB polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DMB polypeptide comprises the following amino acid sequence: GG FVAHVESTCL LDDAGTPKDF TYCISFNKDL LTCWDPEENK MAPCEFGVLN SLANVLSQHL NQKDTLMQRL RNGLQNCATH TQPFWGS LTN RTRPPSVQVA KTTPEFNTREP VMLACYVWGF YPAEVTITWR KNGKLVMPHS SAHKTAQPNG DWTYQTL SHL ALTPSYGDTY TCVVEHTGAP EPILRDW (SEQ ID NO:93), or an allelic variant thereof. In some cases, a DMB polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DMB polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00156] A suitable DMB β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: GG FVAHVESTCL LDDAGTPKDF TYCISFNKDL LTCWDPEENK MAPCEFGVLN SLANVLSQHL NQKDTLMQRL RNGLQNCATH TQPFWGS LTN RT (SEQ ID NO:94); and can have a length of about 94 amino acids (e.g., 92, 93, 94, 95, 96, or 97 amino acids). A suitable DMB β 1 domain can comprise the following amino acid sequence: GG FVAHVESTCL LDDAGTPKDF TYCISFNKDL LTCWDPEENK MAPCEFGVLN SLANVLSQHL NQKDTLMQRL RNGLQNCATH TQPFWGS LTN RT (SEQ ID NO:94), or a naturally-occurring allelic variant.

[00157] A suitable DMB β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: RPPSVQVA KTTPEFNTREP VMLACYVWGF YPAEVTITWR KNGKLVMPHS SAHKTAQPNG DWTYQTL SHL ALTPSYGDTY TCVVEHTGAP EPILRDW (SEQ ID NO:95); and can have a length of about 95 amino acids (e.g., 93, 94, 95, 96, 97, or 98 amino acids). A suitable DMB β 2 domain can comprise the following amino acid sequence: RPPSVQVA KTTPEFNTREP VMLACYVWGF YPAEVTITWR KNGKLVMPHS SAHKTAQPNG DWTYQTL SHL ALTPSYGDTY TCVVEHTGAP EPILRDW (SEQ ID NO:95), or a naturally-occurring allelic variant thereof.

DOB Polypeptides

[00158] In some cases, a suitable MHC class II β chain polypeptide is a DOB polypeptide. A DOB polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 27-214 of the DOB amino acid sequence depicted in FIG. 14. In some cases, the DOB polypeptide has a length of about 188 amino acids (e.g., 186, 187, 188, 189, or 190 amino acids). In some cases, a DOB polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-

type DOB polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00159] A “DOB polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DOB polypeptide comprises the following amino acid sequence: TDSP EDFVIQAKAD CYFTNGTEKV QFVVRFIFNL EEYVRFDSDV GMFVALTKLG QPD AEQWNSR LDLLERSRQA VDGVC RHN YR LGAPFTVGRK VQPEVTVYPE RTPLLHQHNL LHCSVTGFYP GDIKIKWFLN GQEERAGVMS TGPIRNGDWT FQTVVMLEMT PELGHVYTCL VDHSSLLSPV SVEW (SEQ ID NO:96), or an allelic variant thereof. In some cases, a DOB polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DOB polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00160] A suitable DOB β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: TDSP EDFVIQAKAD CYFTNGTEKV QFVVRFIFNL EEYVRFDSDV GMFVALTKLG QPD AEQWNSR LDLLERSRQA VDGVC RHN YR LGAPFTVGRK (SEQ ID NO:129); and can have a length of about 94 amino acids (e.g., 92, 93, 94, 95, 96, or 97 amino acids). A suitable DOB β 1 domain can comprise the following amino acid sequence: TDSP EDFVIQAKAD CYFTNGTEKV QFVVRFIFNL EEYVRFDSDV GMFVALTKLG QPD AEQWNSR LDLLERSRQA VDGVC RHN YR LGAPFTVGRK (SEQ ID NO:129), or a naturally-occurring allelic variant.

[00161] A suitable DOB β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VQPEVTVYPE RTPLLHQHNL LHCSVTGFYP GDIKIKWFLN GQEERAGVMS TGPIRNGDWT FQTVVMLEMT PELGHVYTCL VDHSSLLSPV SVEW (SEQ ID NO:130); and can have a length of about 94 amino acids (e.g., 92, 93, 94, 95, 96, or 97 amino acids). A suitable DOB β 2 domain can comprise the following amino acid sequence: VQPEVTVYPE RTPLLHQHNL LHCSVTGFYP GDIKIKWFLN GQEERAGVMS TGPIRNGDWT FQTVVMLEMT PELGHVYTCL VDHSSLLSPV SVEW (SEQ ID NO:130), or a naturally-occurring allelic variant thereof.

DPB1 Polypeptides

[00162] In some cases, a suitable MHC class II β chain polypeptide is a DPB1 polypeptide. A DPB1 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-215 of any of the DPB1 amino acid sequences depicted in FIG. 16. In some cases, the DPB1 polypeptide has a length of about 186 amino acids (e.g., 184, 185, 186, 187, or 188 amino acids). In an embodiment, a DRB1 β chain

polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*01:01 beta chain amino acid sequence in FIG. 16 IMGT/HLA Acc No: HLA00514. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*01:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA00517. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*03:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA00520. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*04:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA00521, GenBank NP_002112.3. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB106:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA00524. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*11:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA00528. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*71:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA00590. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*104:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA02046. In an embodiment, a DRB3 β chain polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 30-227 of the DPB1*141:01 beta chain amino acid sequence in FIG. 16, IMGT/HLA Acc No: HLA10364. In some cases, a DPB1 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DPB1 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00163] A “DPB1 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DPB1 polypeptide comprises the following amino acid sequence: R ATPENYLFQG RQECYAFNGT QRFLERYIYN REEFARFDSD VGEFRAVTEL GRPAAEYWNS QKDILEEKRA VPDRMCRHNY ELGGPMTLQR RVQPRVNVSP SKKGPLQHHN LLVCHVTDFY

PGSIQVRWFL NGQEETAGVV STNLIRNGDW TFQILVMLEM TPQQGDVYTC QVEHTSLDSP VTVEW (SEQ ID NO:52), or an allelic variant thereof. In some cases, a DPB1 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DPB1 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00164] A suitable DPB1 β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: R ATPENYLFQG RQECYAFNGT QRFLERYIYN REEFARFDSD VGEFRAVTEL GRPAAEYWNS QKDILEEKRA VPDRMCRHNY ELGGPMTLQR R (SEQ ID NO:53); and can have a length of about 92 amino acids (e.g., 90, 91, 92, 93, or 94 amino acids). A suitable DPB1 β 1 domain can comprise the following amino acid sequence: R ATPENYLFQG RQECYAFNGT QRFLERYIYN REEFARFDSD VGEFRAVTEL GRPAAEYWNS QKDILEEKRA VPDRMCRHNY ELGGPMTLQR R (SEQ ID NO:53), or a naturally-occurring allelic variant.

[00165] A suitable DPB1 β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VQPRVNVSP SKKGPLQHHN LLVCHVTDFY PGSIQVRWFL NGQEETAGVV STNLIRNGDW TFQILVMLEM TPQQGDVYTC QVEHTSLDSP VTVEW (SEQ ID NO:54); and can have a length of about 94 amino acids (e.g., 92, 93, 94, 95, 96, or 97 amino acids). A suitable DPB1 β 2 domain can comprise the following amino acid sequence: VQPRVNVSP SKKGPLQHHN LLVCHVTDFY PGSIQVRWFL NGQEETAGVV STNLIRNGDW TFQILVMLEM TPQQGDVYTC QVEHTSLDSP VTVEW (SEQ ID NO:54), or a naturally-occurring allelic variant thereof.

DQB1 Polypeptides

[00166] In some cases, a suitable MHC class II β chain polypeptide is a DQB1 polypeptide. A DQB1 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 33-220 of the DQB1 amino acid sequence depicted in FIG. 19A or FIG. 19B or FIG. 19C. In some cases, the DQB1 polypeptide has a length of about 188 amino acids (e.g., 186, 187, 188, 190, 191, or 192 amino acids). In some cases, a DQB1 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQB1 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00167] A “DQB1 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DQB1 polypeptide comprises the following amino acid sequence: RDSPEDFV FQFKGMCYFT NGTERVRLVT RYIYNREEYA RFDSDVG VYR AVTPQGRPDA

EYWNSQKEVL EGTRAELDTV CRHNYEVAFR GILQRRVEPT VTISPSRTEA LNHHNLLVCS VTDFYPGQIK VRWFRNDQEE TAGVVSTPLI RRGDWTFQIL VMLEMPQRG DVYTCHVEHP SLQSPITVEW (SEQ ID NO:55), or an allelic variant thereof. In some cases, a DQB1 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQB1 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00168] A suitable DQB1 β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: RDSPEDFV FQFKGMCYFT NGTERVRLVT RYIYNREEYA RFDSVDGVYR AVTPQGRPDA EYWNSQKEVL EGTRAELDTV CRHNYEVAFR GILQRR (SEQ ID NO:56); and can have a length of about 94 amino acids (e.g., 92, 93, 94, 95, or 96 amino acids). A suitable DQB1 β 1 domain can comprise the following amino acid sequence: RDSPEDFV FQFKGMCYFT NGTERVRLVT RYIYNREEYA RFDSVDGVYR AVTPQGRPDA EYWNSQKEVL EGTRAELDTV CRHNYEVAFR GILQRR (SEQ ID NO:56), or a naturally-occurring allelic variant.

[00169] A suitable DQB1 β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VEPT VTISPSRTEA LNHHNLLVCS VTDFYPGQIK VRWFRNDQEE TAGVVSTPLI RRGDWTFQIL VMLEMPQRG DVYTCHVEHP SLQSPITVEW (SEQ ID NO:57); and can have a length of about 94 amino acids (e.g., 92, 93, 94, 95, or 96 amino acids). A suitable DQB1 β 2 domain can comprise the following amino acid sequence: VEPT VTISPSRTEA LNHHNLLVCS VTDFYPGQIK VRWFRNDQEE TAGVVSTPLI RRGDWTFQIL VMLEMPQRG DVYTCHVEHP SLQSPITVEW (SEQ ID NO:57), or a naturally-occurring allelic variant thereof.

DQB2 Polypeptides

[00170] In some cases, a suitable MHC class II β chain polypeptide is a DQB2 polypeptide. A DQB2 polypeptide can have at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity with amino acids 33-215 of the DQB2 amino acid sequence depicted in FIG. 20A or FIG. 20. In some cases, the DQB2 polypeptide has a length of about 182 amino acids (e.g., 175, 176, 177, 178, 179, 180, 181, or 182 amino acids). In some cases, a DQB2 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQB2 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00171] A “DQB2 polypeptide” includes allelic variants, e.g., naturally occurring allelic variants. Thus, in some cases, a suitable DQB2 polypeptide comprises the following amino acid sequence:

DFLVQFK GMCYFTNGTE RVRGVARYIY NREEYGRFDS DVGEFQAVTE LGRSIEDWNN YKDFLEQERA AVDKVCRHNY EAELRTTLQR QVEPTVTISP SRTEALNHHN LLVCSVTDFY PAQIKVRWFR NDQEETAGVV STSLIRNGDW TFQILVMLEI TPQRGDIYTC QVEHPSLQSP ITVEW (SEQ ID NO:131), or an allelic variant thereof. In some cases, a DQB2 polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid substitution, relative to a wild-type DQB2 polypeptide, where the amino acid substitution replaces an amino acid (other than a Cys) with a Cys.

[00172] A suitable DQB2 β 1 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: DFLVQFK GMCYFTNGTE RVRGVARYIY NREEYGRFDS DVGEFQAVTE LGRSIEDWNN YKDFLEQERA AVDKVCRHNY EAELRTTLQR QVEPTV (SEQ ID NO:132); and can have a length of about 94 amino acids (e.g., 92 93, 94, 95, 96, or 97 amino acids). A suitable DQB2 β 1 domain can comprise the following amino acid sequence: DFLVQFK GMCYFTNGTE RVRGVARYIY NREEYGRFDS DVGEFQAVTE LGRSIEDWNN YKDFLEQERA AVDKVCRHNY EAELRTTLQR QVEPTV (SEQ ID NO:132), or a naturally-occurring allelic variant.

[00173] A suitable DQB2 β 2 domain comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: TISP SRTEALNHHN LLVCSVTDFY PAQIKVRWFR NDQEETAGVV STSLIRNGDW TFQILVMLEI TPQRGDIYTC QVEHPSLQSP ITVEW (SEQ ID NO:133); and can have a length of about 94 amino acids (e.g., 92 93, 94, 95, 96, or 97 amino acids). A suitable DQB2 β 2 domain can comprise the following amino acid sequence: TISP SRTEALNHHN LLVCSVTDFY PAQIKVRWFR NDQEETAGVV STSLIRNGDW TFQILVMLEI TPQRGDIYTC QVEHPSLQSP ITVEW (SEQ ID NO:133), or a naturally-occurring allelic variant thereof.

DISEASE RISK-ASSOCIATED ALLELES AND HAPLOTYPES

[00174] Certain alleles and haplotypes of MHC class II have been associated with disease, e.g., increased risk of developing a particular disease. See, e.g., Erlich et al. (2008) *Diabetes* 57:1084; Gough and Simmonds (2007) *Curr. Genomics* 8:453; Mitchell et al. (2007) *Robbins Basic Pathology* Philadelphia: Saunders, 8th ed.; Margaritte-Jeannin et al. (2004) *Tissue Antigens* 63:562; and Kurko et al. (2013) *Clin. Rev. Allergy Immunol.* 45:170.

SCAFFOLD POLYPEPTIDES

[00175] A TMMP of the present disclosure, whether multimeric or monomeric, can comprise an immunoglobulin or non-immunoglobulin scaffold. A TMMP polypeptide of the present disclosure,

whether multimeric or monomeric, can comprise an Fc polypeptide, or can comprise another suitable scaffold polypeptide.

[00176] Suitable scaffold polypeptides include antibody-based scaffold polypeptides and non-antibody-based scaffolds. Non-antibody-based scaffolds include, e.g., albumin, an XTEN (extended recombinant) polypeptide, transferrin, an Fc receptor polypeptide, an elastin-like polypeptide (see, e.g., Hassouneh et al. (2012) *Methods Enzymol.* 502:215; e.g., a polypeptide comprising a pentapeptide repeat unit of (Val-Pro-Gly-X-Gly; SEQ ID NO:142), where X is any amino acid other than proline), an albumin-binding polypeptide, a silk-like polypeptide (see, e.g., Valluzzi et al. (2002) *Philos Trans R Soc Lond B Biol Sci.* 357:165), a silk-elastin-like polypeptide (SELP; see, e.g., Megeed et al. (2002) *Adv Drug Deliv Rev.* 54:1075), and the like. Suitable XTEN polypeptides include, e.g., those disclosed in WO 2009/023270, WO 2010/091122, WO 2007/103515, US 2010/0189682, and US 2009/0092582; see also Schellenberger et al. (2009) *Nat Biotechnol.* 27:1186). Suitable albumin polypeptides include, e.g., human serum albumin.

[00177] Suitable scaffold polypeptides will in some cases be half-life extending polypeptides. Thus, in some cases, a suitable scaffold polypeptide increases the *in vivo* half-life (e.g., the serum half-life) of the multimeric polypeptide, compared to a control multimeric polypeptide lacking the scaffold polypeptide. For example, in some cases, a scaffold polypeptide increases the *in vivo* half-life (e.g., the serum half-life) of the multimeric polypeptide, compared to a control multimeric polypeptide lacking the scaffold polypeptide, by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 50%, at least about 2-fold, at least about 2.5-fold, at least about 5-fold, at least about 10-fold, at least about 25-fold, at least about 50-fold, at least about 100-fold, or more than 100-fold. As an example, in some cases, an Fc polypeptide increases the *in vivo* half-life (e.g., the serum half-life) of the multimeric polypeptide, compared to a control multimeric polypeptide lacking the Fc polypeptide, by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 50%, at least about 2-fold, at least about 2.5-fold, at least about 5-fold, at least about 10-fold, at least about 25-fold, at least about 50-fold, at least about 100-fold, or more than 100-fold.

Fc Polypeptides

[00178] In some cases, the first or the second polypeptide chain of a TMMP of the present disclosure comprises an Fc polypeptide. The Fc polypeptide of a TMMP of the present disclosure can be a human IgG1 Fc, a human IgG2 Fc, a human IgG3 Fc, a human IgG4 Fc, etc. In some cases, the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an Fc region depicted in FIG. 12A-12G. In some cases, the Fc region comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least

about 98%, at least about 99%, or 100%, amino acid sequence identity to the human IgG1 Fc polypeptide depicted in FIG. 12A. In some cases, the Fc region comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99%, amino acid sequence identity to the human IgG1 Fc polypeptide depicted in FIG. 12A, and comprises a substitution of N77; e.g., the Fc polypeptide comprises an N77A substitution.

[00179] In some cases, the Ig Fc polypeptide induces cell lysis through activation of complement-dependent cytotoxicity (CDC). In some cases, the Ig Fc polypeptide is a variant that substantially does not induce cell lysis through activation of CDC, e.g., an IgG1 Fc polypeptide comprising L234A and L235A substitutions (L14A and L15A substitution of the amino acid sequence depicted in FIG. 21A). Typically, the TMMPs of this disclosure that employ an Ig Fc polypeptide are meant to engage a target T cell through the MHC-epitope complex and then modulate the activity of a T cell through the immunomodulatory polypeptides, and thus will employ a variant that substantially does not induce cell lysis through activation of CDC.

[00180] In some cases, the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the human IgG2 Fc polypeptide depicted in FIG. 21A; e.g., the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 99-325 of the human IgG2 Fc polypeptide depicted in FIG. 21A. In some cases, the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the human IgG3 Fc polypeptide depicted in FIG. 21A; e.g., the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 19-246 of the human IgG3 Fc polypeptide depicted in FIG. 21A. In some cases, the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the human IgM Fc polypeptide depicted in FIG. 21B; e.g., the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-276 of the human IgM Fc polypeptide depicted in FIG. 21B. In some cases, the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least

about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the human IgA Fc polypeptide depicted in FIG. 21C; e.g., the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-234 to the human IgA Fc polypeptide depicted in FIG. 21C.

[00181] In some cases, the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the human IgG4 Fc polypeptide depicted in FIG. 21C. In some cases, the Fc polypeptide comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 100 to 327 of the human IgG4 Fc polypeptide depicted in FIG. 21C.

[00182] In some cases, the IgG4 Fc polypeptide comprises the following amino acid sequence: PPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:58).

[00183] In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21A (human IgG1 Fc). In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21A (human IgG1 Fc), except for a substitution of N297 (N77 of the amino acid sequence depicted in FIG. 21A) with an amino acid other than asparagine. In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21C (human IgG1 Fc comprising an N297A substitution, which is N77 of the amino acid sequence depicted in FIG. 21A). In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21A (human IgG1 Fc), except for a substitution of L234 (L14 of the amino acid sequence depicted in FIG. 21A) with an amino acid other than leucine. In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21A (human IgG1 Fc), except for a substitution of L235 (L15 of the amino acid sequence depicted in FIG. 21A) with an amino acid other than leucine.

[00184] In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21E. In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21F. In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21G (human IgG1 Fc comprising an L234A substitution and an L235A substitution, corresponding to positions 14 and 15 of the amino acid sequence

depicted in FIG. 21G). In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21A (human IgG1 Fc), except for a substitution of P331 (P111 of the amino acid sequence depicted in FIG. 21A) with an amino acid other than proline; in some cases, the substitution is a P331S substitution. In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21A (human IgG1 Fc), except for substitutions at L234 and L235 (L14 and L15 of the amino acid sequence depicted in FIG. 21A) with amino acids other than leucine. In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21A (human IgG1 Fc), except for substitutions at L234 and L235 (L14 and L15 of the amino acid sequence depicted in FIG. 21A) with amino acids other than leucine, and a substitution of P331 (P111 of the amino acid sequence depicted in FIG. 21A) with an amino acid other than proline. In some cases, the Fc polypeptide present in a TMMP comprises the amino acid sequence depicted in FIG. 21E (human IgG1 Fc comprising L234F, L235E, and P331S substitutions (corresponding to amino acid positions 14, 15, and 111 of the amino acid sequence depicted in FIG. 21E)). In some cases, the Fc polypeptide present in a TMMP is an IgG1 Fc polypeptide that comprises L234A and L235A substitutions (substitutions of L14 and L15 of the amino acid sequence depicted in FIG. 21A with Ala), as depicted in FIG. 21G.

[00185] In some cases, a TMMP of the present disclosure comprises an Ig Fc polypeptide comprising the following amino acid sequence:

DKTHTCPPCPAPEA**AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV**
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:59), which is an IgG1 Fc polypeptide comprising L234A and L235A substitutions (L14A and L15A in this sequence; shown in bold text).

LINKERS

[00186] As discussed above, a TMMP of the present disclosure can include one or more linker peptides between components of the first and second polypeptides of the TMMP, e.g., between an autoimmune disease-associated peptide and an MHC polypeptide; between an MHC polypeptide and an Ig Fc polypeptide; between a first MHC polypeptide and a second MHC polypeptide; between an immunomodulatory polypeptide and an MHC polypeptide; etc. As also noted above, in some cases, a TMMP of the present disclosure can include a Cys-containing peptide linker between the autoimmune disease-associated peptide and an MHC class II polypeptide, e.g., between the autoimmune disease-associated peptide and an MHC class II β chain polypeptide. Generally, a Cys-containing peptide linker will be used in either the first or second polypeptide of a TMMP in order to intentionally facilitate formation of a disulfide bond between the linker and a desired site on the other polypeptide. Where a Cys-containing linker is inserted in one polypeptide of a TMMP, the remaining linkers in the TMMP will

not include a Cys in order to prevent formation of a disulfide bond at an unwanted site in the TMMP, with the exception that a Cys-containing linker could be used in each of the first and second polypeptides when it is desired to link the first and second polypeptides through a disulfide bond formed between the linkers. A TMMP of the present disclosure thus can include: a) a Cys-containing peptide linker between the autoimmune disease-associated peptide and an MHC class II polypeptide, e.g., between the autoimmune disease-associated peptide and an MHC class II β chain polypeptide; and b) at least one additional peptide linker, where the at least one additional peptide linker does not include a Cys.

[00187] Suitable linkers (also referred to as “spacers”) can be readily selected and can be of any of a number of suitable lengths, such as from 1 amino acid to 25 amino acids, from 3 amino acids to 20 amino acids, from 2 amino acids to 15 amino acids, from 3 amino acids to 12 amino acids, including 4 amino acids to 10 amino acids, 5 amino acids to 9 amino acids, 6 amino acids to 8 amino acids, or 7 amino acids to 8 amino acids. A suitable linker can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acids in length. A suitable linker can be from 25 to 35 amino acids in length. A suitable linker can be 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 amino acids in length. A suitable linker can be from 35 to 45 amino acids in length. A suitable linker can be 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 amino acids in length. A suitable linker can be from 45 to 50 amino acids in length. A suitable linker can be 45, 46, 47, 48, 49, or 50 amino acids in length.

Linkers Containing a Cys

[00188] A peptide linker comprising a Cys can comprise an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). In some cases, a TMMP of the present disclosure comprises a heterodimer comprising a first and a second polypeptide, where the first polypeptide comprises an autoimmune disease-associated peptide and an MHC class II polypeptide (e.g., an MHC class II β chain polypeptide), and comprises a linker between the autoimmune disease-associated peptide and the MHC class II polypeptide (e.g., the MHC class II β chain polypeptide), where the linker comprises an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10).

Linkers Not Containing a Cys

[00189] Exemplary linkers include glycine polymers (G)_n, glycine-serine polymers (including, for example, (GS)_n, (GSGGS)_n (SEQ ID NO:60) and (GGGS)_n (SEQ ID NO:61), where n is an integer of

at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers known in the art. Glycine and glycine-serine polymers can be used; both Gly and Ser are relatively unstructured, and therefore can serve as a neutral tether between components. Glycine polymers can be used; glycine accesses significantly more phi-psi space than even alanine, and is much less restricted than residues with longer side chains (see Scheraga, *Rev. Computational Chem.* 11173-142 (1992)). Exemplary linkers can comprise amino acid sequences including, but not limited to, GGSG (SEQ ID NO:62), GGSGG (SEQ ID NO:63), GSGSG (SEQ ID NO:64), GSGGG (SEQ ID NO:65), GGGSG (SEQ ID NO:66), GSSSG (SEQ ID NO:67), and the like. Exemplary linkers can include, e.g., Gly(Ser₄)_n, (SEQ ID NO:68) where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some cases, a linker comprises the amino acid sequence (GSSSS)_n (SEQ ID NO:69), where n is 4. In some cases, a linker comprises the amino acid sequence (GSSSS)_n (SEQ ID NO:70), where n is 5. Exemplary linkers can include, e.g., (GlyGlyGlyGlySer)_n (SEQ ID NO:71) (also referred to as “G4S” linkers), where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:72), where n is 1. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:73), where n is 2. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:74), where n is 3. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:75), where n is 4. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:76), where n is 5. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:77), where n is 6. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:78), where n is 7. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:79), where n is 8. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:80), where n is 9. In some cases, a linker comprises the amino acid sequence (GGGGS)_n (SEQ ID NO:81), where n is 10. In some cases, a linker comprises the amino acid sequence AAAGG (SEQ ID NO:82). In some cases, a linker comprises the amino acid sequence GGSAAAGG (SEQ ID NO:83). The AAAGG (SEQ ID NO:82) and GGSAAAGG (SEQ ID NO:83) linkers have been found to be useful for linking an MHC class II alpha chain polypeptide (e.g., a DRA class II polypeptide) to an Ig Fc polypeptide (e.g., a human IgG1 Fc polypeptide sequence depicted in FIG. 21G comprising an L234A substitution and an L235A substitution, corresponding to positions 14 and 15 of the amino acid sequence depicted in FIG. 21G).

AUTOIMMUNE DISEASE-ASSOCIATED PEPTIDES

[00190] As used herein, an “autoimmune disease-associated peptide” is a peptide that, when present in a TMMP of the present disclosure, presents an autoimmune disease-associated epitope capable of being bound by a TCR on the surface of a T cell. An autoimmune disease-associated peptide can have a length of from about 4 amino acids to about 25 amino acids, e.g., the autoimmune disease-associated peptide can have a length of from 4 amino acids (aa) to 10 aa, from 8 aa to 12 aa, from 10 aa to 15 aa, from 12 aa to 20 aa, from 15 aa to 20 aa, from 15 aa to 25 aa, or from 20 aa to 25 aa. For example, an

autoimmune disease-associated peptide present in a TMMP of the present disclosure can have a length of 4 amino acids (aa), 5 aa, 6 aa, 7, aa, 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa. In some cases, an autoimmune disease-associated peptide present in a TMMP of the present disclosure has a length of from 5 amino acids to 10 amino acids, e.g., 5 aa, 6 aa, 7 aa, 8 aa, 9 aa, or 10 aa.

[00191] An autoimmune disease-associated peptide present in a TMMP of the present disclosure is specifically bound by a T-cell, i.e., the epitope is specifically bound by an epitope-specific T cell. An epitope-specific T cell binds an epitope-presenting peptide having a reference amino acid sequence, but does not substantially bind an epitope that differs from the reference amino acid sequence. For example, an epitope-specific T cell binds an autoimmune disease-associated peptide having a reference amino acid sequence, and binds an epitope that differs from the reference amino acid sequence, if at all, with an affinity that is less than 10^{-6} M, less than 10^{-5} M, or less than 10^{-4} M. An epitope-specific T cell can bind an epitope-presenting peptide for which it is specific with an affinity of at least 10^{-7} M, at least 10^{-8} M, at least 10^{-9} M, or at least 10^{-10} M.

[00192] An autoimmune disease-associated peptide can present an epitope associated with or present in a “self” antigen (an autoantigen). Antigens associated with autoimmune disease can be autoantigens associated with autoimmune diseases such as Addison disease (autoimmune adrenalitis, Morbus Addison), alopecia areata, Addison's anemia (Morbus Biermer), autoimmune hemolytic anemia (AIHA), autoimmune hemolytic anemia (AIHA) of the cold type (cold hemagglutinin disease, cold autoimmune hemolytic anemia (AIHA) (cold agglutinin disease), (CHAD)), autoimmune hemolytic anemia (AIHA) of the warm type (warm AIHA, warm autoimmune hemolytic anemia (AIHA)), autoimmune hemolytic Donath-Landsteiner anemia (paroxysmal cold hemoglobinuria), antiphospholipid syndrome (APS), atherosclerosis, autoimmune arthritis, arteriitis temporalis, Takayasu arteriitis (Takayasu's disease, aortic arch disease), temporal arteriitis/giant cell arteriitis, autoimmune chronic gastritis, autoimmune infertility, autoimmune inner ear disease (AIED), Basedow's disease (Morbus Basedow), Bechterew's disease (Morbus Bechterew, ankylosing spondylitis, spondylitis ankylosans), Behcet's syndrome (Morbus Behcet), bowel disease including autoimmune inflammatory bowel disease (including colitis ulcerosa (Morbus Crohn, Crohn's disease), autoimmune cardiomyopathy, idiopathic dilated cardiomyopathy (DCM), chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy (CIDP), chronic polyarthritis, Churg-Strauss syndrome, cicatricial pemphigoid, Cogan syndrome, CREST syndrome (syndrom with Calcinosis cutis, Raynaud phenomenon, motility disorders of the esophagus, sklerodaktylia and teleangiectasia), Crohn's disease (Morbus Crohn, colitis ulcerosa), dermatitis herpetiformis during, dermatologic autoimmune diseases, dermatomyositis, essential mixed cryoglobulinemia, essential mixed cryoglobulinemia, fibromyalgia, fibromyositis, Goodpasture syndrome (anti-GBM mediated glomerulonephritis), graft versus host

disease, Guillain-Barre syndrome (GBM, Polyradikuloneuritis), hematologic autoimmune diseases, Hashimoto thyroiditis, hemophilia, acquired hemophilia, autoimmune hepatitis, idiopathic pulmonary fibrosis (IPF), idiopathic thrombocytopenic purpura, Immuno-thrombocytopenic purpura (Morbus Werlhof, ITP), IgA nephropathy, autoimmune infertility, juvenile rheumatoid arthritis (Morbus Still, Still syndrome), Lambert-Eaton syndrome, systemic lupus erythematosus (SLE), lupus erythematosus (discoid form), Lyme arthritis (Lyme disease, borrelia arthritis), Meniere's disease (Morbus Meniere); mixed connective tissue disease (MCTD), multiple sclerosis (MS, encephalomyelitis disseminate, Charcot's disease), myasthenia gravis (myasthenia, MG), myositis, polymyositis, neural autoimmune diseases, pemphigus vulgaris, bullous pemphigoid, polyglandular (autoimmune) syndrome (PGA syndrome, Schmidt's syndrome), polymyalgia rheumatica, primary agammaglobulinemia, primary autoimmune cholangitis, progressive systemic sclerosis (PSS), rheumatoid arthritis (RA, chronic polyarthritis, rheumatic disease of the joints, rheumatic fever), sarcoidosis (Morbus Boeck, Besnier-Boeck-Schaumann disease), stiff-man syndrome, Scleroderma, Scleroderma, Sjögren's syndrome, autoimmune uveitis, and Wegner's disease (Morbus Wegner, Wegner's granulomatosis).

[00193] In some cases, an autoimmune disease-associated peptide present in a TMMP of the present disclosure is a peptide associated with Addison's disease, alopecia areata, ankylosing spondylitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune-associated infertility, autoimmune thrombocytopenic purpura, bullous pemphigoid, Crohn's disease, Goodpasture's syndrome, glomerulonephritis (e.g., crescentic glomerulonephritis, proliferative glomerulonephritis), Grave's disease, Hashimoto's thyroiditis, mixed connective tissue disease, multiple sclerosis, myasthenia gravis (MG), pemphigus (e.g., pemphigus vulgaris), pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus (SLE), vasculitis, or vitiligo.

[00194] Autoantigens include, e.g., aggrecan, alanyl-tRNA synthetase (PL-12), alpha beta crystallin, alpha fodrin (Sptan 1), alpha-actinin, $\alpha 1$ antichymotrypsin, $\alpha 1$ antitrypsin, $\alpha 1$ microglobulin, aldolase, aminoacyl-tRNA synthetase, an amyloid, an annexin, an apolipoprotein, aquaporin, bactericidal/permeability-increasing protein (BPI), β -globin precursor BP1, β -actin, β -lactoglobulin A, β -2-glycoprotein I, $\beta 2$ -microglobulin, a blood group antigen, C reactive protein (CRP), calmodulin, calreticulin, cardiolipin, catalase, cathepsin B, a centromere protein, chondroitin sulfate, chromatin, collagen, a complement component, cytochrome C, cytochrome P450 2D6, cytokeratins, decorin, dermatan sulfate, DNA topoisomerase I, elastin, Epstein-Barr nuclear antigen 1 (EBNA1), elastin, entaktin, an extractable nuclear antigen, Factor I, Factor P, Factor B, Factor D, Factor H, Factor X, fibrinogen, fibronectin, formiminotransferase cyclodeaminase (LC-1), gp210 nuclear envelope protein, GP2 (major zymogen granule membrane glycoprotein), a glutenin, glycoprotein gpIIb/IIIa, glial fibrillary acidic protein (GFAP), glycated albumin, glyceraldehyde 3-phosphate dehydrogenase (GAPDH),

haptoglobin A2, heat shock proteins, hemocyanin, heparin, a histone, histidyl-tRNA synthetase (Jo-1), a hordein, hyaluronidase, immunoglobulins, an integrin, interstitial retinol-binding protein 3, intrinsic factor, Ku (p70/p80), lactate dehydrogenase, laminin, liver cytosol antigen type 1 (LC1), liver/kidney microsomal antigen 1 (LKM1), lysozyme, melanoma differentiation-associated protein 5 (MDAS), Mi-2 (chromodomain helicase DNA binding protein 4), a mitochondrial protein, muscarinic receptors, myelin-associated glycoprotein, myosin, myelin basic protein, myelin proteolipid protein, myelin oligodendrocyte glycoprotein, myeloperoxidase (MPO), rheumatoid factor (IgM anti-IgG), neuron-specific enolase, nicotinic acetylcholine receptor A chain, nucleolin, a nucleoporin, nucleosome antigen, PM/Scl100, PM/Scl 75, pancreatic β -cell antigen, pepsinogen, peroxiredoxin 1, phosphoglucose isomerase, phospholipids, phosphatidyl inositol, platelet derived growth factors, polymerase beta (POLB), potassium channel KIR4.1, proliferating cell nuclear antigen (PCNA), proteinase-3, proteolipid protein, proteoglycan, prothrombin, recoverin, rhodopsin, ribonuclease, a ribonucleoprotein, ribosomes, a ribosomal phosphoprotein, RNA, an Sm protein, Sp100 nuclear protein, SRP54 (signal recognition particle 54 kDa), a selectin, smooth muscle proteins, sphingomyelin, streptococcal antigens, superoxide dismutase, synovial joint proteins, T1F1 gamma collagen, threonyl-tRNA synthetase (PL-7), tissue transglutaminase, thyroid peroxidase, thyroglobulin, thyroid stimulating hormone receptor, transferrin, triosephosphate isomerase, tubulin, tumor necrosis factor-alpha, topoisomerase, U1-dnRNP 68/70 kDa, U1-snRNP A, U1-snRNP C, U-snRNP B/B', ubiquitin, vascular endothelial growth factor, vimentin, and vitronectin.

[00195] An autoimmune disease-associated peptide included in a TMMP of the present disclosure is one that is useful for treating an autoimmune disease other than (or in addition to) T1D and celiac disease. Accordingly, the present disclosure encompasses only protein constructs (e.g., TMMPs) and methods of preparing protein constructs (e.g., TMMPs) (as well as compositions comprising such protein constructs) comprising antigens/epitopes useful for treating an autoimmune disease other than (or in addition to) celiac disease or T1D. Likewise, the present disclosure encompasses only methods of treating, and the treatment of, an autoimmune disease other than (or in addition to) T1D or celiac disease. For clarity, an TMMP comprising an autoimmune disease-associated peptide that is useful for treating an autoimmune disease other than T1D and/or celiac disease is not excluded from the scope of this disclosure if it also may provide some therapeutic benefit for the treatment of T1D and/or celiac disease. Likewise, a method of treating, or treatment of, an autoimmune disease other than T1D and/or celiac disease is not excluded from the scope of this disclosure if it also may have a use as a method of treating or treatment of T1D or celiac disease.

[00196] Autoantigens associated with alopecia areata (autoimmune alopecia) include, e.g., hair follicle keratinocyte polypeptides, melanogenesis-associated autoantigens, and melanocyte polypeptides. An example of a melanocyte autoantigen is tyrosinase. Autoantigens associated with autoimmune

alopecia also include trichohyalin (Leung et al. (2010) *J. Proteome Res.* 9:5153) and keratin 16. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of a hair follicle keratinocyte polypeptide, a melanocyte polypeptide, a melanogenesis-associated polypeptide, tyrosinase, trichohyalin, or keratin 16.

[00197] Autoantigens associated with Addison's disease include, e.g., 21-hydroxylase. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of 21-hydroxylase.

[00198] Autoantigens associated with autoimmune thyroiditis (Hashimoto's thyroiditis) include, e.g., thyroglobulin, thyroid peroxidase, thyroid Stimulating Hormone Receptor (TSH-Receptor), thyroidal iodide transporters Na⁺/I⁻ symporter (NIS), pendrin, and the like. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned Hashimoto's thyroiditis-associated polypeptides.

[00199] Autoantigens associated with Crohn's disease include, e.g., pancreatic secretory granule membrane glycoprotein-2 (GP2). A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of GP2.

[00200] Autoantigens associated with Goodpasture's disease include, e.g., the $\alpha 3$ chain of type IV collagen, e.g., amino acids 135-145 of the $\alpha 3$ chain of type IV collagen. Penades et al. (1995) *Eur. J. Biochem.* 229:754; Kalluri et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:6201. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of the $\alpha 3$ chain of type IV collagen.

[00201] Autoantigens associated with Grave's disease include, for example, thyroglobulin, thyroid peroxidase, and thyrotropin receptor (TSH-R). A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned Grave's disease-associated antigens.

[00202] Autoantigens associated with mixed connective tissue disease include, e.g., U1 ribonucleoprotein (U1-RNP) polypeptide (also known as snRNP70). Sato et al. (2010) *Mol. Cell. Biochem.* 106:55. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an autoimmune disease-associated peptide of from 4 amino acids to about 25 amino acids in length of U1-RNP polypeptide.

[00203] Autoantigens associated with multiple sclerosis include, e.g., myelin basic protein, myelin oligodendrocyte glycoprotein, and myelin proteolipid protein. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned multiple sclerosis-associated antigens. As one non-limiting example, the autoimmune disease-associated peptide can comprise the amino acid sequence ENPVVHFFKNIVTPR (SEQ ID NO:134). In some cases, a TMMP of the present disclosure comprises a DRB1*15:01 MHC class II β chain; and a peptide epitope of the amino acid sequence ENPVVHFFKNIVTPR (SEQ ID NO:134).

[00204] Autoantigens associated with myasthenia gravis include, e.g., acetylcholine receptor (AChR; see, e.g., Lindstrom (2000) *Muscle & Nerve* 23:453), muscle-specific tyrosine kinase, and low-density lipoprotein receptor-related protein-4. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned myasthenia gravis-associated antigens. In some cases, a suitable epitope-presenting peptide for inclusion in a TMMP of the present disclosure is an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of an AChR.

[00205] Autoantigens associated with Parkinson's disease include, e.g., α -synuclein. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of α -synuclein. For example, a suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure includes a peptide of from 5 amino acids to the entire length of any one of the following: GKTKEGVLYVGSKTK (SEQ ID NO:135); KTKEGVLYVGSKTKE (SEQ ID NO:136); MPVDPDNEAYEMPSE (SEQ ID NO:137); DNEAYEMPSEEGYQD (SEQ ID NO:138); EMPSEEGYQDYEP (SEQ ID NO:139); and SEEGYQDYEP (SEQ ID NO:140), where "S" denotes phosphoserine.

[00206] Autoantigens associated with pemphigus (e.g., pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid) include pemphigus vulgaris immunogens such as desmosomal cadherin desmoglein 3 (Dsg3); pemphigus foliaceus immunogens such as Dsg1; bullous pemphigoid immunogens such as hemidesmosome peptides including BP230 antigen, GPAG1a, and BPAG1b. See, e.g., Cirillo et al. (2007) *Immunology* 121:377. Autoantigens associated with bullous pemphigoid include bullous pemphigoid antigen 1 (BPAG1; also known as BP230 or dystonin), bullous pemphigoid antigen 2 (BPAG2; also known as BP180 or type XVII collagen), and subunits of human integrins α -5 and β -4. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any of the aforementioned pemphigus-associated antigens.

[00207] Autoantigens associated with myositis (e.g., polymyositis; dermatomyositis) include, e.g., histidyl tRNA synthetase. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of histidyl tRNA synthetase.

[00208] Autoantigens associated with rheumatoid arthritis include, e.g., collagen, vimentin, aggrecan, fibrinogen, cyclic citrullinated peptides, α -enolase, histone polypeptides, lactoferrin, catalase, actinin, and actins (cytoplasmic 1 and 2(β/γ)). A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned rheumatoid arthritis-associated antigens.

[00209] Autoantigens associated with scleroderma include nuclear antigens. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of a nuclear antigen associated with scleroderma.

[00210] Autoantigens associated with Sjögren's syndrome include, e.g., Ro/La ribonucleoprotein (RNP) complex, alpha-fodrin, beta-fodrin, islet cell autoantigen, poly(ADP)ribose polymerase (PARP), nuclear mitotic apparatus (NuMA), NOR-90, Ro60 kD autoantigen, Ro52 antigen, La antigen (see, e.g., GenBank Accession No. NP_001281074.1), and p27 antigen. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned Sjögren's syndrome-associated antigens.

[00211] Autoantigens associated with systemic lupus erythematosus (SLE) include, e.g., Ro60 autoantigen, low-density lipoproteins, Sm antigens of the U-1 small nuclear ribonucleoprotein complex (B/B', D1, D2, D3, E, F, G), α -actin 1, α -actin 4, annexin AI, C1q/tumor necrosis factor-related protein, catalase, defensins, chromatin, histone proteins, transketolase, hCAP18/LL37, and ribonucleoproteins (RNPs). A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned SLE-associated antigens.

[00212] Autoantigens associated with thrombocytopenia purpura include ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), and von Willebrand factor-cleaving protease (VWFCP). A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of an ADAMTS13 polypeptide or a VWFCP polypeptide.

[00213] Autoantigens associated with vasculitis include proteinase-3, lysozyme C, lactoferrin, leukocyte elastase, cathepsin G, and azurocidin. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any of the aforementioned vasculitis-associated antigens.

[00214] Autoantigens associated with vitiligo include SOX9, SOX10, PMEL (Premelanosomal protein), tyrosinase, TYRP1 (Tyrosine related protein 1), DDT (D-Dopachrome tautomerase), Rab38, and MCHR1 (Melanin-concentrating receptor). A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned vitiligo-associated polypeptides.

[00215] Autoantigens associated with autoimmune uveitis include, for example, interphotoreceptor retinoid-binding protein (IRBP). A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length IRBP. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned antigens.

[00216] Autoantigens associated with autoimmune polyendocrine syndrome include, e.g., 17-alpha hydroxylase, histidine decarboxylase, tryptophan hydroxylase, and tyrosine hydroxylase. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of any one of the aforementioned autoimmune polyendocrine syndrome-associated antigens.

[00217] Autoantigens associated with psoriasis include ADAMTS15. See, e.g., Prinz (2017) *Autoimmunity Reviews* 16:970. A suitable autoimmune disease-associated peptide for inclusion in a TMMP of the present disclosure can be an epitope-presenting peptide of from 4 amino acids to about 25 amino acids in length of an ADAMTS15 polypeptide.

[00218] Any of the above-noted autoimmune disease-associated peptides can be represented by the “X_n” in FIG. 24 and FIG. 26, where n is an integer from 4 to 25 (e.g., 4 amino acids (aa), 5 aa, 6 aa, 7, aa, 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

IMMUNOMODULATORY POLYPEPTIDES (“MODS”)

[00219] As noted above, immunomodulatory polypeptides (“MODs”) that are suitable for inclusion in a TMPP of the present disclosure include, but are not limited to, IL-2, TGFβ, CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2, 4-1BBL, OX40L, Fas ligand (FasL), inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM), CD30L, CD40, CD70, CD83, HLA-G,

MICA, MICB, HVEM, lymphotoxin beta receptor, 3/TR6, ILT3, ILT4, and HVEM. In some cases, the immunomodulatory polypeptide is selected from an IL-2 polypeptide, a 4-1BBL polypeptide, an ICOS-L polypeptide, an OX-40L polypeptide, a CD80 polypeptide, a CD86 polypeptide, a PD-L1 polypeptide, a FasL polypeptide, a TGF β polypeptide, and a PD-L2 polypeptide.

[00220] As also noted above, the immunomodulatory polypeptide can comprise a wild-type amino acid sequence, or can comprise one or more amino acid substitutions relative to a wild-type amino acid sequence. The immunomodulatory polypeptide can comprise only the extracellular portion of a full-length immunomodulatory polypeptide. Thus, for example, the immunomodulatory polypeptide can in some cases exclude one or more of a signal peptide, a transmembrane domain, and an intracellular domain normally found in a naturally-occurring immunomodulatory polypeptide.

[00221] In some cases, an immunomodulatory polypeptide suitable for inclusion in a TMPP of the present disclosure comprises all or a portion of (e.g., an extracellular portion of) the amino acid sequence of a naturally-occurring immunomodulatory polypeptide. In other instances, an immunomodulatory polypeptide suitable for inclusion in a TMPP of the present disclosure is a variant immunomodulatory polypeptide that comprises at least one amino acid substitution compared to the amino acid sequence of a naturally-occurring immunomodulatory polypeptide. In some instances, a variant immunomodulatory polypeptide exhibits a binding affinity for a co-immunomodulatory polypeptide that is lower than the affinity of a corresponding naturally-occurring immunomodulatory polypeptide (e.g., an immunomodulatory polypeptide not comprising the amino acid substitution(s) present in the variant) for the co-immunomodulatory polypeptide.

[00222] Suitable immunomodulatory domains that exhibit reduced affinity for a co-immunomodulatory domain can have from 1 amino acid (aa) to 20 aa differences from a wild-type immunomodulatory domain. For example, in some cases, a variant immunomodulatory polypeptide present in a TMPP of the present disclosure differs in amino acid sequence by 1 aa, 2 aa, 3 aa, 4 aa, 5 aa, 6 aa, 7 aa, 8 aa, 9 aa, or 10 aa, from a corresponding wild-type immunomodulatory polypeptide. As another example, in some cases, a variant immunomodulatory polypeptide present in a TMPP of the present disclosure differs in amino acid sequence by 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa, from a corresponding wild-type immunomodulatory polypeptide. As an example, in some cases, a variant immunomodulatory polypeptide present in a TMPP of the present disclosure includes 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions, compared to a corresponding reference (e.g., wild-type) immunomodulatory polypeptide.

[00223] As discussed above, a variant immunomodulatory polypeptide suitable for inclusion in a TMPP of the present disclosure exhibits reduced affinity for a cognate co-immunomodulatory polypeptide, compared to the affinity of a corresponding wild-type immunomodulatory polypeptide for the cognate co-immunomodulatory polypeptide.

[00224] Exemplary pairs of immunomodulatory polypeptide and cognate co-immunomodulatory polypeptide include, but are not limited to those set out in Table 1, below:

Table 1

Immunomodulatory Polypeptide	Cognate Co-Immunomodulatory Polypeptide
4-1BBL	4-1BB
PD-L1	PD-1
IL-2	IL-2 receptor
CD80	CD28
CD86	CD28
OX40L (CD252)	OX40 (CD134)
Fas ligand	Fas
ICOS-L	ICOS
ICAM	LFA-1
CD30L	CD30
CD40	CD40L
CD83	CD83L
HVEM (CD270)	CD160
JAG1 (CD339)	Notch
JAG1	CD46
CD80	CTLA4
CD86	CTLA4
CD70	CD27
TGF β	TGF β receptor

[00225] In some cases, a variant immunomodulatory polypeptide present in a TMPP of the present disclosure has a binding affinity for a cognate co-immunomodulatory polypeptide that is from 100 nM to 100 μ M. For example, in some cases, a variant immunomodulatory polypeptide present in a TMPP of the present disclosure has a binding affinity for a cognate co-immunomodulatory polypeptide that is from about 100 nM to 150 nM, from about 150 nM to about 200 nM, from about 200 nM to about 250 nM, from about 250 nM to about 300 nM, from about 300 nM to about 350 nM, from about 350 nM to about 400 nM, from about 400 nM to about 500 nM, from about 500 nM to about 600 nM, from about 600 nM to about 700 nM, from about 700 nM to about 800 nM, from about 800 nM to about 900 nM, from about 900 nM to about 1 μ M, to about 1 μ M to about 5 μ M, from about 5 μ M to about 10 μ M, from

about 10 μ M to about 15 μ M, from about 15 μ M to about 20 μ M, from about 20 μ M to about 25 μ M, from about 25 μ M to about 50 μ M, from about 50 μ M to about 75 μ M, or from about 75 μ M to about 100 μ M.

[00226] Binding affinity between an immunomodulatory polypeptide and its cognate co-immunomodulatory polypeptide can be determined by bio-layer interferometry (BLI) using purified immunomodulatory polypeptide and purified cognate co-immunomodulatory polypeptide, following the procedure set forth in published PCT Application WO 2020/132138 A1.

Wild-type PD-L1 and PD-L1 variants

[00227] In some cases, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure comprises the amino acid sequence of a wild-type PD-L1 polypeptide. In other instances, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure is a variant PD-L1 polypeptide. Wild-type PD-L1 and variant PD-L1 polypeptides bind to PD1.

[00228] A wild-type human PD-L1 polypeptide can comprise the following amino acid sequence: MRIFAVFIFM TYWHLLNAFT VTVPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME DKNIIQFVHG EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG ADYKRITVKV NAPYNKINQR ILVVDPTSE HELTCQAEQY PKAEVIWTSS DHQVLSGKTT TTNSKREEKL FNVSTSLRIN TTTNEIFYCT FRRLDPEENH TAEVIPGNI LNVSIIKICLT LSPST (SEQ ID NO:97).

[00229] A wild-type PD-L1 polypeptide suitable for inclusion in a TMMP of the present disclosure can comprise the following amino acid sequence: FT VTVPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME DKNIIQFVHG EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG ADYKRITVKV NAPYNKINQR ILVVDPTSE HELTCQAEQY PKAEVIWTSS DHQVLSGKTT TTNSKREEKL FNVSTSLRIN TTTNEIFYCT FRRLDPEENH TAEVIPGNI LNVSIIKI (SEQ ID NO:98).

[00230] A wild-type PD-L1 polypeptide suitable for inclusion in a TMMP of the present disclosure can comprise the following amino acid sequence: FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYR QRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD PVTSEHELTCQAEQYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVSTSLRINTTTNEIFYCTF RRLDPEENHTAEVIPELPLAHPNER (SEQ ID NO:99).

[00231] A wild-type PD-1 polypeptide can comprise the following amino acid sequence: PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA

ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS LVLLVWVLAV ICSRAARGTI
GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP CVPEQTEYAT IVFPSGMGTS
SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO:100).

[00232] In some cases, a variant PD-L1 polypeptide exhibits reduced binding affinity to PD-1 (e.g., a PD-1 polypeptide comprising the amino acid sequence depicted above), compared to the binding affinity of a PD-L1 polypeptide comprising the amino acid sequence:

FTVTVPKDLVYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYR
QRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRINTTTNEIFYCTF
RRLDPEENHTAELVIPPLAHPPNER (SEQ ID NO:99) or the amino acid sequence: FT

VTVPKDLVYV EYGSNMTIEC KFPVEKQLDL AALIVYWEME DKNIIQFVHG EEDLKVQHSS
YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG ADYKRITVKV NAPYNKINQR
ILVVD PVTSE HELTCQAEGY PKAEVIWTSS DHQVLSGKTT TNSKREEKL FNVSTLRIN
TTTNEIFYCT FRRLDPEENH TAEVIPGNI LNVSIIKI (SEQ ID NO:98). For example, in some cases, a variant PD-L1 polypeptide of the present disclosure binds PD-1 (e.g., a PD-1 polypeptide comprising the PD-1 amino acid sequence depicted above) with a binding affinity that is at least 10% less, at least 15% less, at least 20% less, at least 25% less, at least 30% less, at least 35% less, at least 40% less, at least 45% less, at least 50% less, at least 55% less, at least 60% less, at least 65% less, at least 70% less, at least 75% less, at least 80% less, at least 85% less, at least 90% less, at least 95% less, or more than 95% less, than the binding affinity of a PD-L1 polypeptide comprising the amino acid sequence:

FTVTVPKDLVYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYR
QRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVTSTLRINTTTNEIFYCTF
RRLDPEENHTAELVIPPLAHPPNER (SEQ ID NO:99) or the amino acid sequence: FT

VTVPKDLVYV EYGSNMTIEC KFPVEKQLDL AALIVYWEME DKNIIQFVHG EEDLKVQHSS
YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG ADYKRITVKV NAPYNKINQR
ILVVD PVTSE HELTCQAEGY PKAEVIWTSS DHQVLSGKTT TNSKREEKL FNVSTLRIN
TTTNEIFYCT FRRLDPEENH TAEVIPGNI LNVSIIKI (SEQ ID NO:98).

[00233] In some cases, a variant PD-L1 polypeptide has a binding affinity to PD-1 that is from 1nM to 1mM. In some cases, a variant PD-L1 polypeptide of the present disclosure has a binding affinity to PD-1 that is from 100 nM to 100 μ M. As another example, in some cases, a variant PD-L1 polypeptide has a binding affinity for PD1 (e.g., a PD1 polypeptide comprising the PD-1 amino acid sequence depicted above) that is from about 100 nM to 150 nM, from about 150 nM to about 200 nM, from about 200 nM to about 250 nM, from about 250 nM to about 300 nM, from about 300 nM to about 350 nM, from about 350 nM to about 400 nM, from about 400 nM to about 500 nM, from about 500 nM

to about 600 nM, from about 600 nM to about 700 nM, from about 700 nM to about 800 nM, from about 800 nM to about 900 nM, from about 900 nM to about 1 μ M, to about 1 μ M to about 5 μ M, from about 5 μ M to about 10 μ M, from about 10 μ M to about 15 μ M, from about 15 μ M to about 20 μ M, from about 20 μ M to about 25 μ M, from about 25 μ M to about 50 μ M, from about 50 μ M to about 75 μ M, or from about 75 μ M to about 100 μ M.

[00234] In some cases, a variant PD-L1 polypeptide has a single amino acid substitution compared to one of the PD-L1 amino acid sequences depicted above. In some cases, a variant PD-L1 polypeptide has from 2 to 10 amino acid substitutions compared to one of the PD-L1 amino acid sequences depicted above.

Wild-type IL-2 and IL-2 variants

[00235] In some cases, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure comprises the amino acid sequence of a wild-type IL-2 polypeptide. In other instances, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure is a variant IL-2 polypeptide. Wild-type IL-2 and variant IL-2 polypeptides bind to IL-2 receptor (IL-2R) (e.g., bind to one or more polypeptides of an IL-2R).

[00236] A wild-type IL-2 amino acid sequence can be as follows: APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLEELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNRWITFCQSIIS TLT (SEQ ID NO:101).

[00237] Wild-type IL-2 binds to an IL2 receptor (IL2R) on the surface of a cell. An IL2 receptor is in some cases a heterotrimeric polypeptide comprising an alpha chain (IL-2R α ; also referred to as CD25), a beta chain (IL-2R β ; also referred to as CD122; and a gamma chain (IL-2R γ ; also referred to as CD132). Amino acid sequences of human IL-2R α , IL2R β , and IL-2R γ can be as follows.

[00238] Human IL-2R α : ELCDDDPPE IPHATFKAMA YKEGTM LNCE CKRGFRRIKS GSLYMLCTGN SSHSSWDNQC QCTSSATRNT TKQVTPQPEE QKERKTTEMQ SPMQPVDQAS LPGHCREPPP WENEATERIY HFVVGQMVYY QCVQGYRALH RGAESVCKM THGKTRWTQP QLICTGEMET SQFPGEEKPQ ASPEGRPESE TSCLVTTTDF QIQTEMAATM ETSIFTTEYQ VAVAGCVFLL ISVLLLSGLT WQRRQRKSRR TI (SEQ ID NO:102).

[00239] Human IL-2R β : VNG TSQFTCFYNS RANISCVWSQ DGALQDTSCQ VHAWPDRRRW NQTCELLPVS QASWACNLIL GAPDSQKLTT VDIVTLRVLC REGVRWRVMA IQDFKPFENL RLMAPI SLQV VHVETHRCNI SWEISQASHY FERHLEFEAR TLSPGHTWEE APLLT LKQKQ EWICLET LTP DTQYEFQVRV KPLQGEFTTW SPWSQPLAFR TKPAALGKDT IPWLGHLLVG LSGAFGFIL VYLLINCRNT GPWLKKVLKC NTPDPSKFFS QLSSEHGGDV QKWLSPPFPS SSFSPGGLAP EISPLEVLER DKVTQLLLQQ DKVPEPASLS SNHSLTSCFT

NQGYFFFHLP DALEIEACQV YFTYDPYSEE DPDEGVAGAP TGSSPQPLQP LSGEDDAYCT
FPSRDDLLLF SPSLLGGPSP PSTAPGGSGA GEERMPPSLQ ERVPRDWDQP PLGPPTPGVP
DLVDFQPPPE LVLREAGEEV PDAGPREGVS FPWSRPPGQG EFRALNARLP LNTDAYLSLQ
ELQGQDPHTL V (SEQ ID NO:103).

[00240] Human IL-2R γ : LNTTILTP NGNEDTTADF FLTTMPTDSL SVSTLPLPEV
QCFVFNVEYM NCTWNSSSEP QPTNLTLYW YKNSDNDKVQ KCSHYLFSEE ITSGCQLQKK
EIHL YQTFVV QLQDPREPRR QATQMLKLQN LVIPWAPENL TLHKLSESQL ELNWNNRFLN
HCLEHLVQYR TDWDHSWTEQ SVDYRHKFSL PSVDGQKRYT FRVRSRFNPL CGSAQHWSEW
SHPIHWGSNT SKENPFLFAL EAVVISVGSM GLIISLLCVY FWLERTMPRI PTLKNLEDLV
TEYHGNFSAW SGVSKGLAES LQPDYSERLC LVSEIPKGG ALGEGPGASP CNQHSPYWAP
PCYTLKPET (SEQ ID NO:104).

[00241] In some cases, where a TMPP of the present disclosure comprises a variant IL-2 polypeptide, a “cognate co-immunomodulatory polypeptide” is an IL-2R comprising polypeptides comprising the amino acid sequences of human IL-2R α , human IL-2R β , and IL-2R γ shown above.

[00242] In some cases, a variant IL-2 polypeptide exhibits reduced binding affinity to IL-2R, compared to the binding affinity of an IL-2 polypeptide comprising a wild-type IL-2 polypeptide (e.g., a wild-type IL-2 polypeptide having the amino acid sequence shown above). For example, in some cases, a variant IL-2 polypeptide binds IL-2R with a binding affinity that is at least 10% less, at least 15% less, at least 20% less, at least 25%, at least 30% less, at least 35% less, at least 40% less, at least 45% less, at least 50% less, at least 55% less, at least 60% less, at least 65% less, at least 70% less, at least 75% less, at least 80% less, at least 85% less, at least 90% less, at least 95% less, or more than 95% less, than the binding affinity of an IL-2 polypeptide comprising the amino acid sequence APTSSSTKKT
QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLEEELKPLEEVL
NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNRWITFCQSIIS TLT
(SEQ ID NO:101) for an IL-2R (e.g., an IL-2R comprising polypeptides comprising human IL-2R α , human IL-2R β , and IL-2R γ having the amino acid sequences shown above), when assayed under the same conditions.

[00243] In some cases, a variant IL-2 polypeptide has a binding affinity to IL-2R that is from 100 nM to 100 μ M. As another example, in some cases, a variant IL-2 polypeptide has a binding affinity for IL-2R (e.g., an IL-2R comprising human IL-2R α , human IL-2R β , and IL-2R γ having the amino acid sequences shown above) that is from about 100 nM to 150 nM, from about 150 nM to about 200 nM, from about 200 nM to about 250 nM, from about 250 nM to about 300 nM, from about 300 nM to about 350 nM, from about 350 nM to about 400 nM, from about 400 nM to about 500 nM, from about 500 nM to about 600 nM, from about 600 nM to about 700 nM, from about 700 nM to about 800 nM, from about 800 nM to about 900 nM, from about 900 nM to about 1 μ M, to about 1 μ M to about 5 μ M, from about 5

μM to about 10 μM, from about 10 μM to about 15 μM, from about 15 μM to about 20 μM, from about 20 μM to about 25 μM, from about 25 μM to about 50 μM, from about 50 μM to about 75 μM, or from about 75 μM to about 100 μM.

[00244] In some cases, a variant IL-2 polypeptide has a single amino acid substitution, or from 2-10 amino acid substitutions compared to the IL-2 amino acid sequence APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLEEELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNRWITFCQSIIS TLT (SEQ ID NO:101).

[00245] Suitable IL-2 variants include a polypeptide that comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to any one of the following amino acid sequences:

[00246] APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TXKFYMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:105), where X is any amino acid other than Phe. In some cases, X is Ala;

[00247] APTSSSTKKT QLQLEHLLLX LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:106), where X is any amino acid other than Asp. In some cases, X is Ala;

[00248] APTSSSTKKT QLQLXHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:107), where X is any amino acid other than Glu. In some cases, X is Ala;

[00249] APTSSSTKKT QLQLEXLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:108), where X is any amino acid other than His. In some cases, X is Ala. In some cases, X is Arg. In some cases, X is Asn. In some cases, X is Asp. In some cases, X is Cys. In some cases, X is Glu. In some cases, X is Gln. In some cases, X is Gly. In some cases, X is Ile. In some cases, X is Lys. In some cases, X is Leu. In some cases, X is Met. In some cases, X is Phe. In some cases, X is Pro. In some cases, X is Ser. In some cases, X is Thr. In some cases, X is Tyr. In some cases, X is Trp. In some cases, X is Val;

[00250] APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFXMPKKA TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:109), where X is any amino acid other than Tyr. In some cases, X is Ala;

[00251] APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNR WITFCXSIIS TLT (SEQ ID NO:110), where X is any amino acid other than Gln. In
some cases, X is Ala;

[00252] APTSSSTKKT QLQLEX₁LLLD LQMILNGINN YKNPKLTRML TX₂KFYMPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:111), where X₁ is any amino acid other than His, and
where X₂ is any amino acid other than Phe. In some cases, X₁ is Ala. In some cases, X₂ is Ala. In some
cases, X₁ is Ala; and X₂ is Ala. In some cases, X₁ is Thr; and X₂ is Ala;

[00253] APTSSSTKKT QLQLEHLLLDX₁ LQMILNGINN YKNPKLTRML TX₂KFYMPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:112), where X₁ is any amino acid other than Asp; and
where X₂ is any amino acid other than Phe. In some cases, X₁ is Ala. In some cases, X₂ is Ala. In some
cases, X₁ is Ala; and X₂ is Ala;

[00254] APTSSSTKKT QLQLX₁HLLDX₂ LQMILNGINN YKNPKLTRML TX₃KFYMPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:113), where X₁ is any amino acid other than Glu;
where X₂ is any amino acid other than Asp; and where X₃ is any amino acid other than Phe. In some
cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₁ is Ala; X₂ is Ala;
and X₃ is Ala;

[00255] APTSSSTKKT QLQLEX₁LLDX₂ LQMILNGINN YKNPKLTRML TX₃KFYMPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:114), where X₁ is any amino acid other than His;
where X₂ is any amino acid other than Asp; and where X₃ is any amino acid other than Phe. In some
cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₁ is Ala; X₂ is Ala;
and X₃ is Ala;

[00256] APTSSSTKKT QLQLEHLLLDX₁ LQMILNGINN YKNPKLTRML TX₂KFYMPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNR WITFCX₃SIIS TLT (SEQ ID NO:115), where X₁ is any amino acid other than Asp;
where X₂ is any amino acid other than Phe; and where X₃ is any amino acid other than Gln. In some
cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₁ is Ala; X₂ is Ala;
and X₃ is Ala;

[00257] APTSSSTKKT QLQLEHLLLDX₁ LQMILNGINN YKNPKLTRML TX₂KFX₃MPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE

TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:116), where X₁ is any amino acid other than Asp; where X₂ is any amino acid other than Phe; and where X₃ is any amino acid other than Tyr. In some cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₁ is Ala; X₂ is Ala; and X₃ is Ala;

[00258] APTSSSTKKT QLQLEX₁LLLX₂ LQMILNGINN YKNPKLTRML TX₃KFX₄MPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE

TATIVEFLNR WITFCQSIIS TLT (SEQ ID NO:117), where X₁ is any amino acid other than His; where X₂ is any amino acid other than Asp; where X₃ is any amino acid other than Phe; and where X₄ is any amino acid other than Tyr. In some cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₄ is Ala. In some cases, X₁ is Ala; X₂ is Ala; X₃ is Ala; and X₄ is Ala;

[00259] APTSSSTKKT QLQLEHLLLX₁ LQMILNGINN YKNPKLTRML TX₂KFX₃MPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE

TATIVEFLNR WITFCX₄SIIS TLT (SEQ ID NO:118), where X₁ is any amino acid other than Asp; where X₂ is any amino acid other than Phe; where X₃ is any amino acid other than Tyr; and where X₄ is any amino acid other than Gln. In some cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₄ is Ala. In some cases, X₁ is Ala; X₂ is Ala; X₃ is Ala; and X₄ is Ala;

[00260] APTSSSTKKT QLQLEX₁LLLX₂ LQMILNGINN YKNPKLTRML TX₃KFX₄MPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE

TATIVEFLNR WITFCX₅SIIS TLT (SEQ ID NO:119), where X₁ is any amino acid other than His; where X₂ is any amino acid other than Asp; where X₃ is any amino acid other than Phe; where X₄ is any amino acid other than Tyr; and where X₅ is any amino acid other than Gln. In some cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₄ is Ala. In some cases, X₅ is Ala. In some cases, X₁ is Ala; X₂ is Ala; X₃ is Ala; X₄ is Ala; X₅ is Ala; and

[00261] APTSSSTKKT QLQLEX₁LLLD LQMILNGINN YKNPKLTRML TX₂KFYMPKKA
TELKHLQCLE EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE

TATIVEFLNR WITFCX₃SIIS TLT (SEQ ID NO:120), where X₁ is any amino acid other than His; where X₂ is any amino acid other than Phe; and where X₃ is any amino acid other than Gln. In some cases, X₁ is Ala. In some cases, X₂ is Ala. In some cases, X₃ is Ala. In some cases, X₁ is Ala; X₂ is Ala; and X₃ is Ala.

[00262] In some cases, a suitable variant IL-2 polypeptide comprises the amino acid sequence:
APTSSSTKKT QLQLEALLLD LQMILNGINN YKNPKLTRML TAKFYMPKKA
TELKHLQCLEEELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNRWITFCQSIIS TLT (SEQ ID NO:121), i.e., the variant IL-2 polypeptide has the amino acid sequence of wild-type IL-2 but with H16A and F42A substitutions (shown in bold).

Wild-type TGF- β and variant TGF- β polypeptides

[00263] In some cases, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure comprises the amino acid sequence of a wild-type TGF- β polypeptide. In other instances, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure is a variant TGF- β polypeptide. Wild-type TGF- β and variant TGF- β polypeptides bind to TGF receptor.

[00264] As noted above, in some cases, the immunomodulatory polypeptide present in a TMMP of the present disclosure is a TGF- β polypeptide. Amino acid sequences of TGF- β polypeptides are known in the art. In some cases, the immunomodulatory polypeptide present in a TMMP of the present disclosure is a TGF- β 1 polypeptide. immunomodulatory polypeptide present in a TMMP of the present disclosure is a TGF- β 2 polypeptide. immunomodulatory polypeptide present in a TMMP of the present disclosure is a TGF- β 3 polypeptide. A suitable TGF- β polypeptide can comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the mature form of a human TGF- β 1 polypeptide, a human TGF- β 2 polypeptide, or a human TGF- β 3 polypeptide. A suitable TGF- β polypeptide can have a length of from about 100 amino acids to about 125 amino acids; for example, a suitable TGF- β polypeptide can have a length of from about 100 amino acids to about 105 amino acids, from about 105 amino acids to about 110 amino acids, from about 110 amino acids to about 115 amino acids, from about 115 amino acids to about 120 amino acids, or from about 120 amino acids to about 125 amino acids.

[00265] A suitable TGF- β 1 polypeptide can comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following TGF- β 1 amino acid sequence: AL DTNYCFSSTE KNCCVRQLYI DFRKDLGWKW IHEPKGYHAN FCLGPCPYIW SLDTQYSKVL ALYNQHNPQA SAAPCCVPQA LEPLPIVYYV GRKPKVEQLS NMIVRSCKCS (SEQ ID NO:122); or the foregoing sequence comprising a C77S substitution; where the TGF- β 1 polypeptide has a length of about 112 amino acids.

[00266] A suitable TGF- β 2 polypeptide can comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following TGF- β 2 amino acid sequence: ALDAAYCF RNVQDNCCLR PLYIDFKRDL GWKWIHEPKG YNANFCAGAC PYLWSSDTQH SRVLSLYNTI NPEASASPCC VSQDLEPLTI LYYIGKTPKI EQLSNMIVKS CKCS (SEQ ID NO:123); or the foregoing sequence comprising a C79S substitution, where the TGF- β 2 polypeptide has a length of about 112 amino acids.

[00267] A suitable TGF- β 3 polypeptide can comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% amino

acid sequence identity to the following TGF- β 3 amino acid sequence: ALDTNYCFRN LEENCCVRPL YIDFRQDLGW K WVHEPKGY Y ANFCSGPCPY LRSADTTHST VLGLYNTLNP EASASPCCV P QDLEPLTILY YVGRTPKVEQ LSNMVKKSCS CS (SEQ ID NO:124); or the foregoing sequence comprising a C77S substitution, where the TGF- β 3 polypeptide has a length of about 112 amino acids.

FasL and FasL variants

[00268] In some cases, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure comprises the amino acid sequence of a wild-type Fas ligand (FasL) polypeptide. In other instances, at least one of the one or more immunomodulatory polypeptides present in a TMMP of the present disclosure is a variant FasL polypeptide. Wild-type FasL and variant FasL polypeptides bind to Fas receptor (FasR). FasL is also known as CD95L or CD178.

[00269] Human FasL polypeptide can have the following amino acid sequence: MQQPFNYPYP QIYWVDSSAS SPWAPPGTVL PCPTSVPRRP GQRRPPPPPP PPPLPPPPPP PPLPPLPLPP LKKRGNHSTG LCLLMFFMV LVALVGLGLG MFQLFHLQKE LAELRESTSQ MHTASSLEKQ IGHPSPPEK KELRKVAHLT GKSNSRSMPL EWEDTYGIVL LSGVKYKKGG LVINETGLYF VYSKVYFRGQ SCNNLPLSHK VYMRNSKYPQ DLVMMEGKMM SYCTTGQMW A RSSYLGAVFN LTSADHLYVN VSELVLNFE ESQTFGLYK L (SEQ ID NO:125). In some cases, a FasL polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 150 amino acids to about 175, from about 175 amino acids to about 200 amino acids, from about 200 amino acids to about 250 amino acids, or from about 250 amino acids to about 281 amino acids, of the following amino acid sequence: MQQPFNYPYP QIYWVDSSAS SPWAPPGTVL PCPTSVPRRP GQRRPPPPPP PPPLPPPPPP PPLPPLPLPP LKKRGNHSTG LCLLMFFMV LVALVGLGLG MFQLFHLQKE LAELRESTSQ MHTASSLEKQ IGHPSPPEK KELRKVAHLT GKSNSRSMPL EWEDTYGIVL LSGVKYKKGG LVINETGLYF VYSKVYFRGQ SCNNLPLSHK VYMRNSKYPQ DLVMMEGKMM SYCTTGQMW A RSSYLGAVFN LTSADHLYVN VSELVLNFE ESQTFGLYK L (SEQ ID NO:125).

[00270] In some cases, a FasL polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: IGHPSPPEK KELRKVAHLT GKSNSRSMPL EWEDTYGIVL LSGVKYKKGG LVINETGLYF VYSKVYFRGQ SCNNLPLSHK VYMRNSKYPQ DLVMMEGKMM SYCTTGQMW A RSSYLGAVFN LTSADHLYVN VSELVLNFE ESQTFGLYK (SEQ ID NO:141); and has a length of about 150, 151, or 152 amino acids.

[00271] In some cases, a FasL polypeptide suitable for inclusion in a TMMP of the present disclosure comprises an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

QLFHLQKELARESTSQMHTASSLEKQIGHPSPPPEKKELRKVAHLTGKSNSRSMPLWEDTY
GIVLLSGVKYKKGGLVINETGLYFVYSKVYFRGQSCNNLPLSHKVYMRNSKYPQDLVMMEGK
MMSYCTTGQMWARSSYLGAVFNLTSADHLYVNVSELSLVNFEESQTFGLYKL (SEQ ID
NO:126); and can have a length of about 179 amino acids.

[00272] A FasR polypeptide can comprise an amino acid sequence having at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MLGIWTLLPL VLTSVARLSS KSVNAQVTDI
NSKGLRLRKT VTTVETQNLGLHHDGQFCH KPCPPGERKA RDCTVNGDEP DCVPCQEGKE
YTDKAHFSSK CRRRCRLCDEG HGLEVEINCT RTQNTKCRCK PNFFCNSTVC EHCDPCTKCE
HGIKECTLT SNTKCKEEGS RSNLGWLCCLLLPIPLIVWV KRKEVQKTCR KHRKENQGSH
ESPTLNPETV AINLSDVDLS KYITTIAGVM TLSQVKGFVR KNGVNEAKID EIKNDNVQDT
AEQKVQLLRN WHQLHGKKEA YDTLIKDLKK ANLCTLAEKI QTIILKDITS DSENSNFRNE
IQSLV (SEQ ID NO:127).

Exemplary TMMPs

[00273] As noted above, a TMMP of the present disclosure comprises a heterodimer (e.g., comprises two heterodimers), where the heterodimer comprises a first polypeptide chain and a second polypeptide chain that are disulfide bonded to one another.

TMMPs That Are Disulfide Bonded Via a Cys in the MHC Class II Alpha Chain and a Cys in the MHC Class II Beta Chain

[00274] As noted above, in some cases, a TMMP of the present disclosure comprises a heterodimer comprising a first polypeptide chain comprising: i) an autoimmune disease-associated peptide; and ii) a first MHC class II polypeptide; and b) a second polypeptide comprising a second MHC class II polypeptide, where the first and/or the second polypeptides comprise one or more immunomodulatory polypeptides, optionally wherein the first and/or the second polypeptide comprises an Ig Fc polypeptide; where the first MHC class II polypeptide comprises a substitution of an amino acid (other than a Cys) with a Cys (a “first Cys”), and the second MHC class II polypeptide comprises a substitution of an amino acid (other than a Cys) with a Cys (a “second” Cys), where the first polypeptide and the second polypeptide are joined by a disulfide bond formed between the first Cys and the second Cys.

[00275] The first MHC class II polypeptide can be a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at

least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A; and having an amino acid substitution selected from P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C. The second MHC class II polypeptide can be a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22A; and having an amino acid substitution selected from E3C, E4C, F12C, G28C, D29C, I72C, K75C, T80C, P81C, I82C, T93C, N94C, and S95C.

[00276] As one example, in some cases, the first MHC class II polypeptide is a DRB MHC class II polypeptide comprising a substitution at a residue selected from the group consisting of P5C, H33C, G151C, and W153, and the second MHC class II polypeptide is a DRA MHC class II polypeptide comprising a substitution selected from the group consisting of P81C, I82C, and D29C. For example, the MHC class II β chain polypeptide can comprise an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% amino acid sequence identity to the amino acid sequence depicted in FIG. 23H, where the polypeptide comprises a Cys at a residue position selected from the group consisting of 5, 33, 151, and 153; and the MHC class II α chain polypeptide can comprise an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% amino acid sequence identity to the amino acid sequence depicted in FIG. 22F, where the polypeptide comprises a Cys at a residue selected from the group consisting of 81, 82, and 29.

[00277] As another example, the disulfide can be formed between one of the specific pairs of Cys residues in the Table 2, below:

Table 2

DRB MHC Class II Polypeptide Substitution	DRA MHC Class II Polypeptide Substitution
N19C	E3C
G20C	E3C
N19C	E4C
G20C	E4C
F7C	F12C
Q10C	F12C
G151C	G28C
D152C	G28C
W153C	G28C
G151C	D29C
D152C	D29C

DRB MHC Class II Polypeptide Substitution	DRA MHC Class II Polypeptide Substitution
W153C	D29C
F7C	T80C
P5C	T80C
H33C	T80C
P5C	P81C
H33C	P81C
F7C	P81C
H33C	I82C
F7C	I82C
P5C	I82C
Q156C	T93C
W153C	T93C
Q156C	N94C
N120C	N94C
Q156C	S95C
N120C	S95C

[00278] For example, the DRB MHC class II polypeptide can comprise an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% amino acid sequence identity to the amino acid sequence depicted in FIG. 23A, and the DRA MHC class II polypeptide can comprise an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% amino acid sequence identity to the amino acid sequence depicted in FIG. 22A, wherein the β chain polypeptide and α chain polypeptides are joined by a disulfide formed between a pair of Cys residues selected from the group consisting of: β chain polypeptide residue 5 and α chain polypeptide residue 81; β chain polypeptide residue 33 and α chain polypeptide residue 81; β chain polypeptide residue 33 and α chain polypeptide residue 82; β chain polypeptide residue 151 and α chain polypeptide residue 29; and β chain polypeptide residue 153 and α chain polypeptide residue 29.

TMMP bonded through a disulfide bond between β P5C and α P81C

[00279] As one example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising a P5C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) one or more

immunomodulatory polypeptides; ii) a DRA MHC class II polypeptide comprising a P81C substitution; and (optionally) iii) an Ig Fc polypeptide. (See FIG. 5, MOD Position 1.) As another example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising a P5C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a DRA MHC class II polypeptide comprising a P81C substitution; ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3.)

Alternatively, the one or more immunomodulatory polypeptides can be at Position 2, 4 or 5 as those positions are described above and depicted schematically in FIG. 5. In the above embodiments, the first polypeptide and the second polypeptide are linked via a disulfide bond between the Cys at residue 5 in the DRB MHC class II polypeptide and the Cys at residue 81 in the DRA MHC class II α chain polypeptide. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the components of the first or second polypeptide. In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, a TGF- β polypeptide or variant thereof, an IL-2 polypeptide or variant thereof, or a FasL polypeptide or variant thereof. In some cases, the Ig Fc polypeptide is present and is an IgG1 Fc polypeptide, optionally comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the DRB MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23B, and comprises a Cys at position 5. In some cases, the DRA MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22J, and comprises a Cys at position 81. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

TMMP bonded through a disulfide bond between β H33C and α P81C

[00280] As one example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising an H33C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) one or more immunomodulatory polypeptides; ii) a DRA MHC class II polypeptide comprising a P81C substitution;

and (optionally) iii) an Ig Fc polypeptide. (See FIG. 5, MOD Position 1.) As another example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising an H33C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a DRA MHC class II polypeptide comprising a P81C substitution; ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3.) Alternatively, the one or more immunomodulatory polypeptides can be at Position 2, 4, or 5 as those positions are described above and depicted schematically in FIG. 5. In the above embodiments, the first polypeptide and the second polypeptide are linked via a disulfide bond between the Cys at residue 33 in the DRB MHC class II polypeptide and the Cys at residue 81 in the DRA MHC class II polypeptide. In any of the above embodiments, linkers that do not comprise a Cys can be used to connect the components of the first or second polypeptide. In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, a TGF- β polypeptide or variant thereof, an IL-2 polypeptide or variant thereof, or a FasL polypeptide or variant thereof. In some cases, the Ig Fc polypeptide is present and is a human IgG1 Fc polypeptide, optionally comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the DRB MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23G, and comprises a Cys at position 33. In some cases, the DRA MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22J, and comprises a Cys at position 81. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

TMMP bonded through a disulfide bond between β H33C and α I82C

[00281] As one example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising an H33C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) one or more immunomodulatory polypeptides; ii) a DRA MHC class II polypeptide comprising an I82C substitution; and (optionally) iii) an Ig Fc polypeptide. (See FIG. 5, MOD Position 1). As another example, a TMMP

of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising an H33C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a DRA MHC class II polypeptide comprising an I82C substitution; ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3) (See FIG. 5, MOD Position 3.) Alternatively, the one or more immunomodulatory polypeptides can be at Position 2, 4, or 5 as those positions are described above and depicted schematically in FIG. 5. In the above embodiments, the first polypeptide and the second polypeptide are linked via a disulfide bond between the Cys at residue 33 in the DRB MHC class II polypeptide and the Cys at residue 82 in the DRA MHC class II polypeptide. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the components of the first or second polypeptide. In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, a TGF- β polypeptide or variant thereof, an IL-2 polypeptide or variant thereof, or a FasL polypeptide or variant thereof. In some cases, the Ig Fc polypeptide is present and is a human IgG1 Fc polypeptide, optionally comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the DRB MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23G, and comprises a Cys at position 33. In some cases, the DRA MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22K, and comprises a Cys at position 82. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

TMMP bonded through a disulfide bond between β G151C and α D29C

[00282] As one example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising a G151C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) one or more immunomodulatory polypeptides; ii) a DRA MHC class II polypeptide comprising a D29C substitution; and (optionally) iii) an Ig Fc polypeptide. (See FIG. 5, MOD Position 1.) As another example, a TMMP

of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising a G151C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a DRA MHC class II polypeptide comprising a D29C substitution; ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3.) Alternatively, the one or more immunomodulatory polypeptides can be at Position 2, 4, or 5 as those positions are described above and depicted schematically in FIG. 5. In the above embodiments, the first polypeptide and the second polypeptide are linked via a disulfide bond between the Cys at residue 151 in the DRB MHC class II polypeptide and the Cys at residue 29 in the DRA MHC class II polypeptide. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the components of the first or second polypeptide. In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, a TGF- β polypeptide or variant thereof, an IL-2 polypeptide or variant thereof, or a FasL polypeptide or variant thereof. In some cases, the Ig Fc polypeptide is present and is a human IgG1 Fc polypeptide, optionally comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the DRB MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23H, and comprises a Cys at position 151. In some cases, the DRA MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22F, and comprises a Cys at position 29. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

TMMP bonded through a disulfide bond between β W153C and α D29C

[00283] As one example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising a W513C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) one or more immunomodulatory polypeptides; ii) a DRA MHC class II polypeptide comprising a D29C substitution; and (optionally) iii) an Ig Fc polypeptide. (See FIG. 5, MOD Position 1.) As another example, a TMMP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order

from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a DRB MHC class II polypeptide comprising a W513C substitution; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a DRA MHC class II polypeptide comprising a D29C substitution; ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3.) Alternatively, the one or more immunomodulatory polypeptides can be at Position 2, 4 or 5 as those positions are described above and depicted schematically in FIG. 5. In the above embodiments, the first polypeptide and the second polypeptide are linked via a disulfide bond between the Cys at residue 153 in the DRB MHC class II polypeptide and the Cys at residue 29 in the DRA MHC class II polypeptide. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the components of the first or second polypeptide. In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, a TGF- β polypeptide or variant thereof, an IL-2 polypeptide or variant thereof, or a FasL polypeptide or variant thereof. In some cases, the Ig Fc polypeptide is present and is a human IgG1 Fc polypeptide, optionally comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the DRB MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23J, and comprises a Cys at position 153. In some cases, the DRA MHC class II polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22F, and comprises a Cys at position 29. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

TMMPs that are Disulfide Bonded Via a Cys in a Linker Between the Autoimmune Disease-Associated Peptide Epitope and the First MHC Class II Polypeptide and a Cys in the Second MHC Class II Polypeptide

[00284] As noted above, in some cases, a TMMP of the present disclosure comprises a heterodimer comprising a first polypeptide chain comprising: i) an autoimmune disease-associated peptide; ii) a peptide linker comprising a Cys; and iii) a first MHC class II polypeptide; and b) a second polypeptide comprising a second MHC class II polypeptide, where the first or the second polypeptides comprise one or more immunomodulatory polypeptides, optionally wherein the first and/or the second polypeptide comprises an Ig Fc polypeptide, where the second MHC class II polypeptide comprises a substitution of an amino acid (other than a Cys) with a Cys; and where the first and the second

polypeptides are linked via a disulfide bond between the Cys in the peptide linker and the Cys provided by the substitution in the second MHC class II polypeptide.

[00285] For example, in some cases, the peptide linker can comprise an amino acid sequence selected from: (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10); the first MHC class II polypeptide is a DRB MHC class II polypeptide; and the second MHC class II polypeptide is a DRA MHC class II polypeptide that comprises a substitution of an amino acid (other than a Cys) with a Cys.

[00286] Specific examples of the Cys-containing linkers between the autoimmune disease-associated peptide and a DRB MHC class II polypeptide and Cys residues in the DRA MHC class II polypeptide that can form a disulfide bond are provided in the Table 3, below:

Table 3

Cys-Containing Linker Between the Autoimmune Disease-Associated Peptide and the DRB MHC Class II Polypeptide	DRA MHC class II polypeptide substitution
(CGGGS)(GGGGS) _n (SEQ ID NO:1)	I72C
(GCGGS)(GGGGS) _n (SEQ ID NO:2)	I72C
(GGCGS)(GGGGS) _n (SEQ ID NO:3)	I72C
(GGGCS)(GGGGS) _n (SEQ ID NO:4)	I72C
(GGGGC)(GGGGS) _n (SEQ ID NO:5)	I72C

(CGGGS)(GGGGS) _n (SEQ ID NO:1)	K75C
(GCGGS)(GGGGS) _n (SEQ ID NO:2)	K75C
(GGCGS)(GGGGS) _n (SEQ ID NO:3)	K75C
(GGGCS)(GGGGS) _n (SEQ ID NO:4)	K75C
(GGGGC)(GGGGS) _n (SEQ ID NO:5)	K75C

[00287] In some cases, where the first and second MHC class II polypeptides are DRB and DRA polypeptides, respectively, the DRB MHC class II polypeptide can comprise an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A. The DRA MHC class II polypeptide can comprise an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22A, and can comprise a Cys at, e.g., position 72 or position 75. In any of the above embodiments, $n = 0, 1, 2, 3, 4$ or more, with 2 or 3 typically being used to create a total linker length of 15 or 20 amino acids, although longer lengths may be possible. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the other components of the first or second polypeptide. In some cases, the Ig Fc polypeptide is present and is a human IgG1 Fc polypeptide, optionally comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, a TGF- β polypeptide or variant thereof, an IL-2 polypeptide or variant thereof, or a FasL polypeptide or variant thereof. The one or more immunomodulatory polypeptides can be at Position 1, Position 2, Position 3, Position 4, or Position 5; where the immunomodulatory polypeptide positions are described above and are depicted schematically in FIG. 5. In some cases, the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids. In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-

associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

[00288] The following are examples of the TMMPs described above in which the first and the second polypeptides are linked via a disulfide bond between the Cys in the peptide linker and the Cys provided by the substitution in the second MHC class II polypeptide, and wherein the first polypeptide is a DRB MHC class II polypeptide (i.e., a DR β chain polypeptide), and the second polypeptide is a DRA MHC class II polypeptide (i.e., a DR α chain polypeptide).

[00289] As one example, a TMMP of the present disclosure comprises a heterodimer comprising one of the following five first polypeptides and one of the following two second polypeptides to create a heterodimer having one or more immunomodulatory polypeptides at MOD position 1 or 3:

a1) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (CGGGS)(GGGGS) n (SEQ ID NO:1), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a2) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GCGGS)(GGGGS) n (SEQ ID NO:2), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a3) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GGCGS)(GGGGS) n (SEQ ID NO:3), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a4) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GGGCS)(GGGGS) n (SEQ ID NO:4), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a5) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GGGGC)(GGGGS)_n (SEQ ID NO:5), where *n* is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); and

b1) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising a Cys at position 72 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 72); an ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 1); or, alternatively

b2) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising a Cys at position 75 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 75); an ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 1); or, alternatively

b3) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising a Cys at position 72 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98% at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 72); an ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3); or, alternatively

b4) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising a Cys at position 75 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 75); an ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3).

[00290] Each of the above combinations of first and second polypeptides for making a TMMP is thus expressly disclosed, i.e., a1-b1, a2-b1, a3-b1, a4-b1, a5-b1, a1-b2, a2-b2, a3-b2, a4-b2 and a5-b2, a1-b3, a2-b3, a3-b3, a4-b3, a5-b3, and a1-b4, a2-b4, a3-b4, a4-b4, and a5-b4.

[00291] Alternatively, the one or more immunomodulatory polypeptides in the second polypeptide can be at Position 2, Position 4, or Position 5, which are described above and depicted schematically in FIG. 5.

[00292] As one example, a TMMP of the present disclosure comprises a heterodimer comprising the following first and second polypeptides to create a heterodimer having one or more immunomodulatory polypeptides at MOD position 1 or 3:

a1) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising an amino acid sequence selected from the group consisting of (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where *n* is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); and

b1) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising Cys at position 72 or 75 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 72 or 75); an ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. [(See FIG. 5, MOD Position 1); or, alternatively

b2) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising a Cys at position 72 or 75 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98% at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 72 or 75); an ii) an Ig Fc polypeptide; and iii) one or more immunomodulatory polypeptides. (See FIG. 5, MOD Position 3).

[00293] As noted above, in any of the above embodiments, *n* = 0, 1, 2, 3, 4 or more, with 2 or 3 typically being used to create a total linker length of 15 or 20 amino acids, although longer lengths may be usable. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the other components of the second polypeptide (e.g., a (G4S)_n (SEQ ID NO:71) linker can be used between the PD-L1 polypeptide and the DRA MHC class II polypeptide, where *n* = 1,2,3,4,5,6,7,8,9 or 10, and a GGSAAAGG (SEQ ID NO:83) linker or AAAGG (SEQ ID NO:82) linker can be used between the DRA MHC class II polypeptide and the Ig Fc polypeptide). In the above embodiments, in some cases, the Ig Fc polypeptide is a human IgG1 Fc polypeptide comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some

cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

[00294] In any of the above embodiments, in some cases, the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, a TGF- β polypeptide or variant thereof, an IL-2 polypeptide or variant thereof, or a FasL polypeptide or variant thereof. In some cases, when the one or more immunomodulatory polypeptides is a PD-L1 polypeptide or variant thereof, the PD-L1 polypeptide comprises the amino acid sequence

FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYR
QRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTF
RRLDPEENHTAELVIPELPLAHPNER (SEQ ID NO:99).

[00295] In some cases, when the one or more immunomodulatory polypeptides comprises an IL-2 polypeptide or variant thereof, the IL-2 polypeptide comprises the following amino acid sequence:

APTSSSTKKT QLQLEALLLD LQMILNGINN YKNPKLTRML TAKFYMPKKA
TELKHLQCLEEELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE
TATIVEFLNRWITFCQSIIS TLT (SEQ ID NO:121), where the IL-2 polypeptide is a variant comprising H16A and F42A substitutions relative to wild-type IL-2.

[00296] Hence, for example, a TMMP in accordance with the above embodiments can comprise the combination of first polypeptide chain a3 and second polypeptide chain b2, wherein

i) the MHC class II β chain polypeptide is a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A,

ii) the MHC class II α chain polypeptide is a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 75,

iii) the autoimmune disease-associated peptide is selected from a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide,

iv) the linker between the autoimmune disease-associated peptide and the DRB MHC class II polypeptide is (GGCGS)(GGGGS)_n (SEQ ID NO:128), where $n = 2$ (for a total of 15 amino acids in the linker between the autoimmune disease-associated peptide and the DRB MHC class II polypeptide),

v) the Ig Fc polypeptide is a human IgG1 Fc polypeptide comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A),

v) the one or more immunomodulatory polypeptides comprise a PD-L1 polypeptide comprising the sequence:

FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYR
QRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTF
RRLDPEENHTAELVIPELPLAHPNER (SEQ ID NO:99),

vi) there is a (G4S)₄ (SEQ ID NO:75) linker between the PD-L1 polypeptide and the DRA MHC class II polypeptide,

vii) there is a GGSAAAGG (SEQ ID NO:83) linker between the DRA MHC class II polypeptide and the Ig Fc polypeptide, and

viii) there is a disulfide bond joining the Cys in the (GGCGS)(GGGGS)₂ (SEQ ID NO:128) linker and the Cys at the K75C substitution in the DRA MHC class II polypeptide.

ANTIGEN-PRESENTING, DISULFIDE-LINKED HETERODIMERS (I.E., MOD-LESS TMMPs)

[00297] The present disclosure provides an antigen-presenting polypeptide (APP) that comprises a heterodimer (e.g., comprises a heterodimer or a homodimer of two heterodimers), where the heterodimer comprises: a) a first polypeptide comprising an autoimmune disease-associated peptide; and ii) a first MHC class II polypeptide; and b) a second polypeptide comprising a second MHC class II polypeptide, where the heterodimer does not include an immunomodulatory polypeptide, where the first polypeptide and the second polypeptide are disulfide linked to one another, optionally where the first or the second polypeptide comprises an Ig Fc polypeptide. An APP of the present disclosure is depicted schematically in FIG. 25A-25C. An APP of the present disclosure is useful for diagnostic applications and therapeutic applications. As discussed below, when used for diagnostic applications, the APP also can comprise a detectable label so that binding of the APP to a target T cell is detected by detecting the detectable label.

[00298] Any of the TMMPs described above may be used without the immunomodulatory polypeptide(s) component as an APP. Further, because the APP comprises an Ig Fc polypeptide, an APP typically will be a homodimer comprising two heterodimers that are joined by disulfide bonds that spontaneously form between the two Ig Fc polypeptides. The APP comprises an autoimmune disease-associated peptide; suitable autoimmune disease-associated peptides are described above. In some cases, the first MHC class II polypeptide is an MHC class II β chain polypeptide such as a DRB MHC class II polypeptide. In some cases, the second MHC class II polypeptide is an MHC class II α chain polypeptide such as a DRA MHC class II polypeptide. Suitable Ig Fc polypeptides are as described above. In some cases, the Ig Fc polypeptide is one that induces cell lysis through activation of complement-dependent

cytotoxicity (CDC). In some cases, the Ig Fc polypeptide is one that can elicit antibody-dependent cellular cytotoxicity (ADCC). In some cases, the Ig Fc polypeptide binds complement or a complement component. In some cases, the Ig Fc polypeptide is one that substantially does not induce cell lysis through activation of CDC. When the Ig Fc polypeptide is one that that induces cell lysis through activation of CDC, and/or elicits ADCC, the APP can bind to and destroy the target T cell. An APP used for diagnostic purposes typically will have an Ig Fc polypeptide is one that substantially does not induce cell lysis through activation of CDC or elicit ADCC.

[00299] In some cases, therefore, an APP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; and ii) a first MHC class II polypeptide comprising a substitution of an amino acid (other than a Cys) with a Cys (a “first Cys”); and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a second MHC class II polypeptide comprising a substitution of an amino acid (other than a Cys) with a Cys (a “second Cys”); and ii) an Ig Fc polypeptide, where the first polypeptide and the second polypeptide are disulfide bonded via the first Cys and the second Cys. The first MHC class II polypeptide can be a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A; and having an amino acid substitution selected from P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C. The second MHC class II polypeptide can be a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22A; and having an amino acid substitution selected from E3C, E4C, F12C, G28C, D29C, I72C, K75C, T80C, P81C, I82C, T93C, N94C, and S95C. In some cases, the Ig Fc polypeptide induces cell lysis through activation of complement-dependent cytotoxicity (CDC) and/or elicits antibody-dependent cellular cytotoxicity (ADCC). In some cases, the Ig Fc polypeptide is a variant that substantially does not induce cell lysis through activation of CDC, e.g., an IgG1 Fc polypeptide comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the autoimmune disease-associated peptide is a peptide selected from the group consisting of a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison’s disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren’s syndrome-associated peptide, and a psoriasis-associated peptide.

[00300] In some cases, an APP of the present disclosure comprises a heterodimer comprising: a) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising a Cys (a “linker Cys”), and iii) a first MHC class II polypeptide; and b) a second polypeptide comprising, in order from N-terminus to C-terminus: i) a

second MHC class II polypeptide comprising a substitution of an amino acid (other than a Cys) with a Cys (a “second Cys”); and ii) an Ig Fc polypeptide, where the first polypeptide and the second polypeptide are disulfide bonded via the linker Cys and the second Cys. The first MHC class II polypeptide can be a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 100% amino acid sequence identity to the amino acid sequence depicted in FIG. 23A. The second MHC class II polypeptide can be a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22A; and having an amino acid substitution selected from I72C or K75C. In some cases, the Ig Fc polypeptide induces cell lysis through activation of complement-dependent cytotoxicity (CDC) and/or elicits antibody-dependent cellular cytotoxicity (ADCC). In some cases, the Ig Fc polypeptide is a variant that substantially does not induce cell lysis through activation of CDC, e.g., an IgG1 Fc polypeptide comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, autoimmune disease-associated peptide is selected from a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison’s disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren’s syndrome-associated peptide, and a psoriasis-associated peptide.

[00301] For example, in some cases, the peptide linker can comprise an amino acid sequence selected from: (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10 (e.g., where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, with n = 2 or 3 generally being useful); the first MHC class II polypeptide is a DRB MHC class II polypeptide; and the second MHC class II polypeptide is a DRA MHC class II polypeptide that comprises a substitution of an amino acid (other than a Cys) with a Cys.

[00302] Specific examples of the Cys-containing linkers between the autoimmune disease-associated peptide and a DRB MHC class II polypeptide and Cys residues in the DRA MHC class II polypeptide that can form a disulfide bond are provided in the Table 4, below:

Table 4

Cys-Containing Linker Between the Autoimmune Disease-Associated Peptide and the DRB MHC Class II Polypeptide	DRA MHC class II polypeptide substitution
(CGGGS)(GGGGS) _n (SEQ ID NO:1)	I72C

(GCGGS)(GGGGS) _n (SEQ ID NO:2)	I72C
(GGCGS)(GGGGS) _n (SEQ ID NO:3)	I72C
(GGGCS)(GGGGS) _n (SEQ ID NO:4)	I72C
(GGGGC)(GGGGS) _n (SEQ ID NO:5)	I72C
(CGGGS)(GGGGS) _n (SEQ ID NO:1)	K75C
(GCGGS)(GGGGS) _n (SEQ ID NO:2)	K75C
(GGCGS)(GGGGS) _n (SEQ ID NO:3)	K75C
(GGGCS)(GGGGS) _n (SEQ ID NO:4)	K75C
(GGGGC)(GGGGS) _n (SEQ ID NO:5)	K75C

[00303] As noted above, in any of the above APP embodiments, $n = 0, 1, 2, 3, 4$ or more, with 2 or 3 typically being used to create a total linker length of 15 or 20 amino acids, although longer lengths may be possible. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the other components of second polypeptide. In some cases, the Ig Fc polypeptide induces cell lysis through activation of complement-dependent cytotoxicity (CDC) and/or elicits antibody-dependent cellular cytotoxicity (ADCC). In some cases, the Ig Fc polypeptide is present and is a human IgG1 Fc polypeptide, optionally comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the autoimmune disease-associated peptide is selected from a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

[00304] The following are examples of the APPs described above in which the first and the second polypeptides are linked via a disulfide bond between the Cys in the peptide linker and the Cys provided by the substitution in the second MHC class II polypeptide, and wherein the first polypeptide is a DRB MHC class II polypeptide (i.e., a DR β chain polypeptide), and the second polypeptide is a DRA MHC class II polypeptide (i.e., a DR α chain polypeptide).

[00305] As one example, an APP of the present disclosure comprises a heterodimer comprising one of the following five first polypeptides and one of the following two second polypeptides:

a1) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (CGGGS)(GGGGS)_n (SEQ ID NO:1), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a2) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GCGGS)(GGGGS)_n (SEQ ID NO:2), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a3) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GGCGS)(GGGGS)_n (SEQ ID NO:3), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a4) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GGGCS)(GGGGS)_n (SEQ ID NO:4), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); or alternatively

a5) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising the amino acid sequence (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at

least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); and

b1) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising a Cys at position 72 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 72); and an ii) an Ig Fc polypeptide; or, alternatively

b2) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising a Cys at position 75 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 75); and ii) an Ig Fc polypeptide.

[00306] Each of the above combinations of first and second polypeptides for making a TMMP is thus expressly disclosed, i.e., a1-b1, a2-b1, a3-b1, a4-b1, a5-b1, and a1-b2, a2-b2, a3-b2, a4-b2 and a5-b2.

[00307] As one example, a TMMP of the present disclosure comprises a heterodimer comprising the following first and second polypeptides to create a heterodimer having one or more immunomodulatory polypeptides at MOD position 1 or 3:

a1) a first polypeptide comprising, in order from N-terminus to C-terminus: i) an autoimmune disease-associated peptide; ii) a linker comprising an amino acid sequence selected from the group consisting of (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10; and iii) an MHC class II β chain polypeptide (e.g., a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 23A); and

b1) a second polypeptide comprising, in order from N-terminus to C-terminus: i) an MHC class II α chain comprising Cys at position 72 or 75 (e.g., a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 72 or 75); and an ii) an Ig Fc polypeptide.

[00308] As noted above, in any of the above embodiments, n = 0, 1, 2, 3, 4 or more, with 2 or 3 typically being used to create a total linker length of 15 or 20 amino acids, although longer lengths may be usable. In any of the above embodiments, linkers that do not comprise a Cys optionally can be used to connect the components of the second polypeptide (e.g., a GGSAAAGG (SEQ ID NO:83) linker or

AAAGG (SEQ ID NO:82) linker can be used between the DRA MHC class II polypeptide and the Ig Fc polypeptide). In the above embodiments, in some cases, the Ig Fc polypeptide is a human IgG1 Fc polypeptide comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A). In some cases, the Ig Fc polypeptide induces cell lysis through activation of complement-dependent cytotoxicity (CDC) and/or elicits antibody-dependent cellular cytotoxicity (ADCC). In some cases, the autoimmune disease-associated peptide is selected from a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide.

[00309] Hence, for example, a TMMP in accordance with the above embodiments can comprise the combination of first polypeptide chain a3 and second polypeptide chain b2, wherein

i) the MHC class II β chain polypeptide is a DRB MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% amino acid sequence identity to the amino acid sequence depicted in FIG. 23A,

ii) the MHC class II α chain polypeptide is a DRA MHC class II polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 22G, and comprising a Cys at position 75,

iii) the autoimmune disease-associated peptide is selected from a multiple sclerosis-associated peptide, a rheumatoid arthritis-associated peptide, a systemic lupus erythematosus-associated peptide, an Addison's disease-associated peptide, a myasthenia gravis-associated peptide, a Sjögren's syndrome-associated peptide, and a psoriasis-associated peptide,

iv) the linker between the autoimmune disease-associated peptide and the DRB MHC class II polypeptide is (GGCGS)(GGGGS)_n (SEQ ID NO:128), where $n = 2$ (for a total of 15 amino acids in the linker between the autoimmune disease-associated peptide and the DRB MHC class II polypeptide),

v) the Ig Fc polypeptide is a human IgG1 Fc polypeptide comprising the amino acid sequence depicted in FIG. 21A, or a variant thereof such as the amino acid sequence depicted in FIG. 21A comprising L234A and L235A substitutions (L14A and L15A of the amino acid sequence depicted in FIG. 21A),

vi) there is a GGSAAAGG (SEQ ID NO:83) linker between the DRA MHC class II polypeptide and the Ig Fc polypeptide, and

viii) there is a disulfide bond joining the Cys in the (GGCGS)(GGGGS)₂ (SEQ ID NO:128) linker and the Cys at the K75C substitution in the DRA MHC class II polypeptide.

[00310] A disulfide-bonded APP of the present disclosure will in some cases exhibit greater stability than a control non-disulfide-bonded APP, i.e., where the control non-disulfide-bonded APP

comprises first and second polypeptides that have the same amino acid sequence as the disulfide-bonded APP, except lacking the Cys residues that form the disulfide bond present in the disulfide-bonded APP. A disulfide-bonded APP of the present disclosure will in some cases exhibit at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 50%, at least 75%, at least 2-fold, at least 5-fold, at least 10-fold, at least 50-fold, at least 100-fold, or greater than 100-fold, greater stability in the PBS buffer solution containing 500 mM NaCl (described above) *in vitro* over a specified period of time and at a specified temperature (e.g., in a solution at a temperature of from 37°C to 42°C for a period of time of from 1 hour to 28 days; e.g., for 1 hour at 37°C; 1 day at 37°C; 5 days at 37°C; 1 hour at 42°C; 1 day at 42°C; 5 days at 42°C; 5 days at 37°C; 10 days at 37°C; 14 days at 37°C; 28 days at 37°C; and the like) than a control non-disulfide-bonded APP. A disulfide-bonded APP of the present disclosure will in some cases exhibit greater expression than a control non-disulfide-bonded APP. A disulfide-bonded APP of the present disclosure will in some cases exhibit both greater stability and greater expression than a control non-disulfide-bonded APP. For example, in some cases, an APP of the present disclosure is expressed (produced) in a Chinese hamster ovary (CHO) cell *in vitro* at a level that is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, or more than 100-fold, higher than the expression level of a control APP lacking the at least one disulfide bond when expressed under the same conditions and in the same CHO cells. Expression levels can be determined by: i) producing the APP in a mammalian cell *in vitro* in a CHO cell *in vitro*; and ii) determining the amount of APP produced by the mammalian cell. For example, the APP can be isolated from the CHO cells and/or from culture medium in which the CHO cells are cultured, where isolation of the APP can be carried out by affinity chromatography, e.g., on a Protein A column, a Protein G column, or the like. An example of a suitable mammalian cell is a CHO cell; e.g., an Expi-CHO-S™ cell (e.g., ThermoFisher Scientific, Catalog #A29127).

[00311] As one example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26B, comprising an F7C substitution (Cys-7) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 2983, depicted in FIG. 26A, comprising a P81C substitution (Cys-81) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-7 and Cys-81.

[00312] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26C, comprising an P5C substitution (Cys-5) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 2983, depicted in FIG. 26A,

comprising a P81C substitution (Cys-81) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-5 and Cys-81.

[00313] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26D, comprising an H33C substitution (Cys-33) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 2983, depicted in FIG. 26A, comprising a P81C substitution (Cys-81) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-33 and Cys 81.

[00314] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence of construct 2988, depicted in FIG. 26F, comprising an N19C substitution (N19C) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence depicted in FIG. 26E, comprising an E4C substitution (Cys-4) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-19 and Cys-4.

[00315] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26G, comprising a G20C substitution (Cys-20) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 2984, depicted in FIG. 26E, comprising an E4C substitution (Cys-4) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-20 and Cys-4.

[00316] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG 26I, comprising a Q56C substitution (Cys-156) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 2985, depicted in FIG. 26H, comprising a T93C substitution (Cys-93) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-156 and Cys-93.

[00317] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence of construct 3030, depicted in FIG. 26J, comprising a W153C substitution (Cys-153) in the MHC class II β chain relative to the MHC class II β chain sequence

depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 2985, depicted in FIG. 26H, comprising a T93C substitution (Cys-93) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-153 and Cys-93.

[00318] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26B, comprising an F7C substitution (Cys-7) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3018, depicted in FIG. 26K, comprising an F12C substitution (Cys-12) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-7 and Cys-12.

[00319] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26L, comprising a Q10C substitution (Cys-10) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3018, depicted in FIG. 26K, comprising an F12C substitution (Cys-12) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-10 and Cys-12.

[00320] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26B, comprising an F7C substitution (Cys-7) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3019, depicted in FIG. 26M, comprising a T80C substitution (Cys-80) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-7 and Cys-80.

[00321] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26C, comprising a P5C substitution (Cys-5) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3019, depicted in FIG. 26M, comprising a T80C substitution (Cys-80) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-5 and Cys-80.

[00322] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26D, comprising an I82C substitution (Cys-82) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3019, depicted in FIG. 26M, comprising a T80C substitution (Cys-80) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-82 and Cys-80.

[00323] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26B, comprising an F7C substitution (Cys-7) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3018, depicted in FIG. 26K, comprising an F12C substitution (Cys-12) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-7 and Cys-12.

[00324] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26L, comprising a Q10C substitution (Cys-10) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3018, depicted in FIG. 26K, comprising an F12C substitution (Cys-12) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-10 and Cys-12.

[00325] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26B, comprising an F7C substitution (Cys-7) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3019, depicted in FIG. 26M, comprising a T80C substitution (Cys-80) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-7 and Cys-80.

[00326] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26C, comprising a P5C substitution (Cys-5) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3019, depicted in FIG. 26M, comprising a T80C substitution (Cys-80) in the MHC class II α chain relative to the MHC class II α

chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-5 and Cys-80.

[00327] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26D, comprising an I82C substitution (Cys-82) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3019, depicted in FIG. 26M, comprising a T80C substitution (Cys-80) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-82 and Cys-80.

[00328] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26B, comprising an F7C substitution (Cys-7) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3020, depicted in FIG. 26N, comprising an I82C substitution (Cys-82) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-7 and Cys-82.

[00329] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26C, comprising a P5C substitution (Cys-5) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3020, depicted in FIG. 26N, comprising an I82C substitution (Cys-82) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-5 and Cys-82.

[00330] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26O, comprising an H33C substitution (Cys-33) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3020, depicted in FIG. 26N, comprising an I82C substitution (Cys-82) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-33 and Cys-82.

[00331] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26Q, comprising a G151C substitution (Cys-151) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3021, depicted in FIG. 26P,

comprising a G28C substitution (Cys-28) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-151 and Cys-28.

[00332] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26R, comprising a D152C substitution (Cys-152) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3021, depicted in FIG. 26P, comprising a G28C substitution (Cys-28) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-152 and Cys-28.

[00333] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26T, comprising a W153C substitution (Cys-153) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3021, depicted in FIG. 26P, comprising a G28C substitution (Cys-28) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-153 and Cys-28.

[00334] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26Q, comprising a G151C substitution (Cys-151) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3022, depicted in FIG. 26S, comprising a D29C substitution (Cys-29) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-151 and Cys-29.

[00335] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26R, comprising a D152C substitution (Cys-152) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3022, depicted in FIG. 26S, comprising a D29C substitution (Cys-29) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-152 and Cys-29.

[00336] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26J, comprising a W153C substitution (Cys-153) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a

second polypeptide comprising the amino acid sequence of construct 3022, depicted in FIG. 26S, comprising a D29C substitution (Cys-29) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-153 and Cys-29.

[00337] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26I, comprising a Q156C substitution (Cys-156) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3023, depicted in FIG. 26T, comprising an N94C substitution (Cys-94) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-156 and Cys-94.

[00338] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26U, comprising an N120C substitution (Cys-120) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3023, depicted in FIG. 26T, comprising an N94C substitution (Cys-94) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-120 and Cys-94.

[00339] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26I, comprising a Q156C substitution (Cys-156) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3024, depicted in FIG. 26V, comprising an S95C substitution (Cys-95) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-156 and Cys-95.

[00340] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26U, comprising an N120C substitution (Cys-120) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3024, depicted in FIG. 26V, comprising an S95C substitution (Cys-95) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-120 and Cys-95.

[00341] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26F, comprising an N19C substitution (Cys-19) in

the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3025, depicted in FIG. 26W, comprising an E3C substitution (Cys-3) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-19 and Cys-3.

[00342] As another example, an APP of the present disclosure comprises: a) a first polypeptide comprising the amino acid sequence depicted in FIG. 26G, comprising a G20C substitution (Cys-20) in the MHC class II β chain relative to the MHC class II β chain sequence depicted in FIG. 23A; and b) a second polypeptide comprising the amino acid sequence of construct 3025, depicted in FIG. 26W, comprising an E3C substitution (Cys-3) in the MHC class II α chain relative to the MHC class II α chain sequence depicted in FIG. 22A, where the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond between Cys-20 and Cys-3.

NUCLEIC ACIDS

[00343] The present disclosure provides a nucleic acid comprising a nucleotide sequence encoding a TMPP or an APP of the present disclosure. For example, the present disclosure provides a single nucleic acid comprising nucleotide sequences encoding both the first polypeptide and the second polypeptide of a TMPP or an APP of the present disclosure. As another example, the present disclosure provides: a) a first nucleic acid comprising a nucleotide sequence encoding the first polypeptide of a TMPP or an APP of the present disclosure; and b) a second nucleic acid comprising a nucleotide sequence encoding the second polypeptide of a TMPP or an APP of the present disclosure. In some cases, the nucleic acid is a recombinant expression vector; thus, the present disclosure provides a recombinant expression vector comprising a nucleotide sequence encoding a TMPP or an APP of the present disclosure.

Separate Nucleic Acids Encoding Individual Polypeptide Chains of a TMPP or APP

[00344] The present disclosure provides nucleic acids comprising nucleotide sequences encoding a TMPP of the present disclosure. As noted above, in some cases, the individual polypeptide chains of a TMPP of the present disclosure are encoded in separate nucleic acids. In some cases, nucleotide sequences encoding the separate polypeptide chains of a TMPP or an APP of the present disclosure are operably linked to transcriptional control elements, e.g., promoters, such as promoters that are functional in a eukaryotic cell, where the promoter can be a constitutive promoter or an inducible promoter.

[00345] For example, the present disclosure provides a first nucleic acid and a second nucleic acid, where the first nucleic acid comprises a nucleotide sequence encoding the first polypeptide of a TMPP or an APP of the present disclosure, and where the second nucleic acid comprises a nucleotide sequence encoding the second polypeptide of the TMPP or APP. In some cases, the nucleotide sequences encoding the first and the second polypeptides are operably linked to transcriptional control

elements. In some cases, the transcriptional control element is a promoter that is functional in a eukaryotic cell. In some cases, the nucleic acids are present in separate expression vectors.

[00346] In some cases, the nucleotide sequences encoding the first and the second polypeptides are operably linked to transcriptional control elements. In some cases, the transcriptional control element is a promoter that is functional in a eukaryotic cell. In some cases, the nucleic acids are present in separate expression vectors.

Nucleic Acid Encoding Two Or More Polypeptides Present in a TMMP or APP

[00347] The present disclosure provides a nucleic acid comprising nucleotide sequences encoding the first polypeptide and the second polypeptide of a TMMP or an APP of the present disclosure. In some cases, the nucleotide sequences encoding the first polypeptide and the second polypeptide of a TMMP or an APP of the present disclosure includes a proteolytically cleavable linker interposed between the nucleotide sequence encoding the first polypeptide and the nucleotide sequence encoding the second polypeptide. In some cases, the nucleotide sequences encoding the first polypeptide and the second polypeptide of a TMMP or an APP of the present disclosure includes an internal ribosome entry site (IRES) interposed between the nucleotide sequence encoding the first polypeptide and the nucleotide sequence encoding the second polypeptide. In some cases, the nucleotide sequences encoding the first polypeptide and the second polypeptide of a TMMP or an APP of the present disclosure includes a ribosome skipping signal (or *cis*-acting hydrolase element, CHYSEL) interposed between the nucleotide sequence encoding the first polypeptide and the nucleotide sequence encoding the second polypeptide. Examples of nucleic acids are described below, where a proteolytically cleavable linker is provided between nucleotide sequences encoding the first polypeptide and the second polypeptide of a TMMP or an APP of the present disclosure; in any of these embodiments, an IRES or a ribosome skipping signal can be used in place of the nucleotide sequence encoding the proteolytically cleavable linker.

[00348] In some cases, a first nucleic acid (e.g., a recombinant expression vector, an mRNA, a viral RNA, etc.) comprises a nucleotide sequence encoding a first polypeptide chain of a TMMP or an APP of the present disclosure; and a second nucleic acid (e.g., a recombinant expression vector, an mRNA, a viral RNA, etc.) comprises a nucleotide sequence encoding a second polypeptide chain of a TMMP or an APP of the present disclosure. In some cases, the nucleotide sequence encoding the first polypeptide, and the second nucleotide sequence encoding the second polypeptide, are each operably linked to transcriptional control elements, e.g., promoters, such as promoters that are functional in a eukaryotic cell, where the promoter can be a constitutive promoter or an inducible promoter.

RECOMBINANT EXPRESSION VECTORS

[00349] The present disclosure provides recombinant expression vectors comprising nucleic acids of the present disclosure. In some cases, the recombinant expression vector is a non-viral vector. In

some cases, the recombinant expression vector is a viral construct, e.g., a recombinant adeno-associated virus construct (see, e.g., U.S. Patent No. 7,078,387), a recombinant adenoviral construct, a recombinant lentiviral construct, a recombinant retroviral construct, a non-integrating viral vector, etc.

[00350] Suitable expression vectors include, but are not limited to, viral vectors (e.g. viral vectors based on vaccinia virus; poliovirus; adenovirus (see, e.g., Li et al., *Invest Ophthalmol Vis Sci* 35:2543-2549, 1994; Borrás et al., *Gene Ther* 6:515-524, 1999; Li and Davidson, *PNAS* 92:7700-7704, 1995; Sakamoto et al., *Hum Gene Ther* 5:1088-1097, 1999; WO 94/12649, WO 93/03769; WO 93/19191; WO 94/28938; WO 95/11984 and WO 95/00655); adeno-associated virus (see, e.g., Ali et al., *Hum Gene Ther* 9:81-86, 1998; Flannery et al., *PNAS* 94:6916-6921, 1997; Bennett et al., *Invest Ophthalmol Vis Sci* 38:2857-2863, 1997; Jomary et al., *Gene Ther* 4:683-690, 1997; Rolling et al., *Hum Gene Ther* 10:641-648, 1999; Ali et al., *Hum Mol Genet* 5:591-594, 1996; Srivastava in WO 93/09239, Samulski et al., *J. Vir.* (1989) 63:3822-3828; Mendelson et al., *Virology* (1988) 166:154-165; and Flotte et al., *PNAS* (1993) 90:10613-10617); SV40; herpes simplex virus; human immunodeficiency virus (see, e.g., Miyoshi et al., *PNAS* 94:10319-23, 1997; Takahashi et al., *J Virol* 73:7812-7816, 1999); a retroviral vector (e.g., Murine Leukemia Virus, spleen necrosis virus, and vectors derived from retroviruses such as Rous Sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, a lentivirus, human immunodeficiency virus, myeloproliferative sarcoma virus, and mammary tumor virus); and the like. Numerous suitable expression vectors are known to those of skill in the art, and many are commercially available.

[00351] Depending on the host/vector system utilized, any of a number of suitable transcription and translation control elements, including constitutive and inducible promoters, transcription enhancer elements, transcription terminators, etc. may be used in the expression vector (see e.g., Bitter et al. (1987) *Methods in Enzymology*, 153:516-544).

[00352] In some cases, a nucleotide sequence encoding a TMMP of the present disclosure is operably linked to a control element, e.g., a transcriptional control element, such as a promoter. The transcriptional control element may be functional in either a eukaryotic cell, e.g., a mammalian cell; or a prokaryotic cell (e.g., bacterial or archaeal cell). In some cases, a nucleotide sequence encoding a DNA-targeting RNA and/or a site-directed modifying polypeptide is operably linked to multiple control elements that allow expression of the nucleotide sequence encoding a DNA-targeting RNA and/or a site-directed modifying polypeptide in both prokaryotic and eukaryotic cells.

[00353] Non-limiting examples of suitable eukaryotic promoters (promoters functional in a eukaryotic cell) include those from cytomegalovirus (CMV) immediate early, herpes simplex virus (HSV) thymidine kinase, early and late SV40, long terminal repeats (LTRs) from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. The expression vector may also contain a ribosome binding site for translation initiation

and a transcription terminator. The expression vector may also include appropriate sequences for amplifying expression.

GENETICALLY MODIFIED HOST CELLS

[00354] The present disclosure provides a genetically modified host cell, where the host cell is genetically modified with a nucleic acid(s) of the present disclosure.

[00355] Suitable host cells include eukaryotic cells, such as yeast cells, insect cells, and mammalian cells. In some cases, the host cell is a cell of a mammalian cell line. Suitable mammalian cell lines include human cell lines, non-human primate cell lines, rodent (e.g., mouse, rat) cell lines, and the like. Suitable mammalian cell lines include, but are not limited to, HeLa cells (e.g., American Type Culture Collection (ATCC) No. CCL-2), CHO cells (e.g., ATCC Nos. CRL9618, CCL61, CRL9096), 293 cells (e.g., ATCC No. CRL-1573), Vero cells, NIH 3T3 cells (e.g., ATCC No. CRL-1658), Huh-7 cells, BHK cells (e.g., ATCC No. CCL10), PC12 cells (ATCC No. CRL1721), COS cells, COS-7 cells (ATCC No. CRL1651), RAT1 cells, mouse L cells (ATCC No. CCL1.3), human embryonic kidney (HEK) cells (ATCC No. CRL1573), HLHepG2 cells, and the like.

[00356] Genetically modified host cells can be used to produce a TMMP or an APP of the present disclosure. For example, a genetically modified host cell can be used to produce a TMMP of the present disclosure, or an APP of the present disclosure. An expression vector(s) comprising nucleotide sequences encoding the polypeptide(s) is/are introduced into a host cell, generating a genetically modified host cell, which genetically modified host cell produces the polypeptide(s).

METHODS OF PRODUCING A TMMP OR AN APP

[00357] The present disclosure provides methods of producing TMMP or an APP of the present disclosure. The methods generally involve culturing, in a culture medium, a host cell (e.g., a genetically modified host cell of the present disclosure) that is genetically modified with a recombinant expression vector(s) comprising a nucleotide sequence(s) encoding the TMMP or the APP; and isolating the TMMP or the APP from the genetically modified host cell and/or the culture medium. As noted above, in some cases, the individual polypeptide chains of a TMMP or APP of the present disclosure are encoded in separate recombinant expression vectors. In some cases, all polypeptide chains of a TMMP or APP of the present disclosure are encoded in a single recombinant expression vector.

[00358] Isolation of the TMMP or the APP from the expression host cell (e.g., from a lysate of the expression host cell) and/or the culture medium in which the host cell is cultured, can be carried out using standard methods of protein purification.

[00359] For example, a lysate may be prepared of the expression host and the lysate purified using high performance liquid chromatography (HPLC), exclusion chromatography (e.g., size exclusion chromatography), gel electrophoresis, affinity chromatography, or other purification technique.

Alternatively, where the TMMP or APP is secreted from the expression host cell into the culture medium, the TMMP or APP can be purified from the culture medium using HPLC, exclusion chromatography, gel electrophoresis, affinity chromatography, or other purification technique. In some cases, the TMMP or APP is purified, e.g., a composition is generated that comprises at least 80% by weight, at least about 85% by weight, at least about 95% by weight, or at least about 99.5% by weight, of the TMMP or APP in relation to contaminants related to the method of preparation of the product and its purification. The percentages can be based upon total protein.

[00360] In some cases, e.g., where the TMMP or APP comprises an affinity tag, the TMMP or APP can be purified using an immobilized binding partner of the affinity tag. For example, where a TMMP or an APP comprises an Ig Fc polypeptide, the TMMP or the APP can be isolated from genetically modified mammalian host cell and/or from culture medium in which the mammalian cells are cultured, where isolation of the TMMP or APP can be carried out by affinity chromatography, e.g., on a Protein A column, a Protein G column, or the like. An example of a suitable mammalian cell is a CHO cell; e.g., an Expi-CHO-S™ cell (e.g., ThermoFisher Scientific, Catalog #A29127).

[00361] The first and second polypeptides will self-assemble into heterodimers by spontaneously forming disulfide bonds between the above-discussed Cys residues in the first and second polypeptides. As also noted above, when both heterodimers include Ig Fc polypeptides, disulfide bonds will spontaneously form between the respective Ig Fc polypeptides to covalently link the two heterodimers to one another (depicted schematically in FIG. 1E).

COMPOSITIONS

[00362] The present disclosure provides compositions, including pharmaceutical compositions, comprising a TMMP or an APP of the present disclosure. The present disclosure provides compositions, including pharmaceutical compositions, comprising a nucleic acid or a recombinant expression vector of the present disclosure. The discussion, below, of compositions refers to compositions comprising a TMMP of the present disclosure; however, the discussion applies equally to an APP of the present disclosure.

Compositions Comprising a TMMP or an APP

[00363] A composition of the present disclosure can comprise, in addition to a TMMP of the present disclosure, or an APP of the present disclosure, one or more of: a salt, e.g., NaCl, MgCl₂, KCl, MgSO₄, etc.; a buffering agent, e.g., a Tris buffer, N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), 2-(N-Morpholino)ethanesulfonic acid (MES), 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES), 3-(N-Morpholino)propanesulfonic acid (MOPS), N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS), etc.; a solubilizing agent; a detergent, e.g., a non-ionic detergent such as Tween-20, etc.; a protease inhibitor; glycerol; and the like.

[00364] The composition may comprise a pharmaceutically acceptable excipient, a variety of which are known in the art and need not be discussed in detail herein. Pharmaceutically acceptable excipients have been amply described in a variety of publications, including, for example, "Remington: The Science and Practice of Pharmacy", 19th Ed. (1995), or latest edition, Mack Publishing Co; A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy", 20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H.C. Ansel et al., eds 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A.H. Kibbe et al., eds., 3rd ed. Amer. Pharmaceutical Assoc.

[00365] A pharmaceutical composition can comprise: i) a TMMP of the present disclosure; and ii) a pharmaceutically acceptable excipient. A pharmaceutical composition can comprise: i) an APP of the present disclosure; and ii) a pharmaceutically acceptable excipient. In some cases, a subject pharmaceutical composition will be suitable for administration to a subject, e.g., will be sterile. For example, in some embodiments, a subject pharmaceutical composition will be suitable for administration to a human subject, e.g., where the composition is sterile and is free of detectable pyrogens and/or other toxins.

[00366] The protein compositions may comprise other components, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium, carbonate, and the like. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, hydrochloride, sulfate salts, solvates (e.g., mixed ionic salts, water, organics), hydrates (e.g., water), and the like.

[00367] For example, compositions may include aqueous solution, powder form, granules, tablets, pills, suppositories, capsules, suspensions, sprays, and the like. The composition may be formulated according to the various routes of administration described below.

[00368] Where a TMMP of the present disclosure is administered as an injectable (e.g. subcutaneously, intraperitoneally, intramuscularly, intralymphatically, and/or intravenously) directly into a tissue, a formulation can be provided as a ready-to-use dosage form, or as non-aqueous form (e.g. a reconstitutable storage-stable powder) or aqueous form, such as liquid composed of pharmaceutically acceptable carriers and excipients. The protein-containing formulations may also be provided so as to enhance serum half-life of the subject protein following administration. For example, the protein may be provided in a liposome formulation, prepared as a colloid, or other conventional techniques for extending serum half-life. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka

et al. 1980 *Ann. Rev. Biophys. Bioeng.* 9:467, U.S. Pat. Nos. 4,235,871, 4,501,728 and 4,837,028. The preparations may also be provided in controlled release or slow-release forms.

[00369] In some cases, a composition of the present disclosure comprises: a) a TMMP of the present disclosure; and b) saline (e.g., 0.9% NaCl). In some cases, the composition is sterile. In some cases, the composition is suitable for administration to a human subject, e.g., where the composition is sterile and is free of detectable pyrogens and/or other toxins. Thus, the present disclosure provides a composition comprising: a) a TMMP of the present disclosure; and b) saline (e.g., 0.9% NaCl), where the composition is sterile and is free of detectable pyrogens and/or other toxins.

[00370] Other examples of formulations suitable for parenteral administration include isotonic sterile injection solutions, anti-oxidants, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. For example, a subject pharmaceutical composition can be present in a container, e.g., a sterile container, such as a syringe. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets.

[00371] The concentration of a TMMP of the present disclosure in a formulation can vary widely (e.g., from less than about 0.1%, usually at or at least about 2% to as much as 20% to 50% or more by weight) and will usually be selected primarily based on fluid volumes, viscosities, and patient-based factors in accordance with the particular mode of administration selected and the patient's needs.

[00372] The present disclosure provides a container comprising a composition of the present disclosure, e.g., a liquid composition. The container can be, e.g., a syringe, an ampoule, and the like. In some cases, the container is sterile. In some cases, both the container and the composition are sterile.

Compositions Comprising a Nucleic Acid or a Recombinant Expression Vector

[00373] The present disclosure provides compositions, e.g., pharmaceutical compositions, comprising a nucleic acid or a recombinant expression vector of the present disclosure. A wide variety of pharmaceutically acceptable excipients is known in the art and need not be discussed in detail herein. Pharmaceutically acceptable excipients have been amply described in a variety of publications, including, for example, A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy", 20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H. C. Ansel et al., eds 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A. H. Kibbe et al., eds., 3rd ed. Amer. Pharmaceutical Assoc.

[00374] A composition of the present disclosure can include: a) one or more nucleic acids or one or more recombinant expression vectors comprising nucleotide sequences encoding a TMMP or an APP of the present disclosure; and b) one or more of: a buffer, a surfactant, an antioxidant, a hydrophilic polymer, a dextrin, a chelating agent, a suspending agent, a solubilizer, a thickening agent, a stabilizer, a bacteriostatic agent, a wetting agent, and a preservative. Suitable buffers include, but are not limited to, (such as N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), bis(2-hydroxyethyl)amino-tris(hydroxymethyl)methane (BIS-Tris), N-(2-hydroxyethyl)piperazine-N'3-propanesulfonic acid (EPPS or HEPPS), glycylglycine, N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), 3-(N-morpholino)propane sulfonic acid (MOPS), piperazine-N,N'-bis(2-ethane-sulfonic acid) (PIPES), sodium bicarbonate, 3-(N-tris(hydroxymethyl)-methyl-amino)-2-hydroxy-propanesulfonic acid) TAPSO, (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (TES), N-tris(hydroxymethyl)methyl-glycine (Tricine), tris(hydroxymethyl)-aminomethane (Tris), etc.). Suitable salts include, e.g., NaCl, MgCl₂, KCl, MgSO₄, etc.

[00375] A pharmaceutical formulation of the present disclosure can include a nucleic acid or recombinant expression vector of the present disclosure in an amount of from about 0.001% to about 90% (w/w). In the description of formulations, below, "subject nucleic acid or recombinant expression vector" will be understood to include a nucleic acid or recombinant expression vector of the present disclosure. For example, in some cases, a subject formulation comprises a nucleic acid or recombinant expression vector of the present disclosure.

[00376] A subject nucleic acid or recombinant expression vector can be admixed, encapsulated, conjugated or otherwise associated with other compounds or mixtures of compounds; such compounds can include, e.g., liposomes or receptor-targeted molecules. A subject nucleic acid or recombinant expression vector can be combined in a formulation with one or more components that assist in uptake, distribution and/or absorption.

[00377] A subject nucleic acid or recombinant expression vector composition can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. A subject nucleic acid or recombinant expression vector composition can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

[00378] A formulation comprising a subject nucleic acid or recombinant expression vector can be a liposomal formulation. As used herein, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers. Liposomes are unilamellar or multilamellar

vesicles which have a membrane formed from a lipophilic material and an aqueous interior that contains the composition to be delivered. Cationic liposomes are positively charged liposomes that can interact with negatively charged DNA molecules to form a stable complex. Liposomes that are pH sensitive or negatively charged are believed to entrap DNA rather than complex with it. Both cationic and noncationic liposomes can be used to deliver a subject nucleic acid or recombinant expression vector.

[00379] Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome comprises one or more glycolipids or is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. Liposomes and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein by reference in its entirety.

[00380] The formulations and compositions of the present disclosure may also include surfactants. The use of surfactants in drug products, formulations and in emulsions is well known in the art. Surfactants and their uses are further described in U.S. Pat. No. 6,287,860.

[00381] In one embodiment, various penetration enhancers are included, to effect the efficient delivery of nucleic acids. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Penetration enhancers and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein by reference in its entirety.

[00382] Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets, or minitabets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. Suitable oral formulations include those in which a subject antisense nucleic acid is administered in conjunction with one or more penetration enhancers surfactants and chelators. Suitable surfactants include, but are not limited to, fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Suitable bile acids/salts and fatty acids and their uses are further described in U.S. Pat. No. 6,287,860. Also suitable are combinations of penetration enhancers, for example, fatty acids/salts in combination with bile acids/salts. An exemplary suitable combination is the sodium salt of lauric acid, capric acid, and UDCA. Further penetration enhancers include, but are not limited to, polyoxyethylene-9-lauryl ether, and polyoxyethylene-20-cetyl ether. Suitable penetration enhancers also include propylene glycol, dimethylsulfoxide, triethanolamine, N,N-dimethylacetamide, N,N-dimethylformamide, 2-pyrrolidone and derivatives thereof, tetrahydrofurfuryl alcohol, and AZONE™.

METHODS

[00383] A TMMP of the present disclosure is useful for modulating an activity of a T cell. Thus, the present disclosure provides methods of modulating an activity of a T cell, the methods generally involving contacting a target T cell with a TMMP of the present disclosure.

[00384] An APP of the present disclosure is useful for various research, therapeutic, and diagnostic purposes. For example, an APP of the present disclosure can be used to label, directly or indirectly, an antigen-specific T cell. An APP of the present disclosure can provide effector functions in an antigen-specific manner.

Methods of Modulating T Cell Activity

[00385] The present disclosure provides a method of selectively modulating the activity of an epitope-specific T cell, the method comprising contacting the T cell with a TMMP of the present disclosure, where contacting the T cell with a TMMP of the present disclosure selectively modulates the activity of the epitope-specific T cell. In some cases, the contacting occurs *in vivo*. In some cases, the contacting occurs *in vitro*.

[00386] In some cases, a TMMP of the present disclosure reduces activity of an autoreactive T cell and/or an autoreactive B cell. In some cases, a TMMP of the present disclosure increases the number and/or activity of a regulatory T cell (Treg), resulting in reduced activity of an autoreactive T cell and/or an autoreactive B cell.

[00387] In some cases, the T cell being contacted with a TMMP of the present disclosure is a regulatory T cell (Treg). Tregs are CD4⁺, FOXP3⁺, and CD25⁺. Tregs can suppress autoreactive T cells. In some cases, a method of the present disclosure activates Tregs, thereby reducing autoreactive T cell activity.

[00388] The present disclosure provides a method of increasing proliferation of Tregs, the method comprising contacting Tregs with a TMMP of the present disclosure, where the contacting increases proliferation of Tregs. The present disclosure provides a method of increasing the number of Tregs in an individual, the method comprising administering to the individual a TMMP of the present disclosure, where the administering results in an increase in the number of Tregs in the individual. For example, the number of Tregs can be increased by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 2-fold, at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold.

Methods of Detecting an Antigen-Specific T Cell

[00389] The present disclosure provides a method of detecting an antigen-specific T-cell. The methods comprise contacting a T cell with an APP of the present disclosure; and detecting binding of the APP to the T cell.

[00390] The present disclosure provides a method of detecting an antigen-specific T cell, the method comprising contacting a T cell with an APP of the present disclosure, wherein binding of the APP to the T cell indicates that the T cell is specific for the epitope present in the APP.

[00391] In some cases, the APP comprises a detectable label. Suitable detectable labels include, but are not limited to, a radioisotope, a fluorescent polypeptide, or an enzyme that generates a fluorescent product, and an enzyme that generates a colored product. Where the APP comprises a detectable label, binding of the APP to the T cell is detected by detecting the detectable label.

[00392] In some cases, an APP of the present disclosure comprises a detectable label suitable for use in *in vivo* imaging, e.g., suitable for use in positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging, x-ray imaging, computer-assisted tomography (CAT), or magnetic resonance imaging (MRI), or other *in vivo* imaging method. Examples of suitable labels for *in vivo* imaging include gadolinium chelates (e.g., gadolinium chelates with DTPA (diethylenetriamine penta-acetic acid), DTPA-bismethylamide (BMA), DOTA (dodecane tetraacetic acid), or HP-DO3A (1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane)), iron chelates, magnesium chelates, manganese chelates, copper chelates, chromium chelates, iodine-based materials, and radionuclides. Suitable radionuclides include, but are not limited to, ¹²³I, ¹²⁵I, ¹³⁰I, ¹³¹I, ¹³³I, ¹³⁵I, ⁴⁷Sc, ⁷²As, ⁷²Se, ⁹⁰Y, ⁸⁸Y, ⁹⁷Ru, ¹⁰⁰Pd, ¹⁰¹mRh, ¹¹⁹Sb, ¹²⁸Ba, ¹⁹⁷Hg, ²¹¹At, ²¹²Bi, ²¹²Pb, ¹⁰⁹Pd, ¹¹¹In, ⁶⁷Ga, ⁶⁸Ga, ⁶⁴Cu, ⁶⁷Cu, ⁷⁵Br, ⁷⁷Br, ⁹⁹mTc, ¹⁴C, ¹³N, ¹⁵O, ³²P, ³³P, and ¹⁸F. In some cases, the detectable label is a positron-emitting isotope such as ¹¹C, ¹³N, ¹⁵O, ¹⁸F, ⁶⁴Cu, ⁶⁸Ga, ⁷⁸Br, ⁸²Rb, ⁸⁶Y, ⁹⁰Y, ²²Na, ²⁶Al, ⁴⁰K, ⁸³Sr, ⁸⁹Zr, or ¹²⁴I. In some cases, the detectable label is ⁶⁴Cu.

[00393] Suitable fluorescent proteins include, but are not limited to, green fluorescent protein (GFP) or variants thereof, blue fluorescent variant of GFP (BFP), cyan fluorescent variant of GFP (CFP), yellow fluorescent variant of GFP (YFP), enhanced GFP (EGFP), enhanced CFP (ECFP), enhanced YFP (EYFP), GFPS65T, Emerald, Topaz (TYFP), Venus, Citrine, mCitrine, GFPuv, destabilized EGFP (dEGFP), destabilized ECFP (dECFP), destabilized EYFP (dEYFP), mCFPm, Cerulean, T-Sapphire, CyPet, YPet, mKO, HcRed, t-HcRed, DsRed, DsRed2, DsRed-monomer, J-Red, dimer2, t-dimer2(12), mRFP1, pocilloporin, Renilla GFP, Monster GFP, paGFP, Kaede protein and kindling protein, Phycobiliproteins and Phycobiliprotein conjugates including B-Phycoerythrin, R-Phycoerythrin and Allophycocyanin. Other examples of fluorescent proteins include mHoneydew, mBanana, mOrange, dTomato, tdTomato, mTangerine, mStrawberry, mCherry, mGrape1, mRaspberry, mGrape2, mPlum (Shaner et al. (2005) *Nat. Methods* 2:905-909), and the like. Any of a variety of fluorescent and colored proteins from Anthozoan species, as described in, e.g., Matz et al. (1999) *Nature Biotechnol.* 17:969-973, is suitable for use.

[00394] Suitable enzymes include, but are not limited to, horse radish peroxidase (HRP), alkaline phosphatase (AP), beta-galactosidase (GAL), glucose-6-phosphate dehydrogenase, beta-N-acetylglucosaminidase, β -glucuronidase, invertase, Xanthine Oxidase, firefly luciferase, glucose oxidase (GO), and the like.

[00395] In some cases, binding of the APP to the T cell is detected using a detectably labeled antibody specific for the APP. An antibody specific for the APP can comprise a detectable label such as a radioisotope, a fluorescent polypeptide, or an enzyme that generates a fluorescent product, or an enzyme that generates a colored product.

[00396] In some cases, the T cell being detected is present in a sample comprising a plurality of T cells. For example, a T cell being detected can be present in a sample comprising from 10 to 10^9 T cells, e.g., from 10 to 10^2 , from 10^2 to 10^4 , from 10^4 to 10^6 , from 10^6 to 10^7 , from 10^7 to 10^8 , or from 10^8 to 10^9 , or more than 10^9 , T cells.

TREATMENT METHODS

[00397] The present disclosure provides treatment methods, the methods comprising administering to the individual an amount of a TMMP of the present disclosure, or one or more nucleic acids or expression vectors encoding the TMMP, effective to selectively modulate the activity of an epitope-specific T cell in an individual and to treat the individual. In some cases, a treatment method of the present disclosure comprises administering to an individual in need thereof one or more recombinant expression vectors comprising nucleotide sequences encoding a TMMP of the present disclosure. In some cases, a treatment method of the present disclosure comprises administering to an individual in need thereof one or more mRNA molecules comprising nucleotide sequences encoding a TMMP of the present disclosure. In some cases, a treatment method of the present disclosure comprises administering to an individual in need thereof a TMMP of the present disclosure. A TMMP of the present disclosure is useful for treating an autoimmune disease.

[00398] The present disclosure provides a method of selectively modulating the activity of an epitope-specific T cell in an individual, the method comprising administering to the individual an effective amount of a TMMP of the present disclosure, or one or more nucleic acids (e.g., expression vectors; mRNA; etc.) comprising nucleotide sequences encoding the TMMP, where the TMMP selectively modulates the activity of the epitope-specific T cell in the individual. Selectively modulating the activity of an epitope-specific T cell can treat a disease or disorder in the individual. Thus, the present disclosure provides a treatment method comprising administering to an individual in need thereof an effective amount of a TMMP of the present disclosure. A treatment method of the present disclosure, comprising administering an effective amount of a TMMP of the present disclosure, is suitable for treating an autoimmune disease.

[00399] In some cases, the immunomodulatory polypeptide is an inhibitory polypeptide, and a TMMP of the present disclosure inhibits activity of the epitope-specific T cell. In some cases, the epitope is a self-epitope, and a TMMP of the present disclosure selectively inhibits the activity of a T cell specific for the self-epitope.

[00400] The present disclosure provides a method of treating an autoimmune disease in an individual, the method comprising administering to the individual an effective amount of a TMMP of the present disclosure, or one or more nucleic acids comprising nucleotide sequences encoding the TMMP, where the TMMP comprises an autoimmune disease-associated peptide (as described above), and where the TMMP comprises an inhibitory immunomodulatory polypeptide. In some cases, an “effective amount” of a TMMP of the present disclosure is an amount that, when administered in one or more doses to an individual in need thereof, reduces the number of self-reactive (i.e., reactive with an autoimmune disease-associated antigen) CD4⁺ and/or CD8⁺ T cells by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%, compared to number of self-reactive T cells in the individual before administration of the TMMP, or in the absence of administration with the TMMP. In some cases, an “effective amount” of a TMMP of the present disclosure is an amount that, when administered in one or more doses to an individual in need thereof, reduces production of Th2 cytokines in the individual. In some cases, an “effective amount” of a TMMP of the present disclosure is an amount that, when administered in one or more doses to an individual in need thereof, ameliorates one or more symptoms associated with the autoimmune disease in the individual. In some instances, the TMMP reduces the number of CD4⁺ self-reactive T cells (i.e., the number of CD4⁺ T cells reactive with an autoimmune disease-associated antigen), which in turn leads to a reduction in CD8⁺ self-reactive T cells. In some instances, the TMMP increases the number of CD4⁺ Tregs, which in turn reduces the number of CD4⁺ self-reactive T cells and/or CD8⁺ T self-reactive T cells.

[00401] As noted above, in some cases, in carrying out a subject treatment method, a TMMP of the present disclosure is administered to an individual in need thereof, as the polypeptide *per se*. In other instances, in carrying out a subject treatment method, one or more nucleic acids comprising nucleotide sequences encoding a TMMP is/are administering to an individual in need thereof. Thus, in other instances, one or more nucleic acids of the present disclosure, e.g., one or more recombinant expression vectors of the present disclosure, is/are administered to an individual in need thereof.

[00402] The present disclosure also provides treatment methods, the methods comprising administering to the individual an amount of an APP of the present disclosure, or one or more nucleic acids or expression vectors encoding the APP effective to selectively engage with an epitope-specific T cell in an individual in order to treat the individual, e.g., by depleting epitope-specific T cells when the Ig Fc polypeptide is one that that induces cell lysis through activation of CDC, and/or elicits ADCC. In

some cases, a treatment method of the present disclosure comprises administering to an individual in need thereof one or more recombinant expression vectors comprising nucleotide sequences encoding an APP of the present disclosure. In some cases, a treatment method of the present disclosure comprises administering to an individual in need thereof one or more mRNA molecules comprising nucleotide sequences encoding an APP of the present disclosure. In some cases, a treatment method of the present disclosure comprises administering to an individual in need thereof an APP of the present disclosure. An APP of the present disclosure is useful for an autoimmune disease by selectively engaging with an epitope-specific T cell in an individual, including by, e.g., depleting epitope-specific T cells when the Ig Fc polypeptide is one that induces cell lysis through activation of CDC, and/or elicits ADCC.

[00403] The present disclosure provides a method of treating an autoimmune disease in an individual, the method comprising administering to the individual an effective amount of an APP of the present disclosure, or one or more nucleic acids comprising nucleotide sequences encoding the APP, where the APP comprises an autoimmune disease-associated peptide (as described above). In some cases, an “effective amount” of an APP of the present disclosure is an amount that, when administered in one or more doses to an individual in need thereof, reduces the number of self-reactive (i.e., reactive with an autoimmune disease-associated antigen) CD4⁺ and/or CD8⁺ T cells by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%, compared to number of self-reactive T cells in the individual before administration of the APP, or in the absence of administration with the APP. In some cases, an “effective amount” of an APP of the present disclosure is an amount that, when administered in one or more doses to an individual in need thereof, reduces production of Th2 cytokines in the individual. In some cases, an “effective amount” of an APP of the present disclosure is an amount that, when administered in one or more doses to an individual in need thereof, ameliorates one or more symptoms associated with an autoimmune disease in the individual. In some instances, the APP reduces the number of CD4⁺ self-reactive T cells (i.e., the number of CD4⁺ T cells reactive with an autoimmune disease-associated antigen), which in turn leads to a reduction in CD8⁺ self-reactive T cells. In some instances (e.g., when the Ig Fc polypeptide of the APP substantially does not induce cell lysis through activation of CDC, and/or elicits ADCC), the APP increases the number of CD4⁺ Tregs, which in turn reduces the number of CD4⁺ self-reactive T cells and/or CD8⁺ T self-reactive T cells.

[00404] As noted above, in some cases, in carrying out a subject treatment method, an APP of the present disclosure is administered to an individual in need thereof, as the polypeptide *per se*. In other instances, in carrying out a subject treatment method, one or more nucleic acids comprising nucleotide sequences encoding an APP is/are administering to an individual in need thereof. Thus, in other instances, one or more nucleic acids of the present disclosure, e.g., one or more recombinant expression vectors of the present disclosure, is/are administered to an individual in need thereof.

Formulations

[00405] Suitable formulations are described above, where suitable formulations include a pharmaceutically acceptable excipient. In some cases, a suitable formulation comprises: a) a TMMP or APP of the present disclosure; and b) a pharmaceutically acceptable excipient. In some cases, a suitable formulation comprises: a) a nucleic acid comprising a nucleotide sequence encoding a TMMP or APP of the present disclosure; and b) a pharmaceutically acceptable excipient; in some instances, the nucleic acid is an mRNA. In some cases, a suitable formulation comprises: a) a first nucleic acid comprising a nucleotide sequence encoding the first polypeptide of a TMMP or APP of the present disclosure; b) a second nucleic acid comprising a nucleotide sequence encoding the second polypeptide of a TMMP or APP of the present disclosure; and c) a pharmaceutically acceptable excipient. In some cases, a suitable formulation comprises: a) a recombinant expression vector comprising a nucleotide sequence encoding a TMMP or APP of the present disclosure; and b) a pharmaceutically acceptable excipient. In some cases, a suitable formulation comprises: a) a first recombinant expression vector comprising a nucleotide sequence encoding the first polypeptide of a TMMP or APP of the present disclosure; b) a second recombinant expression vector comprising a nucleotide sequence encoding the second polypeptide of a TMMP or APP of the present disclosure; and c) a pharmaceutically acceptable excipient.

[00406] Suitable pharmaceutically acceptable excipients are described above.

Dosages

[00407] A suitable dosage can be determined by an attending physician or other qualified medical personnel, based on various clinical factors. As is well known in the medical arts, dosages for any one patient depend upon many factors, including the patient's size, body surface area, age, the particular polypeptide or nucleic acid to be administered, sex of the patient, time, and route of administration, general health, and other drugs being administered concurrently. A TMMP or APP (whether as a single heterodimer or, as described above, as a homodimer comprising two heterodimers linked together) of the present disclosure may be administered in amounts between 1 ng/kg body weight and 20 mg/kg body weight per dose, e.g. between 0.1 mg/kg body weight to 10 mg/kg body weight, e.g. from 0.1 mg/kg body weight to 0.5 mg/kg body weight, from 0.5 mg/kg body weight to 1 mg/kg body weight, from 1.0 mg/kg body weight to 5 mg/kg body weight, from 5 mg/kg body weight to 10 mg/kg body weight, from 10 mg/kg body weight to 15 mg/kg body weight, and from 15 mg/kg body weight to 20 mg/kg body weight; however, doses below 0.1 mg/kg body weight or above 20 mg/kg are envisioned, especially considering the aforementioned factors. Amounts thus include from about 0.1 mg/kg body weight to about 0.5 mg/kg body weight, from about 0.5 mg/kg body weight to about 1 mg/kg body weight, from about 1.0 mg/kg body weight to about 5 mg/kg body weight, from about 5 mg/kg body weight to about 10 mg/kg body weight, from about 10 mg/kg body weight to about 15 mg/kg body weight, from about 15 mg/kg body weight to about 20 mg/kg body weight, from about 20 mg/kg body

weight to about 25 mg/kg body weight, from about 25 mg/kg body weight to about 30 mg/kg body weight, from about 30 mg/kg body weight to about 35 mg/kg body weight, from about 35 mg/kg body weight to about 40 mg/kg body weight, or from about 40 mg/kg body weight to about 50 mg/kg body weight. If the regimen is a continuous infusion, it can also be in the range of 1 μ g to 10 mg per kilogram of body weight per minute.

[00408] Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the administered agent in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the autoimmune disease state, wherein a TMMP or APP of the present disclosure is administered in maintenance doses, ranging from those recited above, i.e., 0.1 mg/kg body weight to about 0.5 mg/kg body weight, from about 0.5 mg/kg body weight to about 1 mg/kg body weight, from about 1.0 mg/kg body weight to about 5 mg/kg body weight, from about 5 mg/kg body weight to about 10 mg/kg body weight, from about 10 mg/kg body weight to about 15 mg/kg body weight, from about 15 mg/kg body weight to about 20 mg/kg body weight, from about 20 mg/kg body weight to about 25 mg/kg body weight, from about 25 mg/kg body weight to about 30 mg/kg body weight, from about 30 mg/kg body weight to about 35 mg/kg body weight, from about 35 mg/kg body weight to about 40 mg/kg body weight, or from about 40 mg/kg body weight to about 50 mg/kg body weight.

[00409] Those of skill will readily appreciate that dose levels can vary as a function of the specific TMMP or APP, the severity of the symptoms and the susceptibility of the subject to side effects. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means.

[00410] In some cases, multiple doses of a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure are administered. The frequency of administration of a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure can vary depending on any of a variety of factors, e.g., severity of the symptoms, patient response, etc. For example, in some cases, a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure is administered once per month, twice per month, three times per month, every other week (qow), one every three weeks, once every four weeks, once per week (qw), twice per week (biw), three times per week (tiw), four times per week, five times per week, six times per week, every other day (qod), daily (qd), twice a day (qid), or three times a day (tid).

[00411] The duration of administration of a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure, e.g., the

period of time over which a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure is administered, can vary, depending on any of a variety of factors, e.g., patient response, etc. For example, a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure can be administered over a period of time ranging from about one day to about one week, from about two weeks to about four weeks, from about one month to about two months, from about two months to about four months, from about four months to about six months, from about six months to about eight months, from about eight months to about 1 year, from about 1 year to about 2 years, or from about 2 years to about 4 years, or more, including continued administration for the patient's life.

[00412] Where treatment is of a finite duration, following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the autoimmune disease state, wherein a TMMP or APP of the present disclosure is administered in maintenance doses, ranging from those recited above, i.e., 0.1 mg/kg body weight to about 0.5 mg/kg body weight, from about 0.5 mg/kg body weight to about 1 mg/kg body weight, from about 1.0 mg/kg body weight to about 5 mg/kg body weight, from about 5 mg/kg body weight to about 10 mg/kg body weight, from about 10 mg/kg body weight to about 15 mg/kg body weight, from about 15 mg/kg body weight to about 20 mg/kg body weight, from about 20 mg/kg body weight to about 25 mg/kg body weight, from about 25 mg/kg body weight to about 30 mg/kg body weight, from about 30 mg/kg body weight to about 35 mg/kg body weight, from about 35 mg/kg body weight to about 40 mg/kg body weight, or from about 40 mg/kg body weight to about 50 mg/kg body weight.

Routes of administration

[00413] An active agent (a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure) is administered to an individual using any available method and route suitable for drug delivery, including *in vivo* and *in vitro* methods, as well as systemic and localized routes of administration. A TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure can be administered to a host using any available conventional methods and routes suitable for delivery of conventional drugs, including systemic or localized routes. In general, routes of administration contemplated for use in a method of the present disclosure include, but are not necessarily limited to, enteral, parenteral, and inhalational routes.

[00414] Conventional and pharmaceutically acceptable routes of administration include intramuscular, intratracheal, intralymphatic, subcutaneous, intradermal, topical application, intravenous, intraarterial, rectal, nasal, oral, and other enteral and parenteral routes of administration. Of these, intravenous, intramuscular and subcutaneous may be more commonly employed. Routes of

administration may be combined, if desired, or adjusted depending upon the TMMP or APP and/or the desired effect. A TMMP or APP of the present disclosure, or a nucleic acid or recombinant expression vector of the present disclosure, can be administered in a single dose or in multiple doses.

[00415] In some cases, a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure is administered intravenously. In some cases, a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure is administered intramuscularly. In some cases, a TMMP or APP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure is administered intralymphatically. In some cases, a TMMP of the present disclosure, a nucleic acid of the present disclosure, or a recombinant expression vector of the present disclosure is administered subcutaneously.

Subjects suitable for treatment

[00416] Subjects suitable for treatment with a method of the present disclosure include individuals who have an autoimmune disease, including individuals who have been diagnosed as having an autoimmune disease, and individuals who have been treated for an autoimmune disease but who failed to respond to the treatment.

METHODS OF SELECTIVELY DELIVERING AN IMMUNOMODULATORY POLYPEPTIDE

[00417] The present disclosure provides a method of delivering an immunomodulatory polypeptide (such as a wild-type (wt) or variant of immunomodulatory polypeptide described herein, e.g., PD-L1, IL-2, TGF β , or FasL) to a selected T cell or a selected T cell population, e.g., in a manner such that a TCR specific for a given autoimmune disease-associated epitope is targeted. The present disclosure provides a method of delivering a wt or variant immunomodulatory polypeptide disclosed herein selectively to a target T cell bearing a TCR specific for the epitope present in a TMMP of the present disclosure. In this context, the term “selective delivery” means that the immunomodulatory polypeptide is not delivered to all T cells, but rather that the majority of T cells to which the immunomodulatory polypeptide is delivered are T cells specific for the autoimmune disease-associated peptide, thereby minimizing the modulation of non-target T cells. Thus, e.g., less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 4%, 3%, 2% or 1%, of the non-target T cells bind the TMMP and, as a result, the immunomodulatory polypeptide is not delivered to the non-target T cells that do not bind the TMMP.

[00418] The method comprises contacting a population of T cells, *in vivo* or *in vitro*, with a TMMP of the present disclosure. The population of T cells can be a mixed population that comprises: i) the target T cell; and ii) non-target T cells that are not specific for the epitope (e.g., T cells that are specific for an epitope(s) other than the epitope to which the epitope-specific T cell binds). The epitope-specific T cell is specific for the autoimmune disease-associated epitope present in the TMMP binds to

the TMMP. Contacting the population of T cells with the TMMP thus delivers the immunomodulatory polypeptide present in the TMMP selectively to the T cell(s) that are specific for the epitope present in the TMMP. Thus, e.g., less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 4%, 3%, 2% or 1%, of the non-target T cells bind the TMMP and, as a result, the immunomodulatory polypeptide is not delivered to the non-target T cells that are not bound to the TMMP.

[00419] In some cases, the population of T cells is *in vivo*. In some cases, the population of T cells is *in vitro*, and a biological response (e.g., T cell activation and/or expansion and/or phenotypic differentiation) of the target T cell population to the TMMP of the present disclosure is elicited in the context of an *in vitro* culture. For example, a mixed population of T cells can be obtained from an individual, and can be contacted with the TMMP *in vitro*. Such contacting can comprise single or multiple exposures of the population of T cells to a defined dose(s) and/or exposure schedule(s). In some cases, said contacting results in selectively modulating target T cells within the population of T cells and results, e.g., in generation of a population of activated and/or expanded target T cells. As an example, a mixed population of T cells can be peripheral blood mononuclear cells (PBMC). For example, PBMC from a patient can be obtained by standard blood drawing and PBMC enrichment techniques before being exposed to 0.1-1000 nM of a TMMP of the present disclosure under standard lymphocyte culture conditions. At time points before, during, and after exposure of the mixed T cell population at a defined dose and schedule, the abundance of target T cells in the *in vitro* culture can be monitored by specific peptide-MHC multimers and/or phenotypic markers and/or functional activity (e.g. cytokine ELISpot assays). In some cases, upon achieving an optimal abundance and/or phenotype of antigen specific cells *in vitro*, all or a portion of the population of activated and/or expanded target T cells is administered to the individual (the individual from whom the mixed population of T cells was obtained).

[00420] In some cases, the population of T cells is *in vitro*. For example, a mixed population of T cells is obtained from an individual, and is contacted with a TMMP of the present disclosure *in vitro*. Such contacting, which can comprise single or multiple exposures of the T cells to a defined dose(s) and/or exposure schedule(s) in the context of *in vitro* cell culture, can be used to determine whether the mixed population of T cells includes T cells that are specific for the epitope presented by the TMMP. The presence of T cells that are specific for the autoimmune disease-associated peptide of the TMMP can be determined by assaying a sample comprising a mixed population of T cells, which population of T cells comprises T cells that are not specific for the epitope (non-target T cells) and may comprise T cells that are specific for the epitope (target T cells). Known assays can be used to detect activation and/or proliferation of the target T cells, thereby providing an *in vitro* assay that can determine whether a particular TMMP possesses an epitope that binds to T cells present in the individual and thus whether the TMMP has potential use as a therapeutic composition for that individual. Suitable known assays for

detection of activation and/or proliferation of target T cells include, e.g., flow cytometric characterization of T cell phenotype and/or antigen specificity and/or proliferation. Such an assay to detect the presence of epitope-specific T cells, e.g., a companion diagnostic, can further include additional assays (e.g. effector cytokine ELISpot assays) and/or appropriate controls (e.g. antigen-specific and antigen-nonspecific multimeric peptide-HLA staining reagents) to determine whether the TMMP is selectively binding/activating and/or expanding the target T cell. Thus, for example, the present disclosure provides a method of detecting, in a mixed population of T cells obtained from an individual, the presence of a target T cell that binds an epitope of interest, the method comprising: a) contacting *in vitro* the mixed population of T cells with a TMMP of the present disclosure, wherein the multimeric polypeptide comprises the epitope of interest; and b) detecting activation and/or proliferation of T cells in response to said contacting, wherein activated and/or proliferated T cells indicates the presence of the target T cell. Alternatively, and/or in addition, if activation and/or expansion (proliferation) of the desired T cell population is obtained using the TMMP, then all or a portion of the population of T cells comprising the activated/expanded T cells can be administered back to the individual as a therapy.

[00421] In some instances, the population of T cells is *in vivo* in an individual. In such instances, a method of the present disclosure for selectively delivering an immunomodulatory polypeptide as described herein to an epitope-specific T cell comprises administering the TMMP to the individual.

[00422] The epitope-specific T cell to which an immunomodulatory polypeptide is being selectively delivered is also referred to herein as a “target T cell.” In some cases, the target T cell is a regulatory T cell (Treg). In some cases, the Treg inhibits or suppresses activity of an autoreactive T cell.

[00423] The present disclosure provides a method of delivering an inhibitory immunomodulatory polypeptide (such as wt or variant of PD-L1 or FasL) to a selected T cell or a selected T cell population, e.g., in a manner such that a TCR specific for a given epitope is targeted. The present disclosure provides a method of delivering such an inhibitory immunomodulatory polypeptide selectively to a target T cell bearing a TCR specific for the epitope present in a TMMP of the present disclosure. The method comprises contacting a population of T cells with a TMMP of the present disclosure. The population of T cells can be a mixed population that comprises: i) the target T cell; and ii) non-target T cells that are not specific for the epitope (e.g., T cells that are specific for an epitope(s) other than the epitope to which the epitope-specific T cell binds). The epitope-specific T cell is specific for the epitope-presenting peptide present in the TMMP, and binds to the TMMP. Contacting the population of T cells with the TMMP thus delivers the inhibitory immunomodulatory polypeptide present in the TMMP selectively to the T cell(s) that are specific for the autoimmune disease-associated peptide present in the TMMP.

[00424] For example, a TMMP of the present disclosure is contacted with a population of T cells comprising: i) a target T cell(s) that is specific for the epitope present in the TMMP; and ii) a non-target T cell(s), e.g., a T cell(s) that is specific for a second epitope(s) that is not the epitope present in the

TMMP. Contacting the population results in selective delivery of an inhibitory immunomodulatory polypeptide(s) an inhibitory immunomodulatory polypeptide (such as wt or variant of PD-L1 or FasL) which is present in the TMMP, to the target T cell. Thus, e.g., less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 4%, 3%, 2% or 1%, of the non-target T cells bind the TMMP and, as a result, the immunomodulatory polypeptide is not delivered to the non-target T cells.

[00425] In some cases, the population of T cells is *in vitro*. In some cases, the population of T cells is *in vitro*, and a biological response (e.g., T cell activation and/or expansion and/or phenotypic differentiation) of the target T cell population to the TMMP of the present disclosure is elicited in the context of an *in vitro* culture. For example, a mixed population of T cells can be obtained from an individual, and can be contacted with the TMMP *in vitro*. Such contacting can comprise single or multiple exposures of the population of T cells to a defined dose(s) and/or exposure schedule(s). In some cases, said contacting results in selectively binding/activating and/or expanding target T cells within the population of T cells, and results in generation of a population of activated and/or expanded target T cells. As an example, a mixed population of T cells can be peripheral blood mononuclear cells (PBMC). For example, PBMC from a patient can be obtained by standard blood drawing and PBMC enrichment techniques before being exposed to 0.1-1000 nM of a TMMP of the present disclosure under standard lymphocyte culture conditions. At time points before, during, and after exposure of the mixed T cell population at a defined dose and schedule, the abundance of target T cells in the *in vitro* culture can be monitored by specific peptide-MHC multimers and/or phenotypic markers and/or functional activity (e.g. cytokine ELISpot assays). In some cases, upon achieving an optimal abundance and/or phenotype of antigen specific cells *in vitro*, all or a portion of the population of activated and/or expanded target T cells is administered to the individual (the individual from whom the mixed population of T cells was obtained).

[00426] In some cases, the population of T cells is *in vitro*. For example, a mixed population of T cells is obtained from an individual, and is contacted with a TMMP of the present disclosure *in vitro*. Such contacting, which can comprise single or multiple exposures of the T cells to a defined dose(s) and/or exposure schedule(s) in the context of *in vitro* cell culture, can be used to determine whether the mixed population of T cells includes T cells that are specific for the epitope presented by the TMMP. The presence of T cells that are specific for the autoimmune disease-associated peptide epitope of the TMMP can be determined by assaying a sample comprising a mixed population of T cells, which population of T cells comprises T cells that are not specific for the epitope (non-target T cells) and may comprise T cells that are specific for the epitope (target T cells). Known assays can be used to detect activation and/or proliferation of the target T cells, thereby providing an *in vitro* assay that can determine whether a particular TMMP possesses an epitope that binds to T cells present in the individual and thus

whether the TMMP has potential use as a therapeutic composition for that individual. Suitable known assays for detection of activation and/or proliferation of target T cells include, e.g., flow cytometric characterization of T cell phenotype and/or antigen specificity and/or proliferation. Such an assay to detect the presence of epitope-specific T cells, e.g., a companion diagnostic, can further include additional assays (e.g. effector cytokine ELISpot assays) and/or appropriate controls (e.g. antigen-specific and antigen-nonspecific multimeric peptide-HLA staining reagents) to determine whether the TMMP is selectively binding/activating and/or expanding the target T cell. Thus, for example, the present disclosure provides a method of detecting, in a mixed population of T cells obtained from an individual, the presence of a target T cell that binds an epitope of interest, the method comprising: a) contacting *in vitro* the mixed population of T cells with a TMMP of the present disclosure, wherein the multimeric polypeptide comprises the epitope of interest; and b) detecting activation and/or proliferation of T cells in response to said contacting, wherein activated and/or proliferated T cells indicates the presence of the target T cell. Alternatively, and/or in addition, if activation and/or expansion (proliferation) of the desired T cell population is obtained using the TMMP, then all or a portion of the population of T cells comprising the activated/expanded T cells can be administered back to the individual as a therapy.

[00427] In some instances, the population of T cells is *in vivo* in an individual. In such instances, a method of the present disclosure for selectively delivering an inhibitory immunomodulatory polypeptide (such as wt or variant of PD-L1 or FasL) to an epitope-specific T cell comprises administering the TMMP to the individual.

[00428] The epitope-specific T cell to which an inhibitory immunomodulatory polypeptide is being selectively delivered is also referred to herein as a “target T cell.” In some cases, the target T cell is a regulatory T cell (Treg). In some cases, the Treg inhibits or suppresses activity of an autoreactive T cell. In some cases, the target T cell is a CD4⁺ T cell. In some cases, the target T cell is a CD4⁺ T cell that is specific for an autoantigen.

Examples of Non-Limiting Aspects of the Disclosure

[00429] Aspects, including embodiments, of the present subject matter described above may be beneficial alone or in combination, with one or more other aspects or embodiments. Without limiting the foregoing description, certain non-limiting aspects of the disclosure are provided below. As will be apparent to those of skill in the art upon reading this disclosure, each of the individually numbered aspects may be used or combined with any of the preceding or following individually numbered aspects. This is intended to provide support for all such combinations of aspects and is not limited to combinations of aspects explicitly provided below:

[00430] 1. A T-cell modulatory multimeric polypeptide (TMMP) comprising at least one heterodimer, wherein each heterodimer comprises:

a) a first polypeptide comprising:

i) an autoimmune disease-associated peptide that displays an autoimmune disease-associated epitope useful for treating an autoimmune disease other than Type 1 Diabetes (T1D) or celiac disease, wherein the epitope is capable of being bound by a T-cell receptor (TCR); and

ii) a first major histocompatibility complex (MHC) class II polypeptide; and

b) a second polypeptide comprising a second MHC class II polypeptide,

wherein one or both polypeptides of the heterodimer comprises one or more immunomodulatory polypeptides,

wherein either the first or second polypeptide is an MHC class II α chain polypeptide and the other is an MHC class II β chain polypeptide,

wherein the first and the second polypeptide of the heterodimer are covalently linked to one another via at least one disulfide bond, and

wherein one or both polypeptides of the heterodimer optionally comprises an immunoglobulin (Ig) Fc polypeptide or a non-Ig scaffold.

[00431] 2. A TMMP of aspect 1, wherein

a1) the first polypeptide comprises, in order from N-terminus to C-terminus:

i) the autoimmune disease-associated peptide; and

ii) an MHC class II β polypeptide; and

b1) the second polypeptide comprises, in order from N-terminus to C-terminus:

i) the one or more immunomodulatory polypeptides;

ii) an MHC class II α polypeptide; and

iii) an Ig Fc polypeptide; or

a2) the first polypeptide comprises, in order from N-terminus to C-terminus:

i) the autoimmune disease-associated peptide; and

ii) an MHC class II β polypeptide; and

b2) the second polypeptide comprises, in order from N-terminus to C-terminus:

i) an MHC class II α polypeptide;

ii) the one or more immunomodulatory polypeptides; and

iii) an Ig Fc polypeptide; or

a3) the first polypeptide comprises, in order from N-terminus to C-terminus:

i) the autoimmune disease-associated peptide;

ii) an MHC class II β polypeptide; and

b3) the second polypeptide comprises, in order from N-terminus to C-terminus:

i) an MHC class II α polypeptide;

ii) an Ig Fc polypeptide; and

- iii) the one or more immunomodulatory polypeptides; or
- a4) the first polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the one or more immunomodulatory polypeptides;
 - ii) the autoimmune disease-associated peptide; and
 - iii) an MHC class II β polypeptide; and
- b4) the second polypeptide comprises, in order from N-terminus to C-terminus:
 - i) an MHC class II α polypeptide; and
 - ii) an Ig Fc polypeptide; or
- a5) the first polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the autoimmune disease-associated peptide;
 - ii) an MHC class II β polypeptide; and
 - iii) the one or more immunomodulatory polypeptides; and
- b5) the second polypeptide comprises, in order from N-terminus to C-terminus:
 - i) an MHC class II α polypeptide; and
 - ii) an Ig Fc polypeptide.

[00432] 3. A TMMP of aspect 1 or aspect 2, wherein MHC class II polypeptides comprise:
 i) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA1*01:01 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB1 polypeptide; or

ii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA1 polypeptide; and an MHC class II DRB1 chain polypeptide having at least 90% amino acid sequence identity to a DRB1 polypeptide of one of the following alleles: DRB1*01:01, DRB1*01:02, DRB1*01:03, DRB1*03:01, DRB1*03:02, DRB1*03:04, DRB1*04:01, DRB1*04:02, DRB1*04:03, DRB1*04:04, DRB1*04:05, DRB1*04:06, DRB1*04:08, DRB1*08:03, DRB1*09:01, DRB1*10:01, DRB1*11:04, DRB1*13:01, DRB1*14:02, DRB1*15:01, DRB1*15:02, and DRB1*15:03;
 or

iii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DQA1 polypeptide of one of the following alleles: DQA1*01:01, DQA1*01:02, DQA1*01:04, DQA1*03:01, DQA1*03:02, DQA1*04:01, DQA1*05:01; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DQB1 polypeptide; or

iv) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DQA1 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DQB1 polypeptide of one of the following alleles: DQB1*02:01, DQB1*03:01, DQB1*03:03, DQB1*04:01, DQB1*04:02, DQB1*05:01, DQB1*05:03, DQB1*06:01, and DQB1*06:02; or

v) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA3 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB3 polypeptide of one of the following alleles: DRB3*01:01 and DRB3*03:01; or

vi) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA4 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB4*01:01 polypeptide; or

vii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA1 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB5*01:01 polypeptide; or

viii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DPA1 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DPB1 polypeptide of one of the following alleles: DPB1*03:01, DPB1*09:01, and DPB1*13:01.

[00433] 4. The multimeric T-cell modulatory antigen-presenting polypeptide of aspect 2, wherein:

a) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or

b) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*04:01 polypeptide; or

c) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB5*01:01 polypeptide; or

d) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*06:02 polypeptide; or

e) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:01 polypeptide; and the MHC class II β polypeptide

comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:03 polypeptide; or

f) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:04 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or

g) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*01:01 polypeptide; or

h) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*04:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*04:02 polypeptide; or

i) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:01 polypeptide.

[00434] 5. The T-cell modulatory antigen-presenting polypeptide of any one of aspects 1-4, wherein the immunomodulatory polypeptide:

a) comprises the amino acid sequence of a naturally-occurring immunomodulatory polypeptide; or

b) is a variant immunomodulatory polypeptide that comprises an amino acid sequence having from 1 to 10 amino acid substitutions compared to the amino acid sequence of a naturally-occurring immunomodulatory polypeptide, wherein the variant immunomodulatory polypeptide has reduced affinity for a co-immunomodulatory polypeptide, compared to the affinity of the naturally-occurring immunomodulatory polypeptide for the co-immunomodulatory polypeptide.

[00435] 6. A TMMP of any one of aspects 1-5, wherein the one or more immunomodulatory polypeptides are selected from the group consisting of an IL-2 polypeptide, PD-L1 polypeptide, a FasL polypeptide, a TGF- β polypeptide, and combinations thereof.

[00436] 7. A TMMP of any one of aspects 1-5, wherein at least one of the one or more immunomodulatory polypeptides is a PD-L1 polypeptide.

[00437] 8. A TMMP of aspect 7, wherein the immunomodulatory polypeptide comprises a PD-L1 polypeptide extracellular domain.

- [00438] 9. A TMMP of aspect 8, wherein the immunomodulatory polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to the PD-L1 amino acid sequence depicted in FIG. 22O, and has a length of about 220 amino acids.
- [00439] 10. A TMMP of any one of aspects 1-9, wherein the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids.
- [00440] 11. A TMMP of any one of aspects 1-10, wherein the peptide is a multiple sclerosis-associated peptide.
- [00441] 12. A TMMP of any one of aspects 1-10, wherein the peptide is a rheumatoid arthritis-associated peptide.
- [00442] 13. A TMMP of any one of aspects 1-10, wherein the peptide is a systemic lupus erythematosus-associated peptide.
- [00443] 14. A TMMP of any one of aspects 1-10, wherein the peptide is an Addison's disease-associated peptide or a Sjögren's syndrome-associated peptide.
- [00444] 15. A TMMP of any one of aspects 1-10, wherein the peptide is a myasthenia gravis-associated peptide or a psoriasis-associated peptide.
- [00445] 16. A TMMP of any one of aspects 1-15, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide, and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.
- [00446] 17. A TMMP of any one of aspects 1-16, wherein the disulfide bond is formed between:
- [00447] i) a Cys in a linker between the autoimmune disease-associated-epitope and the first MHC class II polypeptide in the first polypeptide; and
- [00448] ii) a Cys in the second MHC class II polypeptide.
- [00449] 18. A TMMP of aspect 17, wherein the linker comprises an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10.
- [00450] 19. A TMMP of aspect 17, wherein the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.
- [00451] 20. A TMMP of aspect 19, wherein the second MHC class II polypeptide is a DRA MHC class II polypeptide.
- [00452] 21. A TMMP of aspect 19 or aspect 20, wherein the non-naturally occurring Cys residue is located at an amino acid residue from amino acids 55 to 110 of the second MHC Class II polypeptide.

- [00453] 22. A TMMP of any one of aspects 19-21, wherein the second MHC class II polypeptide is a variant DRA MHC class II polypeptide comprising a Cys at position 72 or 75 based on the amino acid numbering depicted in FIG. 22A.
- [00454] 23. A TMMP of any one of aspects 1-22, wherein the variant DRA MHC class II polypeptide comprises a K75C substitution.
- [00455] 24. A TMMP of any one of aspects 1-22, wherein the variant DRA MHC class II polypeptide comprises an I72C substitution.
- [00456] 25. A TMMP of any one of aspects 1-16, wherein the disulfide bond is formed between:
- i) a Cys in the first MHC class II polypeptide; and
 - ii) a Cys in the second MHC class II polypeptide.
- [00457] 26. A TMMP of aspect 25, wherein:
- i) the first MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue; and
 - ii) the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.
- [00458] 27. A TMMP of aspect 25 or aspect 26, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide, and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.
- [00459] 28. A TMMP of aspect 27, wherein the MHC class II polypeptide is a variant DRB MHC class II polypeptide that comprises an amino acid substitution selected from P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C.
- [00460] 29. A TMMP of aspect 27 or aspect 28, wherein the MHC class II polypeptide is a variant DRA MHC class II polypeptide that comprises an amino acid substitution selected from E3C, E4C, F12C, G28C, D29C, I72C, K75C, T80C, P81C, I82C, T93C, N94C, and S95C.
- [00461] 30. A TMMP of aspect 28 or 29, wherein:
- a) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is F7C;
 - b) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is P5C;
 - c) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is H33C;
 - d) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is N19C;

- e) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is G20C;
- f) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is Q156C;
- g) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is W153C;
- h) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is F7C;
- i) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is Q10C;
- j) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is F7C;
- k) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is P5C;
- l) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is I82C;
- m) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is F7C;
- n) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is P5C;
- o) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is H33C;
- p) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is G151C;
- q) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is D152C;
- r) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is W153C;
- s) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is G151C;
- t) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is D152C;
- u) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is W153C;

- v) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is Q156C;
- w) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is N120C;
- y) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is Q156C;
- z) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is N120C;
- aa) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is N19C; or
- bb) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is G20C.

[00462] 31. A TMMP of any of aspects 1-30, wherein the second polypeptide of the heterodimer comprises an MHC class II α chain polypeptide and an immunoglobulin (Ig) Fc polypeptide.

[00463] 32. A TMMP comprising two heterodimers according to any one of aspects 1-31, wherein the heterodimers are covalently linked to each other.

[00464] 33. A composition comprising:

- a) a T-cell modulatory antigen-presenting polypeptide of any one of aspects 1-32; and
- b) a pharmaceutically acceptable excipient.

[00465] 34. One or more nucleic acids comprising nucleotide sequences encoding the T-cell modulatory multimeric polypeptide of any one of aspects 1-32.

[00466] 35. One or more expression vectors comprising the one or more nucleic acids of aspect 34.

[00467] 36. A host cell genetically modified with the one or more nucleic acids of aspect 29 or the one or more expression vectors of aspect 35.

[00468] 37. A method of reducing the number and/or activity of CD4⁺ and/or CD8⁺ self-reactive T cells in an individual, the method comprising contacting the CD4⁺ T cells with the T-cell modulatory multimeric polypeptide of any one of aspects 1-32 or an effective amount of a composition according to aspect 33, wherein said contacting reduces the number and/or activity of the CD4⁺ and/or CD8⁺ T cells.

[00469] 38. A method of treating an autoimmune disease in an individual, the method comprising administering to an individual in need thereof an effective amount of the T-cell modulatory multimeric polypeptide of any one of aspects 1-32, or an effective amount of the composition of aspect

33, wherein said administering treats the autoimmune disease in the individual, and wherein the autoimmune disease is other than T1D or celiac disease.

[00470] 39. A method of aspect 38, wherein the autoimmune disease is selected from the group consisting of Addison's disease, alopecia areata, ankylosing spondylitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune-associated infertility, autoimmune thrombocytopenic purpura, bullous pemphigoid, Crohn's disease, Goodpasture's syndrome, glomerulonephritis (e.g., crescentic glomerulonephritis, proliferative glomerulonephritis), Grave's disease, Hashimoto's thyroiditis, mixed connective tissue disease, multiple sclerosis, myasthenia gravis (MG), pemphigus (e.g., pemphigus vulgaris), pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus (SLE), vasculitis, vitiligo, and combinations thereof.

[00471] 40. An antigen-presenting polypeptide (APP) comprising at least one heterodimer, wherein each heterodimer comprises:

a) a first polypeptide comprising:

i) a peptide epitope that displays an autoimmune disease-associated epitope useful for treating an autoimmune disease other than Type 1 Diabetes (T1D) or celiac disease, wherein the epitope is capable of being bound by a T-cell receptor (TCR); and

ii) a first major histocompatibility complex (MHC) class II polypeptide; and

b) a second polypeptide comprising a second MHC class II polypeptide,

wherein either the first or second polypeptide is an MHC class II α chain polypeptide and the other is an MHC class II β chain polypeptide,

wherein the first and the second polypeptide of the heterodimer are covalently linked to one another via at least one disulfide bond,

wherein one or both polypeptides of the heterodimer comprises an immunoglobulin (Ig) Fc polypeptide, and

wherein the APP does not include an immunomodulatory polypeptide.

[00472] 41. An APP of aspect 40, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.

[00473] 42. An APP of aspect 41, wherein:

a) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or

b) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*04:01 polypeptide; or

c) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB5*01:01 polypeptide; or

d) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*06:02 polypeptide; or

e) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:03 polypeptide; or

f) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:04 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or

g) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*01:01 polypeptide; or

h) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*04:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*04:02 polypeptide; or

i) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:01 polypeptide.

[00474] 43. An APP of any one of aspects 40-42, wherein the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids.

[00475] 44. An APP of any one of aspects 40-43, wherein the peptide is:

- a) a multiple sclerosis-associated peptide; or
- b) a rheumatoid arthritis-associated peptide; or
- c) a systemic lupus erythematosus-associated peptide; or
- d) an Addison's disease-associated peptide; or
- e) a myasthenia gravis-associated peptide; or
- f) a Sjögren's syndrome-associated peptide; or
- g) a psoriasis-associated peptide.

[00476] 45. An APP of any one of aspects 40-44, wherein the disulfide bond is formed between:

- i) a Cys in a linker between the autoimmune disease-associated-epitope and the first MHC class II polypeptide in the first polypeptide; and
- ii) a Cys in the second MHC class II polypeptide.

[00477] 46. An APP of aspect 45, wherein the linker comprises an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10.

[00478] 47. An APP of aspect 45 or aspect 46, wherein the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.

[00479] 48. An APP of aspect 47, wherein the second MHC class II polypeptide is an MHC class II alpha polypeptide.

[00480] 49. An APP of aspect 47 or aspect 48, wherein the non-naturally occurring Cys residue is located at an amino acid residue from amino acids 55 to 110 of the second MHC Class II polypeptide.

[00481] 50. An APP of any one of aspects 45-49, wherein the second MHC class II polypeptide is a variant DRA MHC class II polypeptide comprising a Cys at position 72 or 75 based on the amino acid numbering depicted in FIG. 22A.

[00482] 51. An APP of aspect 50, wherein the variant DRA MHC class II polypeptide comprises a K75C substitution.

[00483] 52. An APP of aspect 50, wherein the variant DRA MHC class II polypeptide comprises an I72C substitution.

[00484] 53. An APP of any one of aspects 40-44, wherein the disulfide bond is formed between:

- i) a Cys in the first MHC class II polypeptide in the first polypeptide; and
- ii) a Cys in the second MHC class II polypeptide in the second polypeptide.

[00485] 54. An APP of aspect 53, wherein:

- i) the first MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue; and
- ii) the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.

[00486] 55. An APP of aspect 53 or aspect 54, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide, and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.

[00487] 56. An APP of aspect 55, wherein the MHC class II polypeptide is a variant DRB MHC class II polypeptide that comprises an amino acid substitution selected from the group consisting of P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C.

[00488] 57. An APP of aspect 55 or aspect 56, wherein the MHC class II polypeptide is a variant DRA MHC class II polypeptide that comprises an amino acid substitution selected from E3C, E4C, F12C, G28C, D29C, I72C, K75C, T80C, P81C, I82C, T93C, N94C, and S95C.

[00489] 58. An APP of aspect 56 or 57, wherein:

- a) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is F7C;
- b) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is P5C;
- c) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is H33C;
- d) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is N19C;
- e) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is G20C;
- f) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is Q156C;
- g) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is W153C;
- h) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is F7C;
- i) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is Q10C;

- j) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is F7C;
- k) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is P5C;
- l) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is I82C;
- m) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is F7C;
- n) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is P5C;
- o) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is H33C;
- p) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is G151C;
- q) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is D152C;
- r) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is W153C;
- s) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is G151C;
- t) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is D152C;
- u) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is W153C;
- v) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is Q156C;
- w) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is N120C;
- y) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is Q156C;
- z) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is N120C;
- aa) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is N19C; or

bb) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is G20C.

[00490] 59. An APP of any of aspects 40-58, wherein the second polypeptide of the heterodimer comprises an MHC class II α chain polypeptide and an immunoglobulin (Ig) Fc polypeptide.

[00491] 60. An APP comprising two heterodimers according to any one of aspects 40-59, wherein the heterodimers are covalently linked to each other.

[00492] 61. A composition comprising:

- a) an APP of any one of aspects 40-60; and
- b) a pharmaceutically acceptable excipient.

[00493] 62. One or more nucleic acids comprising nucleotide sequences encoding the APP of any one of aspects 1-60.

[00494] 63. One or more expression vectors comprising the one or more nucleic acids of aspect 62.

[00495] 64. A host cell genetically modified with the one or more nucleic acids of aspect 61 or the one or more expression vectors of aspect 63.

[00496] 65. A method of reducing the number and/or activity of CD4⁺ and/or CD8⁺ self-reactive T cells in an individual, the method comprising contacting the CD4⁺ T cells with the APP of any one of aspects 40-60 or an effective amount of a composition according to aspect 61, wherein said contacting reduces the number and/or activity of the CD4⁺ and/or CD8⁺ T cells.

[00497] 66. A method of treating an autoimmune disease in an individual, the method comprising administering to an individual in need thereof an effective amount of the T-cell modulatory multimeric polypeptide of any one of aspects 40-60 or an effective amount of a composition according to aspect 61, wherein said administering treats the autoimmune disease in the individual, and wherein the autoimmune disease is other than T1D or celiac disease.

[00498] 67. A method of aspect 66, wherein the autoimmune disease is selected from the group consisting of Addison's disease, alopecia areata, ankylosing spondylitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune-associated infertility, autoimmune thrombocytopenic purpura, bullous pemphigoid, Crohn's disease, Goodpasture's syndrome, glomerulonephritis (e.g., crescentic glomerulonephritis, proliferative glomerulonephritis), Grave's disease, Hashimoto's thyroiditis, mixed connective tissue disease, multiple sclerosis, myasthenia gravis (MG), pemphigus (e.g., pemphigus vulgaris), pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus (SLE), vasculitis, vitiligo, and combinations thereof.

- [00499] 68. A TMMP according to aspect 32, wherein at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of an initial quantity of TMMP monomer remains present as a monomer in a PBS buffer solution after 3 days at 37°C at a TMMP concentration of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL,
- [00500] wherein the PBS buffer solution, not including the TMMP monomer, comprises sodium chloride (500 mM), sodium phosphate dibasic (10 mM), potassium phosphate monobasic (2 mM), potassium chloride (2.7 mM), and water, and has a pH of 7.5 ± 0.15 , and
- [00501] wherein the amount of monomer is determined using size exclusion chromatography using a Superdex 200 Increase (3.2x300 mm) column (e.g., from GE Healthcare), with a running buffer of the PBS buffer solution, and wherein the flow rate is 0.15 ml/minute.
- [00502] 69. A TMMP according to aspect 32, wherein at least 50%, at least 60%, at least 70%, or at least 80% of an initial quantity of TMMP monomer remains present as a monomer in a PBS buffer solution after 5 days at 37°C at a TMMP concentration of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL,
- [00503] wherein the PBS buffer solution, not including the TMMP monomer, comprises sodium chloride (500 mM), sodium phosphate dibasic (10 mM), potassium phosphate monobasic (2 mM), potassium chloride (2.7 mM), and water, and has a pH of 7.5 ± 0.15 , and
- [00504] wherein the amount of monomer is determined using size exclusion chromatography using a Superdex 200 Increase (3.2x300 mm) column (e.g., from GE Healthcare), with a running buffer of the PBS buffer solution, and wherein the flow rate is 0.15 ml/minute.
- [00505] 70. A TMMP according to aspect 32, wherein at least 50%, at least 60%, or at least 70% of an initial quantity of TMMP monomer remains present as a monomer in a PBS buffer solution after 3 days at 42°C at a TMMP concentration of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL,
- [00506] wherein the PBS buffer solution, not including the TMMP monomer, comprises sodium chloride (500 mM), sodium phosphate dibasic (10 mM), potassium phosphate monobasic (2 mM), potassium chloride (2.7 mM), and water, and has a pH of 7.5 ± 0.15 , and
- [00507] wherein the amount of monomer is determined using size exclusion chromatography using a Superdex 200 Increase (3.2x300 mm) column (e.g., from GE Healthcare), with a running buffer of the PBS buffer solution, and wherein the flow rate is 0.15 ml/minute.
- [00508] 71. A TMMP according to aspect 32, wherein at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of an initial quantity of TMMP monomer remains present as a monomer in a PBS buffer solution after 5 days at 42°C at a TMMP concentration of 9.5 mg/mL, 1 mg/mL, or 0.1 mg/mL,

[00509] wherein the PBS buffer solution, not including the TMMP monomer, comprises sodium chloride (500 mM), sodium phosphate dibasic (10 mM), potassium phosphate monobasic (2 mM), potassium chloride (2.7 mM), and water, and has a pH of 7.5 ± 0.15 , and

[00510] wherein the amount of monomer is determined using size exclusion chromatography using a Superdex 200 Increase (3.2x300 mm) column (e.g., from GE Healthcare), with a running buffer of the PBS buffer solution, and wherein the flow rate is 0.15 ml/minute.

[00511] 72. A TMMP according to any one of aspects 68-71, wherein the TMMP is in the PBS buffer solution at a concentration of 9.5 mg/mL.

[00512] 73. A TMMP according to any one of aspects 68-71, wherein the TMMP is in the PBS buffer solution at a concentration of 1 mg/mL.

[00513] 74. A TMMP according to any one of aspects 68-71, wherein the TMMP is in the PBS buffer solution at a concentration of 0.1 mg/mL.

[00514] While the present disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the claims appended hereto.

CLAIMS

What is claimed is:

1. A T-cell modulatory multimeric polypeptide (TMMP) comprising at least one heterodimer, wherein each heterodimer comprises:
 - a) a first polypeptide comprising:
 - i) an autoimmune disease-associated peptide epitope that displays an autoimmune disease-associated epitope useful for treating an autoimmune disease other than Type 1 Diabetes (T1D) or celiac disease, wherein the epitope is capable of being bound by a T-cell receptor (TCR); and
 - ii) a first major histocompatibility complex (MHC) class II polypeptide; and
 - b) a second polypeptide comprising a second MHC class II polypeptide, wherein one or both polypeptides of the heterodimer comprises one or more immunomodulatory polypeptides, wherein either the first or second polypeptide is an MHC class II α chain polypeptide and the other is an MHC class II β chain polypeptide, wherein the first and the second polypeptide of the heterodimer are covalently linked to one another via at least one disulfide bond, and wherein one or both polypeptides of the heterodimer optionally comprises an immunoglobulin (Ig) Fc polypeptide or a non-Ig scaffold.
2. A TMMP of claim 1, wherein
 - a1) the first polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the autoimmune disease-associated peptide; and
 - ii) an MHC class II β polypeptide; and
 - b1) the second polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the one or more immunomodulatory polypeptides;
 - ii) an MHC class II α polypeptide; and
 - iii) an Ig Fc polypeptide; or
 - a2) the first polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the autoimmune disease-associated peptide; and
 - ii) an MHC class II β polypeptide; and
 - b2) the second polypeptide comprises, in order from N-terminus to C-terminus:

- i) an MHC class II α polypeptide;
 - ii) the one or more immunomodulatory polypeptides; and
 - iii) an Ig Fc polypeptide; or
- a3) the first polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the autoimmune disease-associated peptide;
 - ii) an MHC class II β polypeptide; and
- b3) the second polypeptide comprises, in order from N-terminus to C-terminus:
 - i) an MHC class II α polypeptide;
 - ii) an Ig Fc polypeptide; and
 - iii) the one or more immunomodulatory polypeptides; or
- a4) the first polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the one or more immunomodulatory polypeptides;
 - ii) the autoimmune disease-associated peptide; and
 - iii) an MHC class II β polypeptide; and
- b4) the second polypeptide comprises, in order from N-terminus to C-terminus:
 - i) an MHC class II α polypeptide; and
 - ii) an Ig Fc polypeptide; or
- a5) the first polypeptide comprises, in order from N-terminus to C-terminus:
 - i) the autoimmune disease-associated peptide;
 - ii) an MHC class II β polypeptide; and
 - iii) the one or more immunomodulatory polypeptides; and
- b5) the second polypeptide comprises, in order from N-terminus to C-terminus:
 - i) an MHC class II α polypeptide; and
 - ii) an Ig Fc polypeptide.
- 3. A TMMP of claim 1 or claim 2, wherein MHC class II polypeptides comprise:
 - i) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA1*01:01 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB1 polypeptide; or
 - ii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA1 polypeptide; and an MHC class II DRB1 chain polypeptide having at least 90% amino acid sequence identity to a DRB1 polypeptide of one of the following alleles: DRB1*01:01, DRB1*01:02,

DRB1*01:03, DRB1*03:01, DRB1*03:02, DRB1*03:04, DRB1*04:01, DRB1*04:02, DRB1*04:03, DRB1*04:04, DRB1*04:05, DRB1*04:06, DRB1*04:08, DRB1*08:03, DRB1*09:01, DRB1*10:01, DRB1*11:04, DRB1*13:01, DRB1*14:02, DRB1*15:01, DRB1*15:02, and DRB1*15:03; or

iii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DQA1 polypeptide of one of the following alleles: DQA1*01:01, DQA1*01:02, DQA1*01:04, DQA1*03:01, DQA1*03:02, DQA1*04:01, DQA1*05:01; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DQB1 polypeptide; or

iv) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DQA1 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DQB1 polypeptide of one of the following alleles: DQB1*02:01, DQB1*03:01, DQB1*03:03, DQB1*04:01, DQB1*04:02, DQB1*05:01, DQB1*05:03, DQB1*06:01, and DQB1*06:02; or

v) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA3 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB3 polypeptide of one of the following alleles: DRB3*01:01 and DRB3*03:01; or

vi) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA4 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB4*01:01 polypeptide; or

vii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DRA1 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DRB5*01:01 polypeptide; or

viii) an MHC class II α chain polypeptide having at least 90% amino acid sequence identity to a DPA1 polypeptide; and an MHC class II β chain polypeptide having at least 90% amino acid sequence identity to a DPB1 polypeptide of one of the following alleles: DPB1*03:01, DPB1*09:01, and DPB1*13:01.

4. The multimeric T-cell modulatory antigen-presenting polypeptide of claim 2, wherein:

a) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or

b) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*04:01 polypeptide; or

- c) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB5*01:01 polypeptide; or
- d) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*06:02 polypeptide; or
- e) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:03 polypeptide; or
- f) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:04 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or
- g) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*01:01 polypeptide; or
- h) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*04:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*04:02 polypeptide; or
- i) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:01 polypeptide.

5. The T-cell modulatory antigen-presenting polypeptide of any one of claims 1-4, wherein the immunomodulatory polypeptide:

- a) comprises the amino acid sequence of a naturally-occurring immunomodulatory polypeptide; or
- b) is a variant immunomodulatory polypeptide that comprises an amino acid sequence having from 1 to 10 amino acid substitutions compared to the amino acid sequence of a naturally-occurring immunomodulatory polypeptide, wherein the variant immunomodulatory polypeptide has reduced affinity for a co-immunomodulatory polypeptide, compared to the affinity of the naturally-occurring immunomodulatory polypeptide for the co-immunomodulatory polypeptide.

6. A TMMP of any one of claims 1-5, wherein the one or more immunomodulatory polypeptides are selected from the group consisting of an IL-2 polypeptide, PD-L1 polypeptide, a FasL polypeptide, a TGF- β polypeptide, and combinations thereof.

7. A TMMP of any one of claims 1-5, wherein at least one of the one or more immunomodulatory polypeptides is a PD-L1 polypeptide.
8. A TMMP of claim 7, wherein the immunomodulatory polypeptide comprises a PD-L1 polypeptide extracellular domain.
9. A TMMP of claim 8, wherein the immunomodulatory polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to the PD-L1 amino acid sequence depicted in FIG. 22O, and has a length of about 220 amino acids.
10. A TMMP of any one of claims 1-9, wherein the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids.
11. A TMMP of any one of claims 1-10, wherein the peptide is a multiple sclerosis-associated peptide.
12. A TMMP of any one of claims 1-10, wherein the peptide is a rheumatoid arthritis-associated peptide.
13. A TMMP of any one of claims 1-10, wherein the peptide is a systemic lupus erythematosus-associated peptide.
14. A TMMP of any one of claims 1-10, wherein the peptide is an Addison's disease-associated peptide or a Sjögren's syndrome-associated peptide.
15. A TMMP of any one of claims 1-10, wherein the peptide is a myasthenia gravis-associated peptide or a psoriasis-associated peptide.
16. A TMMP of any one of claims 1-15, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide, and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.
17. A TMMP of any one of claims 1-16, wherein the disulfide bond is formed between:

- i) a Cys in a linker between the autoimmune disease-associated-associated epitope and the first MHC class II polypeptide in the first polypeptide; and
- ii) a Cys in the second MHC class II polypeptide.

18. A TMMP of claim 17, wherein the linker comprises an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10.

19. A TMMP of claim 17, wherein the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.

20. A TMMP of claim 19, wherein the second MHC class II polypeptide is a DRA MHC class II polypeptide.

21. A TMMP of claim 19 or claim 20, wherein the non-naturally occurring Cys residue is located at an amino acid residue from amino acids 55 to 110 of the second MHC Class II polypeptide.

22. A TMMP of any one of claims 19-21, wherein the second MHC class II polypeptide is a variant DRA MHC class II polypeptide comprising a Cys at position 72 or 75 based on the amino acid numbering depicted in FIG. 22A.

23. A TMMP of any one of claims 1-22, wherein the variant DRA MHC class II polypeptide comprises a K75C substitution.

24. A TMMP of any one of claims 1-22, wherein the variant DRA MHC class II polypeptide comprises an I72C substitution.

25. A TMMP of any one of claims 1-16, wherein the disulfide bond is formed between:

- i) a Cys in the first MHC class II polypeptide; and
- ii) a Cys in the second MHC class II polypeptide.

26. A TMMP of claim 25, wherein:

- i) the first MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue ; and

ii) the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.

27. A TMMP of claim 25 or claim 26, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide, and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.

28. A TMMP of claim 27, wherein the MHC class II polypeptide is a variant DRB MHC class II polypeptide that comprises an amino acid substitution selected from P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C.

29. A TMMP of claim 27 or claim 28, wherein the MHC class II polypeptide is a variant DRA MHC class II polypeptide that comprises an amino acid substitution selected from E3C, E4C, F12C, G28C, D29C, I72C, K75C, T80C, P81C, I82C, T93C, N94C, and S95C.

30. A TMMP of claim 28 or 29, wherein:

- a) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is F7C;
- b) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is P5C;
- c) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is H33C;
- d) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is N19C;
- e) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is G20C;
- f) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is Q156C;
- g) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is W153C;
- h) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is F7C;
- i) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is Q10C;

- j) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is F7C;
- k) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is P5C;
- l) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is I82C;
- m) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is F7C;
- n) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is P5C;
- o) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is H33C;
- p) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is G151C;
- q) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is D152C;
- r) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is W153C;
- s) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is G151C;
- t) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is D152C;
- u) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is W153C;
- v) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is Q156C;
- w) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is N120C;
- y) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is Q156C;
- z) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is N120C;
- aa) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is N19C; or

bb) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is G20C.

31. A TMMP of any of claims 1-30, wherein the second polypeptide of the heterodimer comprises an MHC class II α chain polypeptide and an immunoglobulin (Ig) Fc polypeptide.

32. A TMMP comprising two heterodimers according to any one of claims 1-31, wherein the heterodimers are covalently linked to each other.

33. A pharmaceutical composition comprising:
a T-cell modulatory antigen-presenting polypeptide of any one of claims 1-32.

34. One or more nucleic acids comprising nucleotide sequences encoding the T-cell modulatory multimeric polypeptide of any one of claims 1-32.

35. One or more expression vectors comprising the one or more nucleic acids of claim 34.

36. A host cell genetically modified with the one or more nucleic acids of claim 29 or the one or more expression vectors of claim 35.

37. A method of reducing the number and/or activity of CD4⁺ and/or CD8⁺ self-reactive T cells in an individual, the method comprising contacting the CD4⁺ T cells with the T-cell modulatory multimeric polypeptide of any one of claims 1-32 or an effective amount of a composition according to claim 33, wherein said contacting reduces the number and/or activity of the CD4⁺ and/or CD8⁺ T cells.

38. A method of treating an autoimmune disease in an individual, the method comprising administering to an individual in need thereof an effective amount of the T-cell modulatory multimeric polypeptide of any one of claims 1-32, or an effective amount of the composition of claim 33, wherein said administering treats the autoimmune disease in the individual, and wherein the autoimmune disease is other than T1D or celiac disease.

39. A method of claim 38, wherein the autoimmune disease is selected from the group consisting of Addison's disease, alopecia areata, ankylosing spondylitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune-associated infertility, autoimmune thrombocytopenic purpura, bullous pemphigoid, Crohn's disease, Goodpasture's syndrome,

glomerulonephritis (e.g., crescentic glomerulonephritis, proliferative glomerulonephritis), Grave's disease, Hashimoto's thyroiditis, mixed connective tissue disease, multiple sclerosis, myasthenia gravis (MG), pemphigus (e.g., pemphigus vulgaris), pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus (SLE), vasculitis, vitiligo, and combinations thereof.

40. An antigen-presenting polypeptide (APP) comprising at least one heterodimer, wherein each heterodimer comprises:

a) a first polypeptide comprising:

i) a peptide epitope that displays an autoimmune disease-associated epitope useful for treating an autoimmune disease other than Type 1 Diabetes (T1D) or celiac disease, wherein the epitope is capable of being bound by a T-cell receptor (TCR); and

ii) a first major histocompatibility complex (MHC) class II polypeptide; and

b) a second polypeptide comprising a second MHC class II polypeptide,

wherein either the first or second polypeptide is an MHC class II α chain polypeptide and the other is an MHC class II β chain polypeptide,

wherein the first and the second polypeptide of the heterodimer are covalently linked to one another via at least one disulfide bond,

wherein one or both polypeptides of the heterodimer comprises an immunoglobulin (Ig) Fc polypeptide, and

wherein the APP does not include an immunomodulatory polypeptide.

41. An APP of claim 40, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.

42. An APP of claim 41, wherein:

a) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or

b) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*04:01 polypeptide; or

c) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB5*01:01 polypeptide; or

d) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*06:02 polypeptide; or

e) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:03 polypeptide; or

f) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*01:04 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*05:01 polypeptide; or

g) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRA1*01:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DRB1*01:01 polypeptide; or

h) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*04:01 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*04:02 polypeptide; or

i) the MHC class II α polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQA1*03:02 polypeptide; and the MHC class II β polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to a DQB1*03:01 polypeptide.

43. An APP of any one of claims 40-42, wherein the autoimmune disease-associated peptide has a length of from about 4 amino acids to about 25 amino acids.

44. An APP of any one of claims 40-43, wherein the peptide is:

- a) a multiple sclerosis-associated peptide; or
- b) a rheumatoid arthritis-associated peptide; or
- c) a systemic lupus erythematosus-associated peptide; or
- d) an Addison's disease-associated peptide; or
- e) a myasthenia gravis-associated peptide; or
- f) a Sjögren's syndrome-associated peptide; or
- g) a psoriasis-associated peptide.

45. An APP of any one of claims 40-44, wherein the disulfide bond is formed between:

- i) a Cys in a linker between the autoimmune disease-associated-associated epitope and the first MHC class II polypeptide in the first polypeptide; and
- ii) a Cys in the second MHC class II polypeptide.

46. An APP of claim 45, wherein the linker comprises an amino acid sequence selected from (CGGGS)(GGGGS)_n (SEQ ID NO:1), (GCGGS)(GGGGS)_n (SEQ ID NO:2), (GGCGS)(GGGGS)_n (SEQ ID NO:3), (GGGCS)(GGGGS)_n (SEQ ID NO:4), and (GGGGC)(GGGGS)_n (SEQ ID NO:5), where n is an integer from 1 to 10.
47. An APP of claim 45 or claim 46, wherein the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.
48. An APP of claim 47, wherein the second MHC class II polypeptide is an MHC class II alpha polypeptide.
49. An APP of claim 47 or claim 48, wherein the non-naturally occurring Cys residue is located at an amino acid residue from amino acids 55 to 110 of the second MHC Class II polypeptide.
50. An APP of any one of claims 45-49, wherein the second MHC class II polypeptide is a variant DRA MHC class II polypeptide comprising a Cys at position 72 or 75 based on the amino acid numbering depicted in FIG. 22A.
51. An APP of claim 50, wherein the variant DRA MHC class II polypeptide comprises a K75C substitution.
52. An APP of claim 50, wherein the variant DRA MHC class II polypeptide comprises an I72C substitution.
53. An APP of any one of claims 40-44, wherein:
the disulfide bond is formed between:
i) a Cys in the first MHC class II polypeptide in the first polypeptide; and
ii) a Cys in the second MHC class II polypeptide in the second polypeptide.
54. An APP of claim 53, wherein:
i) the first MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue; and
ii) the second MHC class II polypeptide is a variant MHC class II polypeptide that comprises a non-naturally occurring Cys residue.

55. An APP of claim 53 or claim 54, wherein the first MHC class II polypeptide is an MHC class II β chain polypeptide, and wherein the second MHC class II polypeptide is an MHC class II α chain polypeptide.

56. An APP of claim 55, wherein the MHC class II polypeptide is a variant DRB MHC class II polypeptide that comprises an amino acid substitution selected from the group consisting of P5C, F7C, Q10C, N19C, G20C, H33C, G151C, D152C, and W153C.

57. An APP of claim 55 or claim 56, wherein the MHC class II polypeptide is a variant DRA MHC class II polypeptide that comprises an amino acid substitution selected from E3C, E4C, F12C, G28C, D29C, I72C, K75C, T80C, P81C, I82C, T93C, N94C, and S95C.

58. An APP of claim 56 or 57, wherein:

- a) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is F7C;
- b) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is P5C;
- c) the amino acid substitution in the MHC class II α chain is P81C; and the amino acid substitution in the MHC class II β chain is H33C;
- d) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is N19C;
- e) the amino acid substitution in the MHC class II α chain is E4C; and the amino acid substitution in the MHC class II β chain is G20C;
- f) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is Q156C;
- g) the amino acid substitution in the MHC class II α chain is T93C; and the amino acid substitution in the MHC class II β chain is W153C;
- h) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is F7C;
- i) the amino acid substitution in the MHC class II α chain is F12C; and the amino acid substitution in the MHC class II β chain is Q10C;
- j) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is F7C;

- k) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is P5C;
- l) the amino acid substitution in the MHC class II α chain is T80C; and the amino acid substitution in the MHC class II β chain is I82C;
- m) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is F7C;
- n) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is P5C;
- o) the amino acid substitution in the MHC class II α chain is I82C; and the amino acid substitution in the MHC class II β chain is H33C;
- p) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is G151C;
- q) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is D152C;
- r) the amino acid substitution in the MHC class II α chain is G28C; and the amino acid substitution in the MHC class II β chain is W153C;
- s) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is G151C;
- t) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is D152C;
- u) the amino acid substitution in the MHC class II α chain is D29C; and the amino acid substitution in the MHC class II β chain is W153C;
- v) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is Q156C;
- w) the amino acid substitution in the MHC class II α chain is N94C; and the amino acid substitution in the MHC class II β chain is N120C;
- y) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is Q156C;
- z) the amino acid substitution in the MHC class II α chain is S95C; and the amino acid substitution in the MHC class II β chain is N120C;
- aa) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is N19C; or
- bb) the amino acid substitution in the MHC class II α chain is E3C; and the amino acid substitution in the MHC class II β chain is G20C.

59. An APP of any of claims 40-58, wherein the second polypeptide of the heterodimer comprises an MHC class II α chain polypeptide and an immunoglobulin (Ig) Fc polypeptide.
60. An APP comprising two heterodimers according to any one of claims 40-59, wherein the heterodimers are covalently linked to each other.
61. A composition comprising:
a) an APP of any one of claims 40-60; and
b) a pharmaceutically acceptable excipient.
62. One or more nucleic acids comprising nucleotide sequences encoding the APP of any one of claims 1-60.
63. One or more expression vectors comprising the one or more nucleic acids of claim 62.
64. A host cell genetically modified with the one or more nucleic acids of claim 61 or the one or more expression vectors of claim 63.
65. A method of reducing the number and/or activity of CD4⁺ and/or CD8⁺ self-reactive T cells in an individual, the method comprising contacting the CD4⁺ T cells with the APP of any one of claims 40-60 or an effective amount of a composition according to claim 61, wherein said contacting reduces the number and/or activity of the CD4⁺ and/or CD8⁺ T cells.
66. A method of treating an autoimmune disease in an individual, the method comprising administering to an individual in need thereof an effective amount of the T-cell modulatory multimeric polypeptide of any one of claims 40-60 or an effective amount of a composition according to claim 61, wherein said administering treats the autoimmune disease in the individual, and wherein the autoimmune disease is other than T1D or celiac disease.
67. A method of claim 66, wherein the autoimmune disease is selected from the group consisting of Addison's disease, alopecia areata, ankylosing spondylitis, autoimmune encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune-associated infertility, autoimmune thrombocytopenic purpura, bullous pemphigoid, Crohn's disease, Goodpasture's syndrome, glomerulonephritis (e.g., crescentic glomerulonephritis, proliferative glomerulonephritis), Grave's disease, Hashimoto's thyroiditis, mixed connective tissue disease, multiple sclerosis, myasthenia gravis

(MG), pemphigus (e.g., pemphigus vulgaris), pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus (SLE), vasculitis, vitiligo, and combinations thereof.

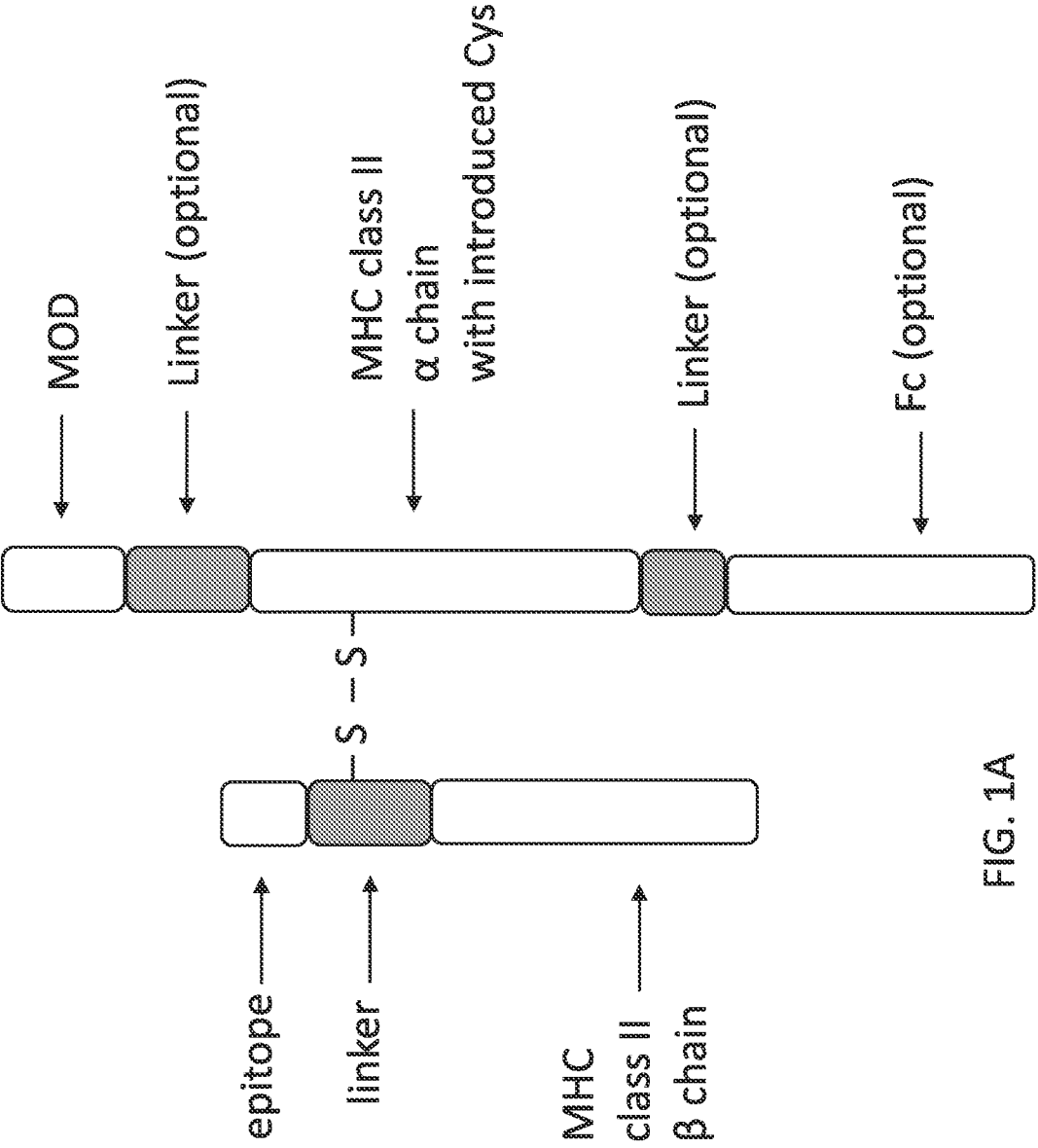


FIG. 1A

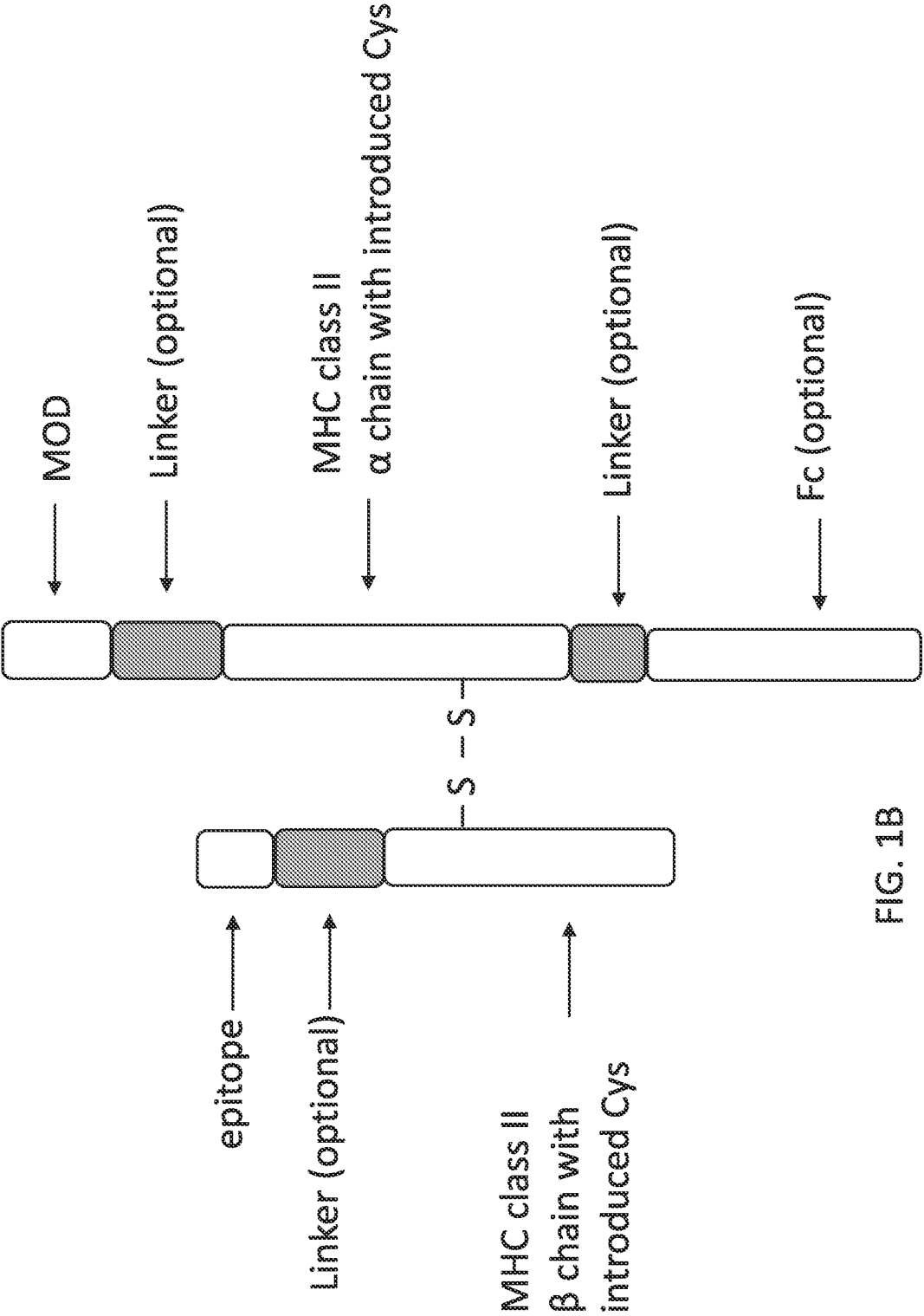


FIG. 1B

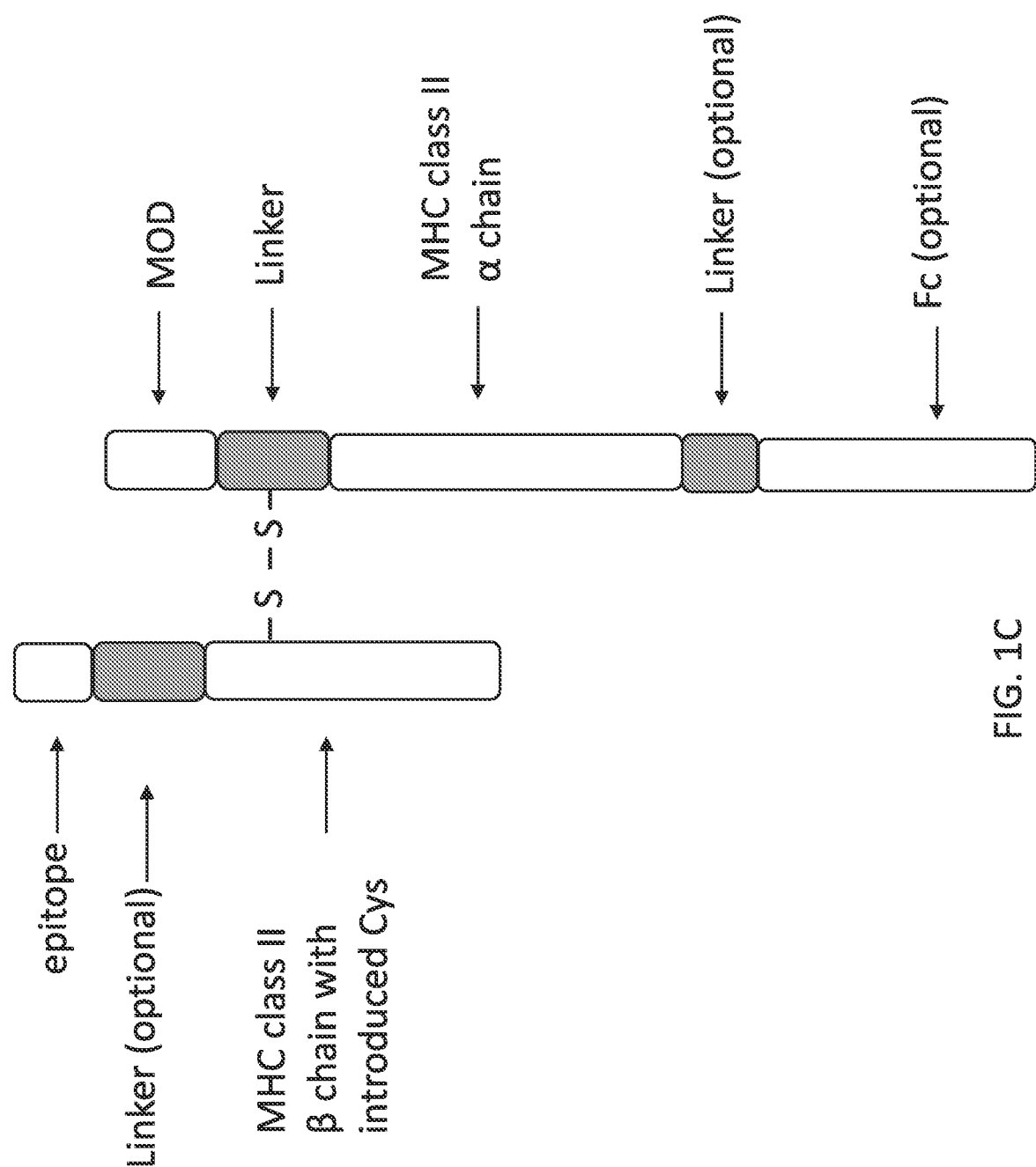


FIG. 1C

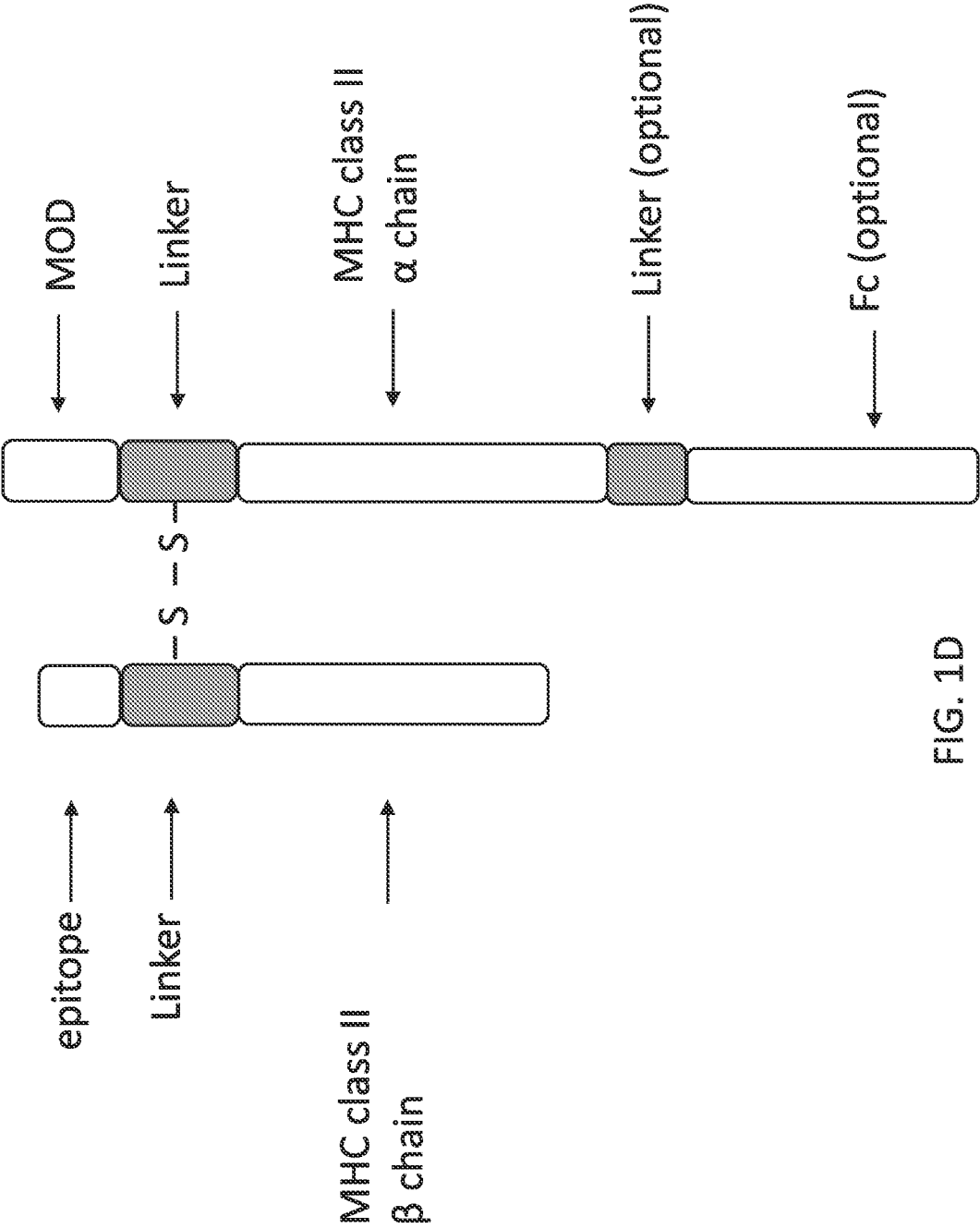
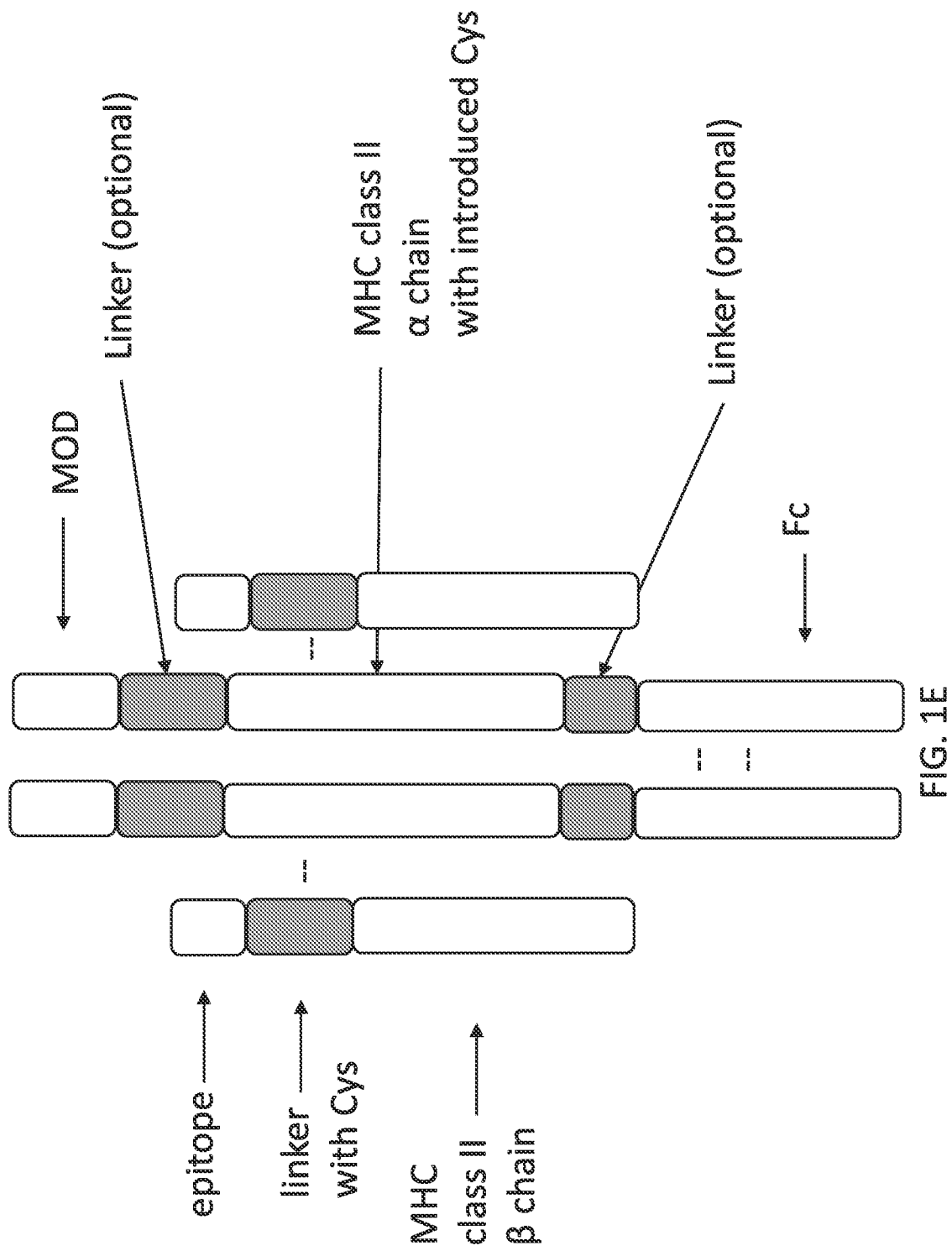


FIG. 1D



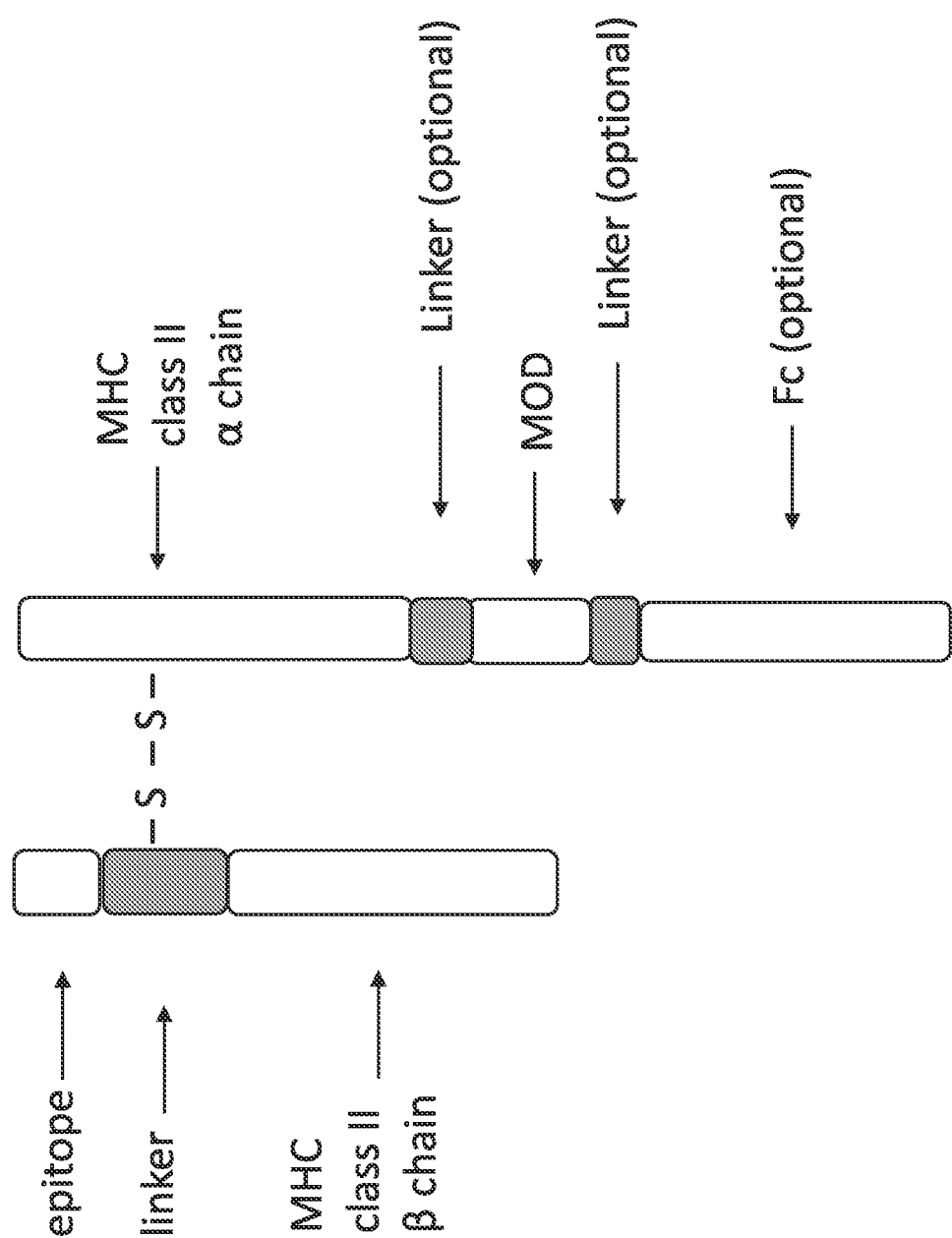


FIG. 2A

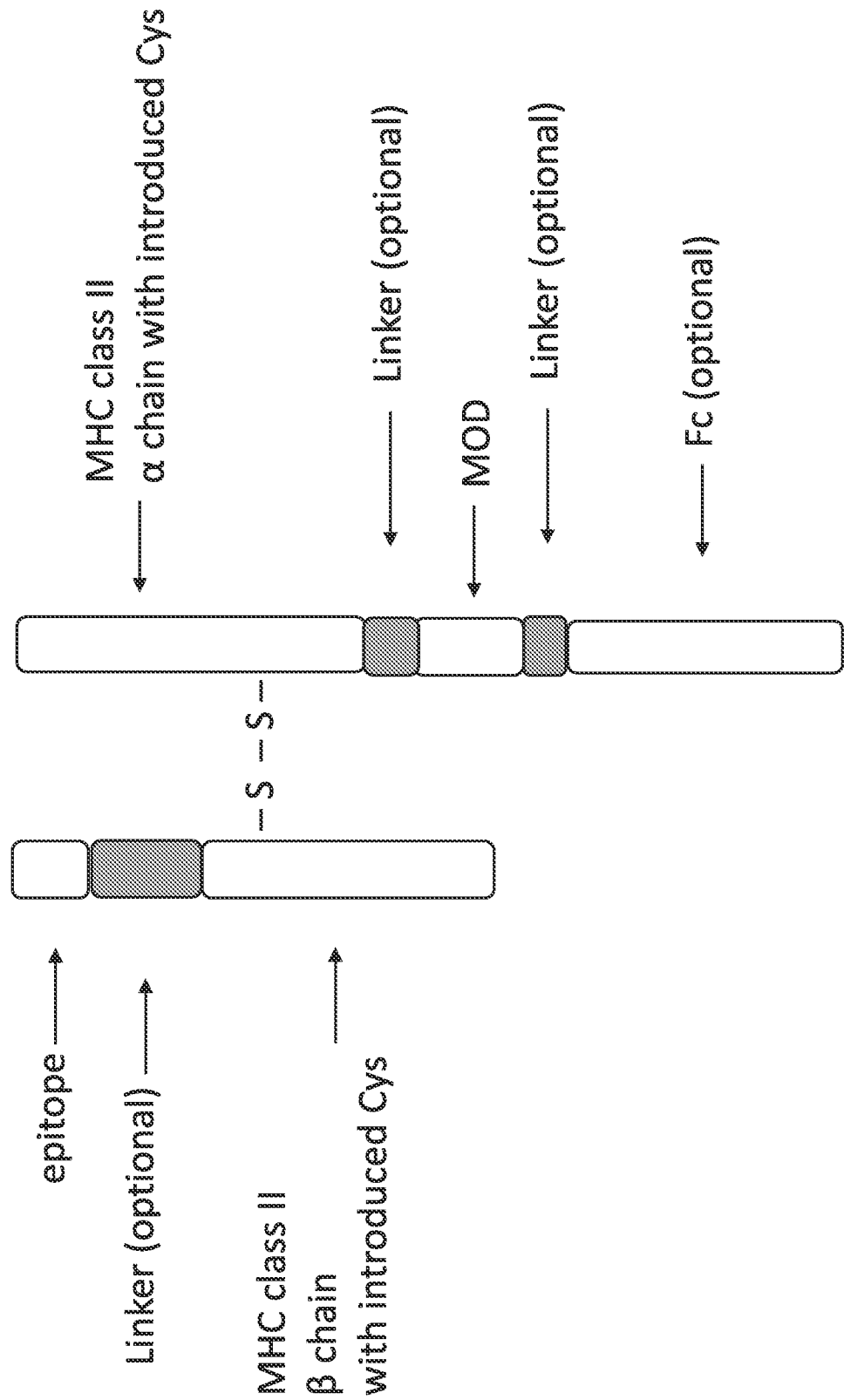


FIG. 2B

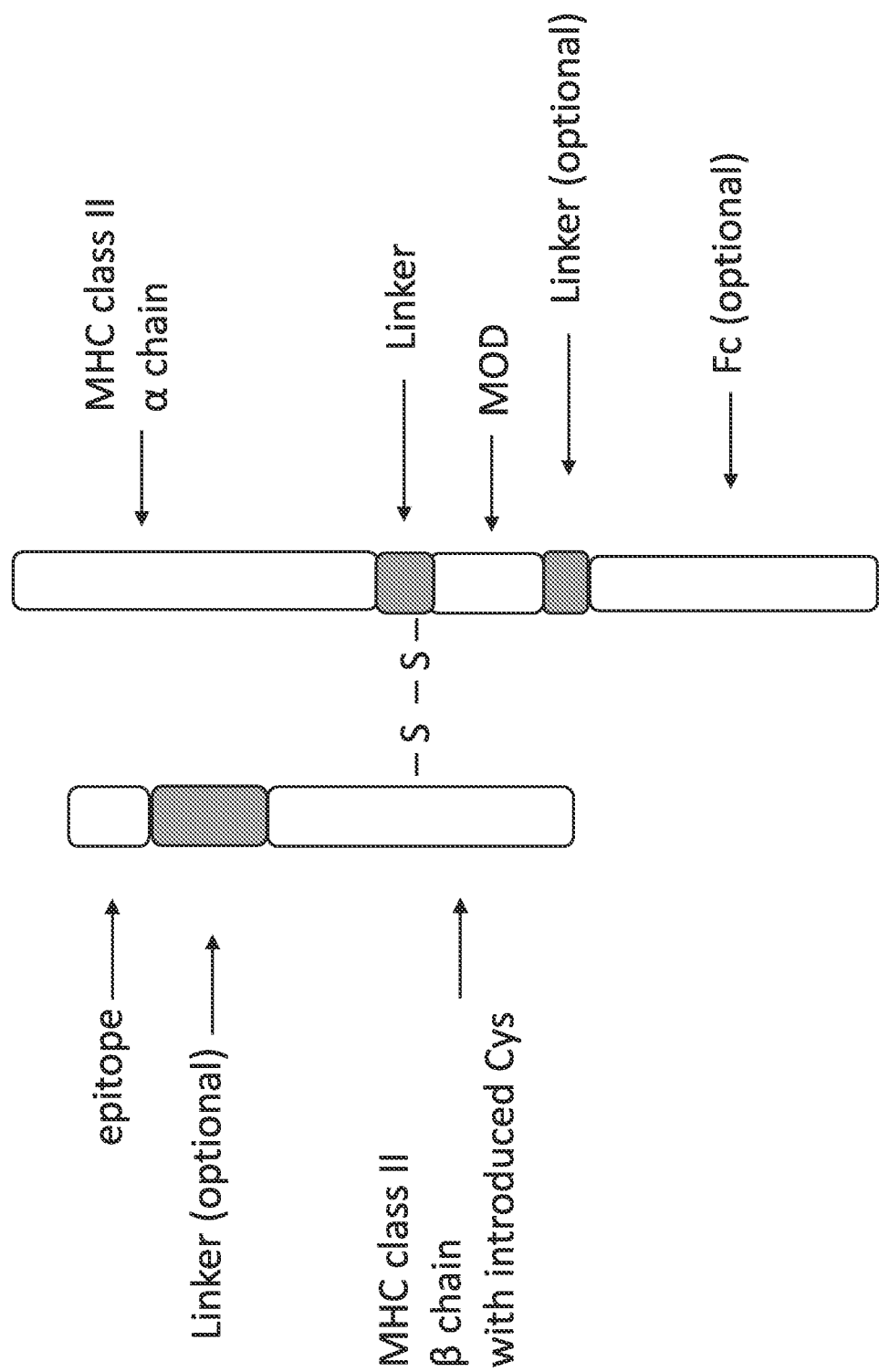


FIG. 2C

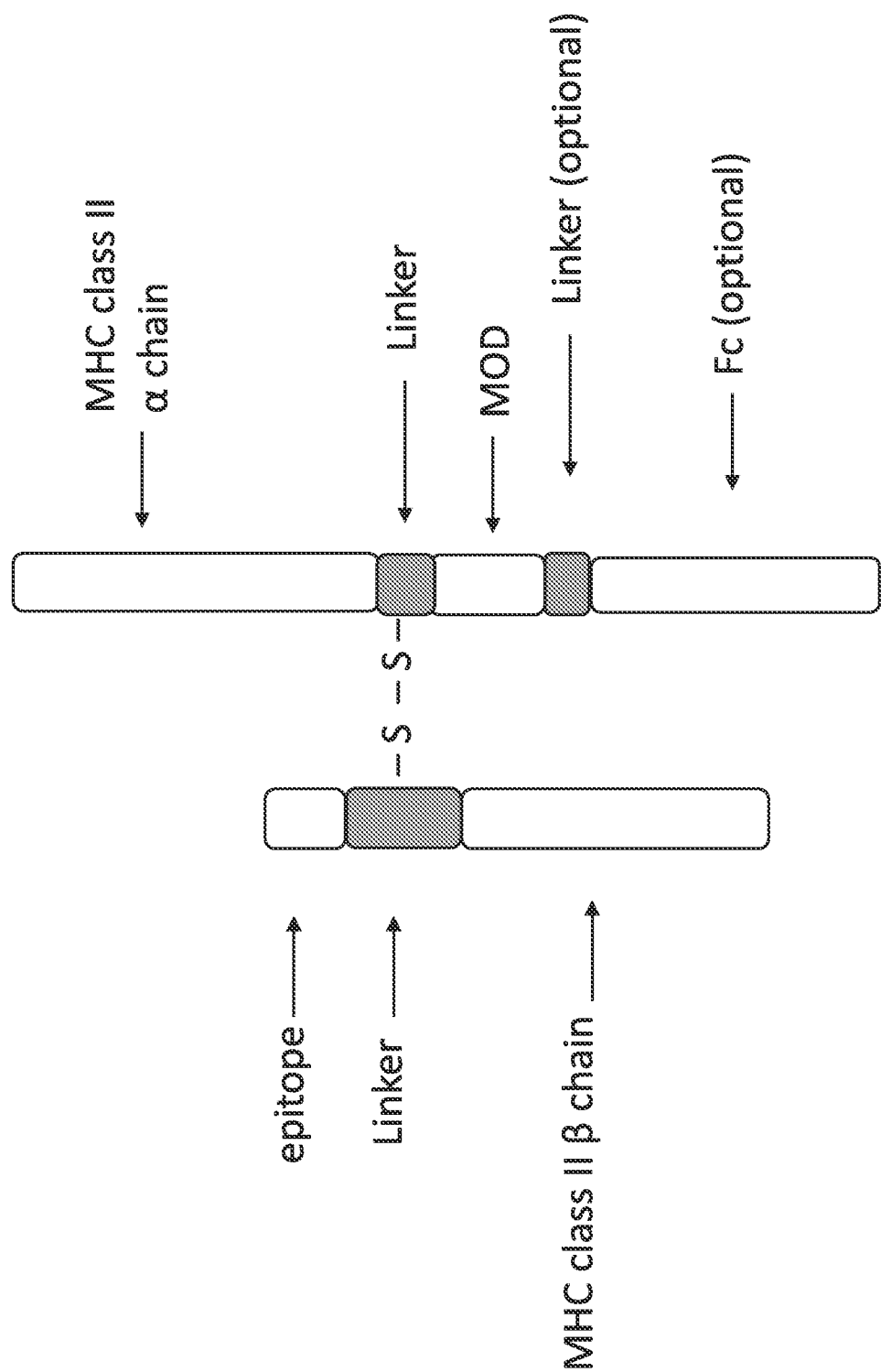


FIG. 2D

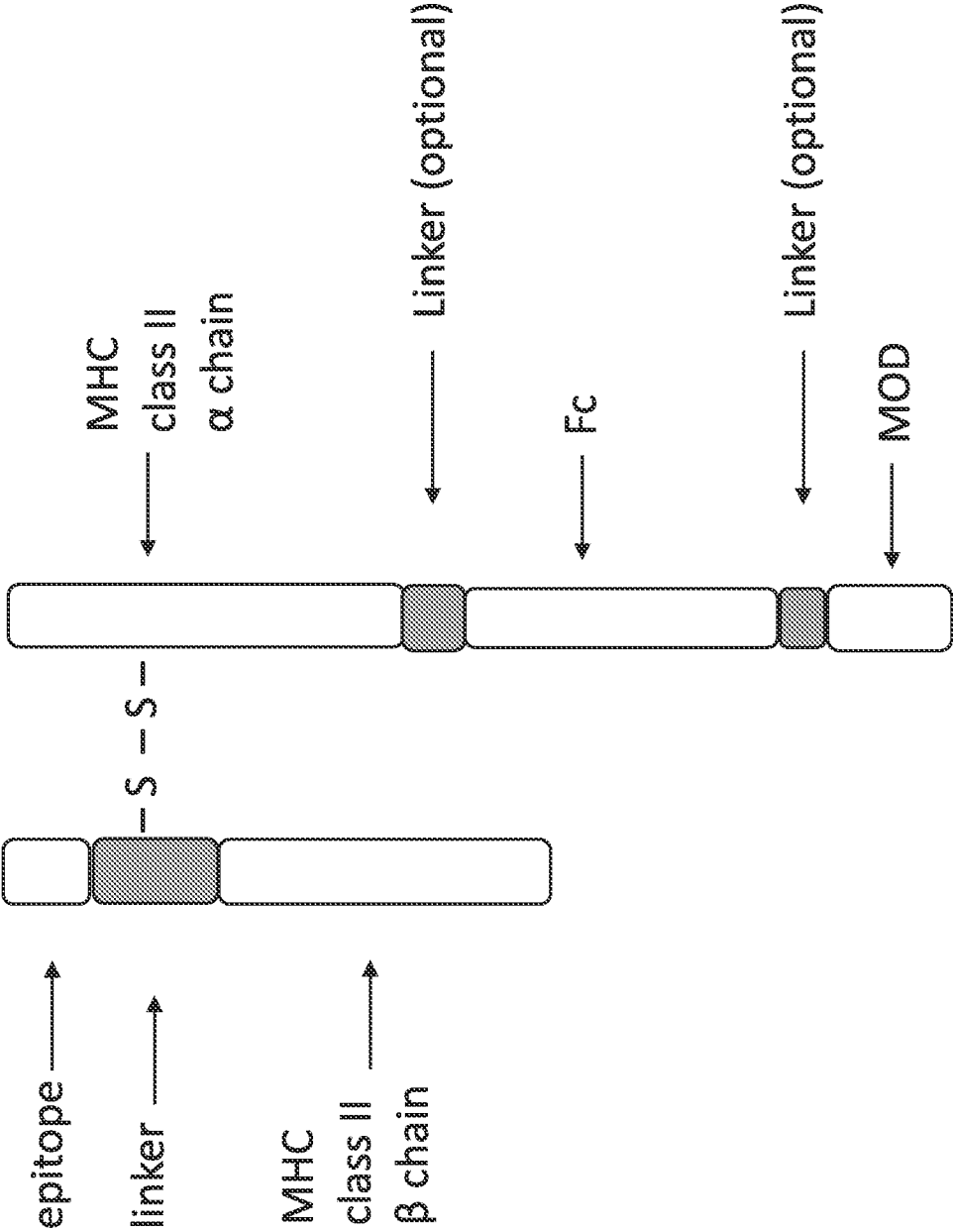


FIG. 3A

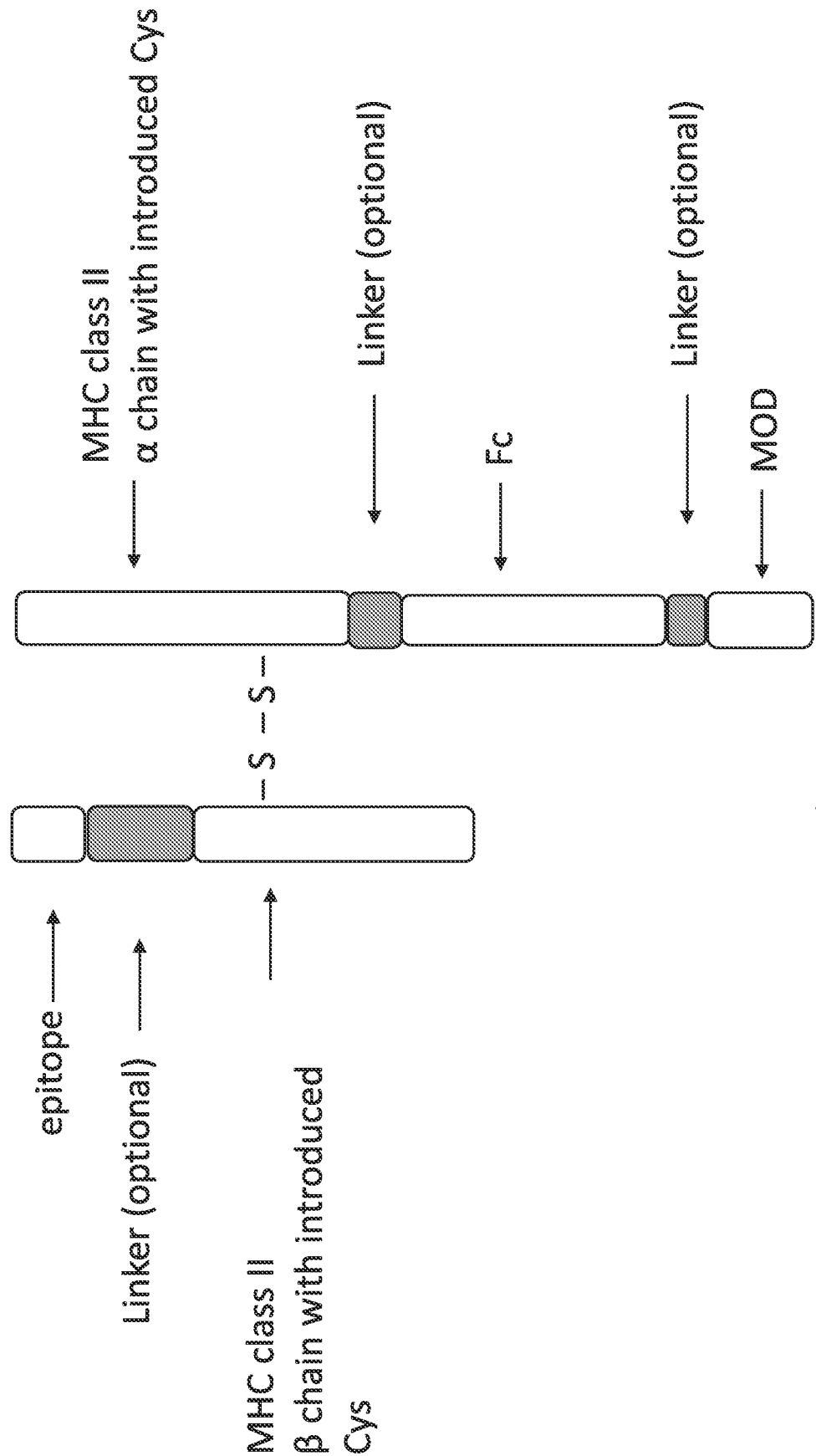


FIG. 3B

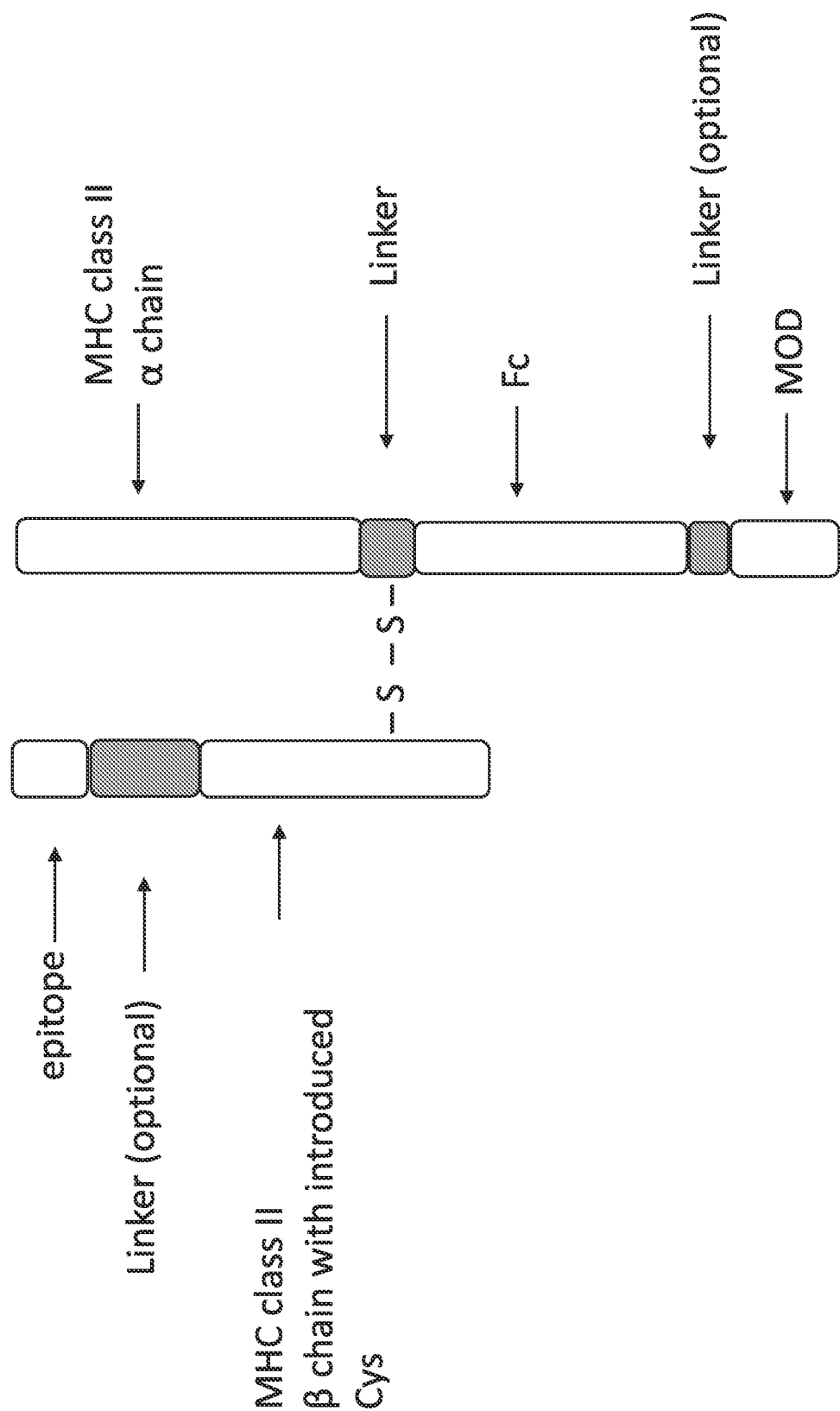


FIG. 3C

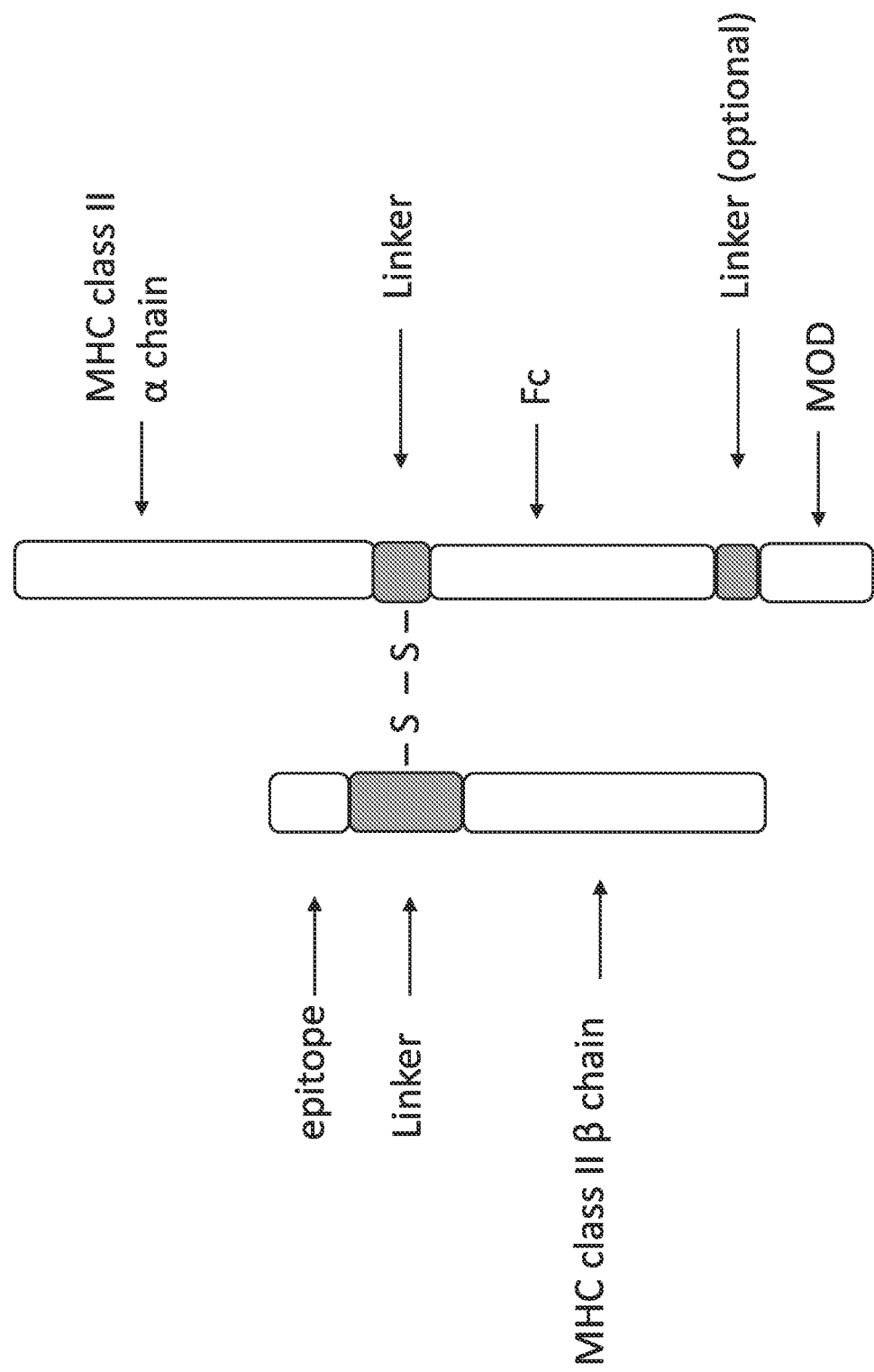


FIG. 3D

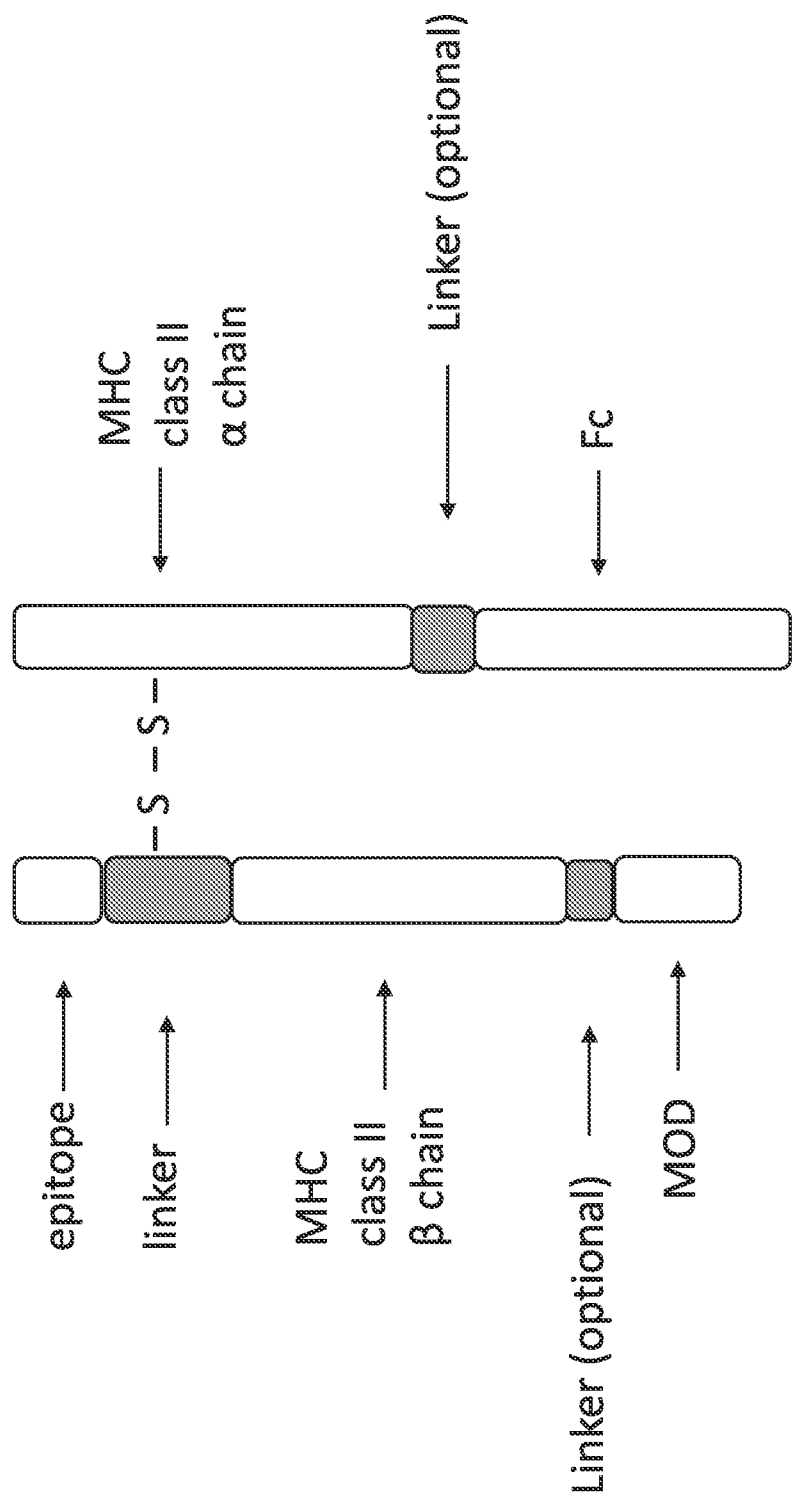


FIG. 4A

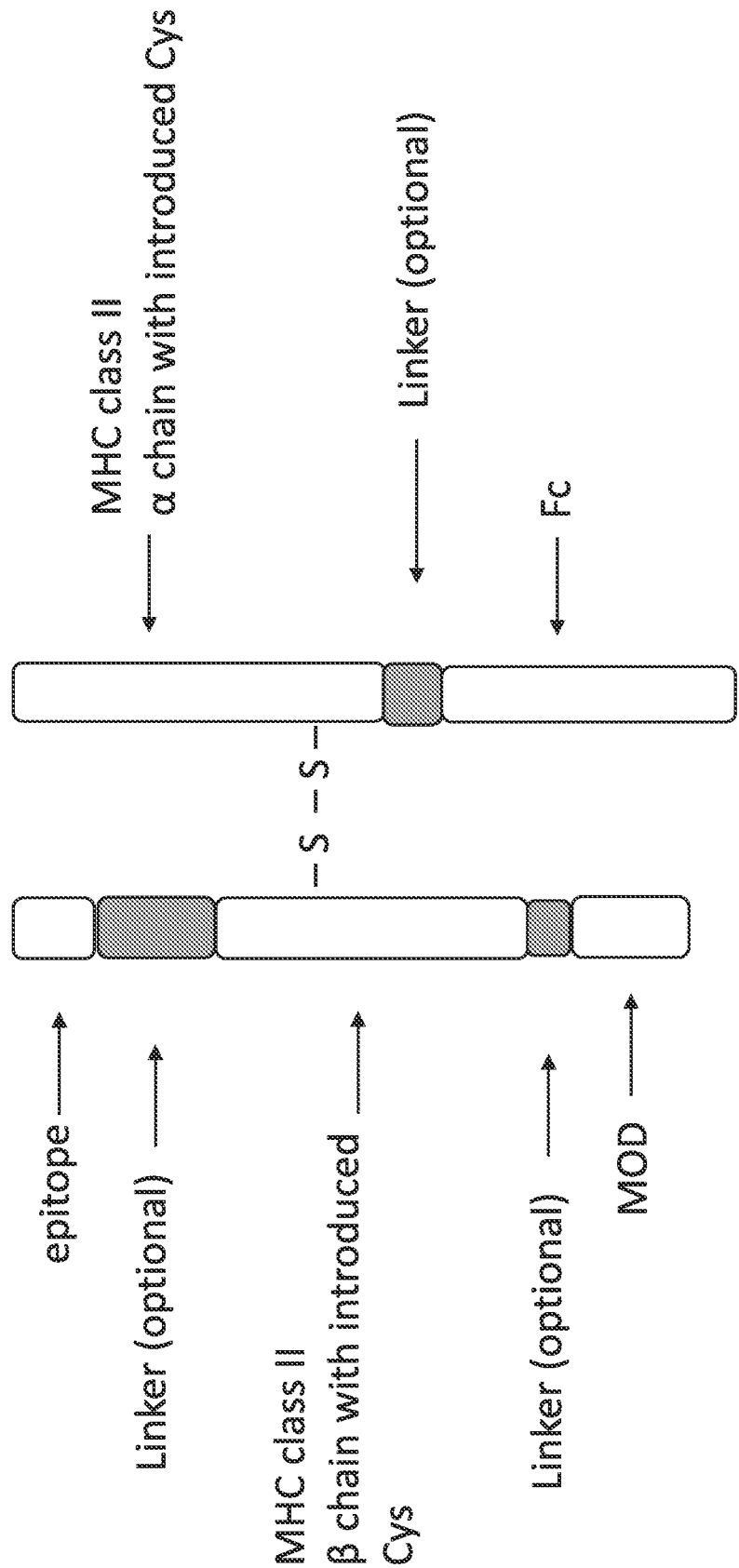


FIG. 4B

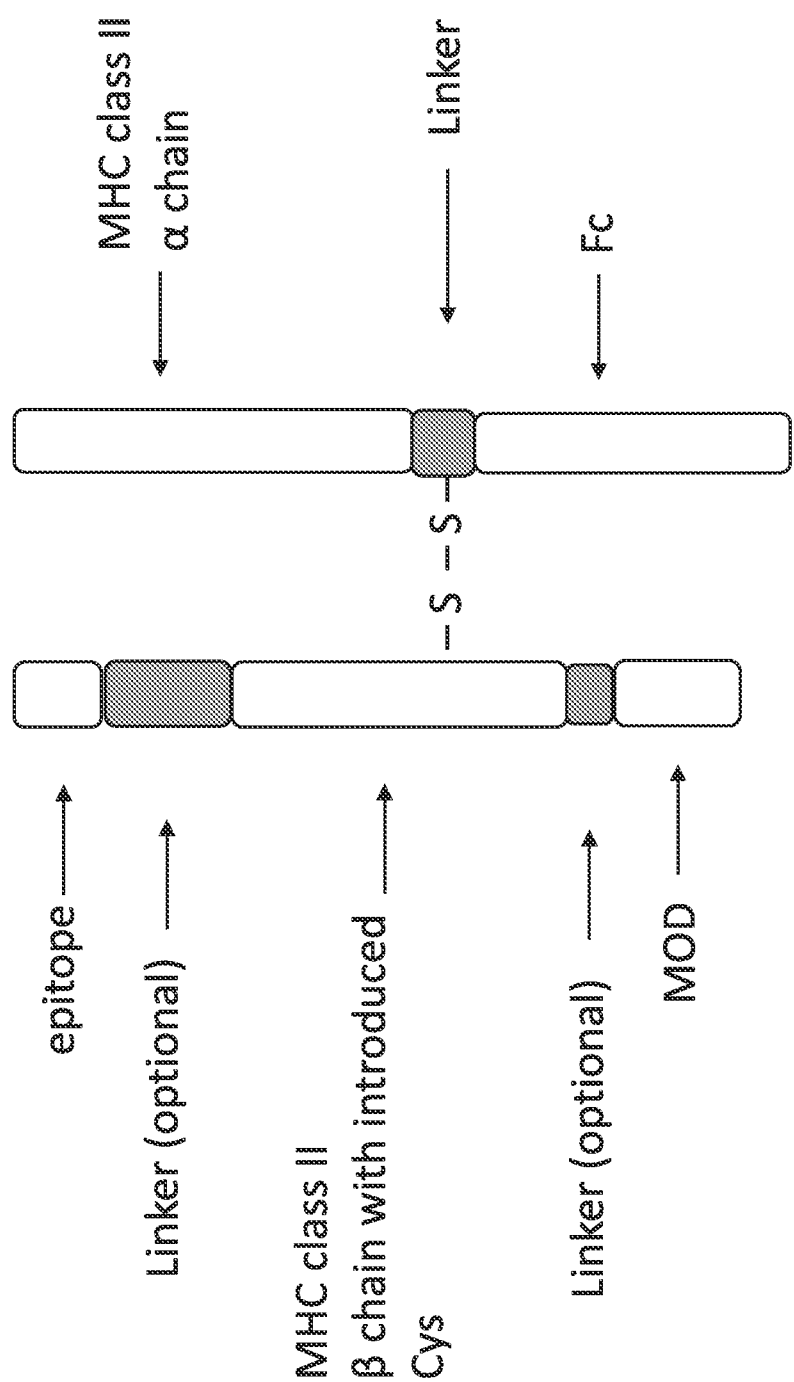


FIG. 4C

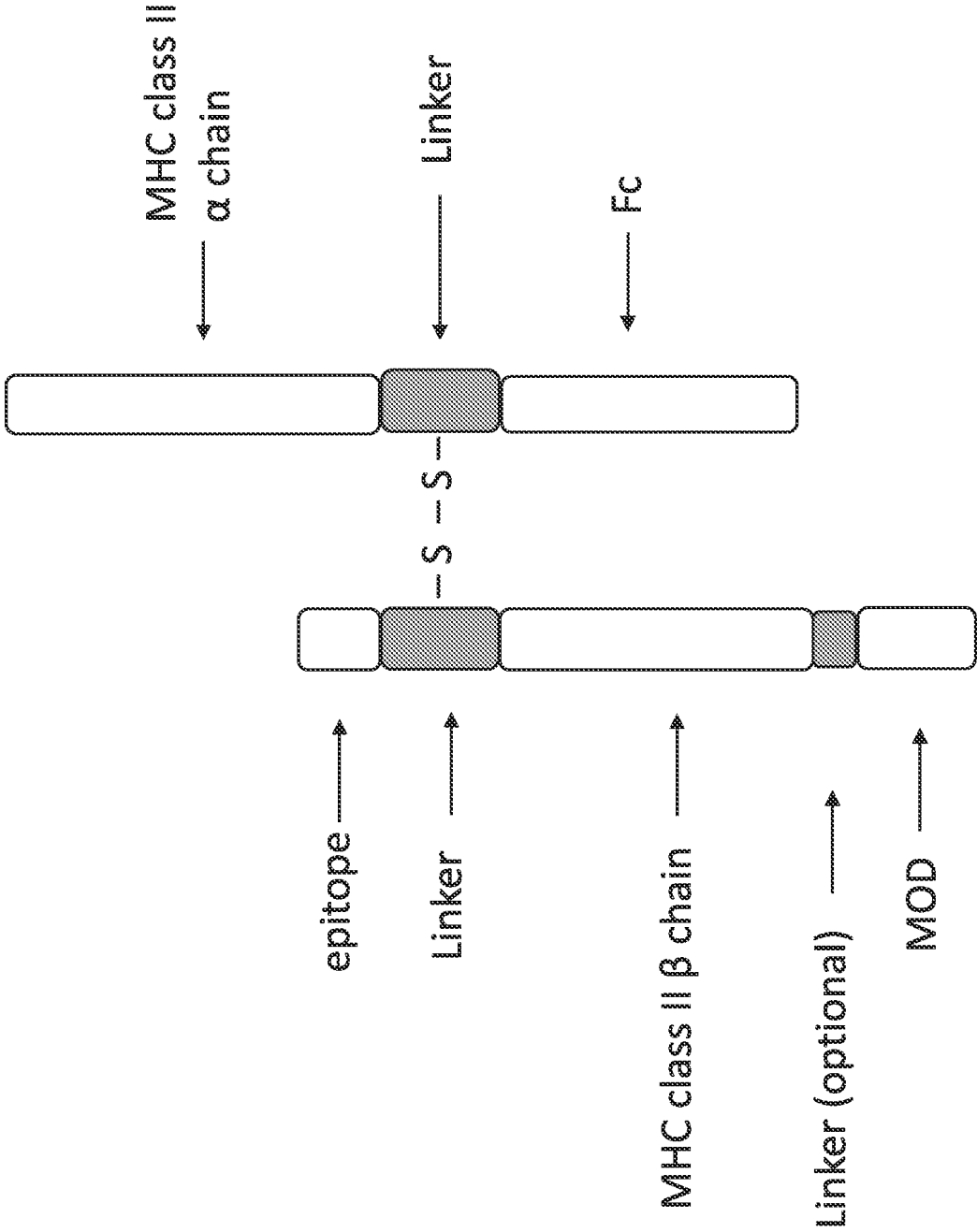


FIG. 4D

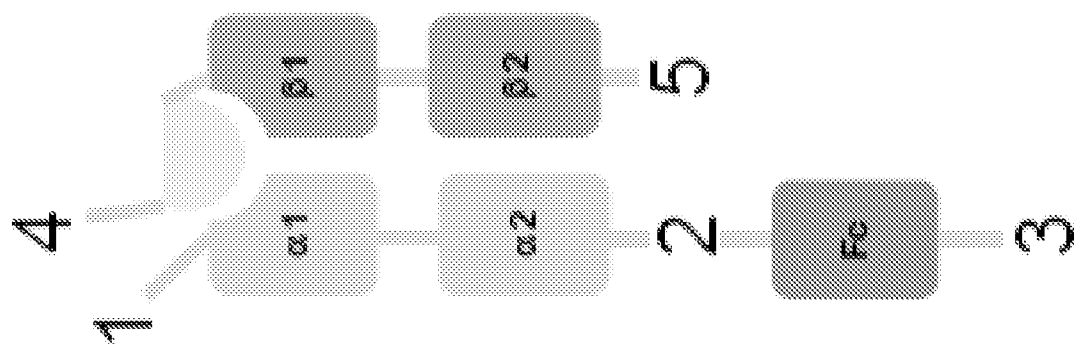


FIG. 5

FIG. 6

MHC Class II DRA alpha chain*Homo sapiens*

GenBank NP_061984 MHC Class II DRA(DRA*01:02) alpha chain

```
1  MAISGVFVLG FFIIAVLMSA QESWAIKEEH VIIQAETFLN PDQSGEFMD FDGDEIFHVD
61  MARKETVWRL EEFGRFASFE AQQALANIAV DKANLEIMTK RSNYTPITNV PPEVTVLTNS
121 PVELREPVL ICFIDKFTFP VVNVTWLRNG KPVTTGVSET VFLPREDHLF RKFHYLPFLP
181 STEDVYDCRV EHWGLDEPLL KHWEEFAPSP LPETTENVVC ALGLTVGLVG IIIGTIFLIK
241 GLRKSNAER RGPL
```

Amino acids 1-25 = signal peptide

Amino acids 26-109 = $\alpha 1$ Amino acids 110-203 = $\alpha 2$

Amino acids 204-216 = connecting peptide

Amino acids 217-239 = TM

* DRA*01:01 contains a Val residue at position 242 in place of the Leu in DRA*01:02

DRB1*01:01	MVCLKLPGGSCMTALTVTITLMVLSSPLALAGDTRPRFLWQLKFECHEFFNGTERVRLLERCI	60
DRB1*03:01	MVCLRLPGGSCMAVLTVTITLMVLSSPLALAGDTRPRFLEYSTSECHFFNGTERVRYLDRYF	60
DRB1*04:01	MVCLKFPGGSCMAALTVTITLMVLSSPLALAGDTRPRFLEQVKHECHFFNGTERVRFDRYF	60
DRB1*07:01	MVCLKLPGGSCMAALTVTITLMVLSSPLALAGDTPRFLWQKGYKCHFFNGTERVQFLERLF	60
DRB1*08:01	MVCLRLPGGSCMAVLTVTITLMVLSSPLALAGDTRPRFLEYSTGECYFFNGTERVRFDRYF	60
DRB1*09:01	MVCLKLPGGSCMAALTVTITLMVLSSPLALAGDTPRFLQDKKFECHEFFNGTERVRYLHRGI	60
DRB1*10:01	MVCLRLPGGSCMAVLTVTITLMVLSSPLALAGDTRPRFLEEKFECHFFNGTERVRLLERRV	60
DRB1*11:01	MVCLRLPGGSCMAVLTVTITLMVLSSPLALAGDTRPRFLEYSTSECHFFNGTERVRFDRYF	60
DRB1*12:01	MVCLRLPGGSCMAVLTVTITLMVLSSPLALAGDTRPRFLEYSTGECYFFNGTERVRLLERRH	60
DRB1*13:01	MVCLRLPGGSCMAVLTVTITLMVLSSPLALAGDTRPRFLEYSTSECHFFNGTERVRFDRYF	60
DRB1*14:01	MVCLRLPGGSCMAVLTVTITLMVLSSPLALAGDTRPRFLEYSTSECHFFNGTERVRFDRYF	60
DRB1*15:01	MVCLKLPGGSCMTALTVTITLMVLSSPLALS GDTRPRFLWQPKRECHFFNGTERVRFDRYF	60
DRB1*16:01	MVCLKLPGGSCMTALTVTITLMVLSSPLALAGDTRPRFLWQPKRECHFFNGTERVRFDRYF	60
	::**:*****:***:***** . :*:*****:*. *	
DRB1*01:01	YNQESVRFSDSDVGEYRAVTELGRPD AEYWSNQKDLLEQRRAAVD TYCRHNYGVGESFTV	120
DRB1*03:01	HNQEENVRFDSDVGEFRAVTELGRPD AEYWSNQKDLLEQKRGVNDYCRHNYGVVESFTV	120
DRB1*04:01	YNQEEYVRFDSDVGEYRAVTELGRPD AEYWSNQKDLLEQKRAAVD TYCRHNYGVGESFTV	120
DRB1*07:01	YNQEEFVRFDSDVGEYRAVTELGRPVAESWNSQKD ILEDRRGQVD TYCRHNYGVGESFTV	120
DRB1*08:01	YNQEEYVRFDSDVGEYRAVTELGRPFAEYWSNQKDFLEDRRAVD TYCRHNYGVGESFTV	120
DRB1*09:01	YNQEEENVRFDSDVGEYRAVTELGRPFAEYWSNQKDFLEDRRAVD TYCRHNYGVGESFTV	120
DRB1*10:01	HNQEEYARYDSDVGEYRAVTELGRPD AEYWSNQKDLLERRRAVD TYCRHNYGVGESFTV	120
DRB1*11:01	YNQEEYVRFDSDVGEFRAVTELGRPD EYWSNQKDFLEDRRAVD TYCRHNYGVGESFTV	120
DRB1*12:01	HNQEEELLRFSDSDVGEFRAVTELGRPVAESWNSQKD ILEDRAAVD TYCRHNYGAVESFTV	120
DRB1*13:01	HNQEENVRFDSDVGEFRAVTELGRPD AEYWSNQKDFLEDERAAVD TYCRHNYGVVESFTV	120
DRB1*14:01	HNQEEFVRFDSDVGEYRAVTELGRPAAEHWNSQKDLLERRRAVD TYCRHNYGVVESFTV	120
DRB1*15:01	YNQESVRFSDSDVGEFRAVTELGRPD AEYWSNQKDI LEQARAVD TYCRHNYGVVESFTV	120
DRB1*16:01	YNQESVRFSDSDVGEYRAVTELGRPD AEYWSNQKDFLEDRRAVD TYCRHNYGVGESFTV	120
	::** *::*****:*****:*****:*****:*****:*****:*****:*****	
DRB1*01:01	QRRVPEKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKAGVVSTGLIQNG	180
DRB1*03:01	QRRVHPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKTGUVSTGLIHNG	180
DRB1*04:01	QRRVYPEVTIVYPAKTQPLQHNNLLVCSVNGFYPGSIEVRWFRNGQEEKTGUVSTGLIQNG	180
DRB1*07:01	QRRVHPEVTIVYPAKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKAGVVSTGLIQNG	180
DRB1*08:01	QRRVHPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKTGUVSTGLIHNG	180
DRB1*09:01	QRRVHPEVTIVYPAKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKAGVVSTGLIQNG	180
DRB1*10:01	QRRVQPKVTIVYPSKTQPLQHNNLLVCSVNGFYPGSIEVRWFRNGQEEKTGUVSTGLIQNG	180
DRB1*11:01	QRRVHPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKTGUVSTGLIHNG	180
DRB1*12:01	QRRVHPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKTGUVSTGLIHNG	180
DRB1*13:01	QRRVHPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKTGUVSTGLIHNG	180
DRB1*14:01	QRRVHPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFRNGQEEKTGUVSTGLIHNG	180
DRB1*15:01	QRRVQPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFLNGQEEKAGMVSTGLIQNG	180
DRB1*16:01	QRRVQPKVTIVYPSKTQPLQHNNLLVCSVSGFYPGSIEVRWFLNGQEEKAGMVSTGLIQNG	180
	:**:*****:*****:*****:*****:*****:*****:*****:*****	

FIG. 7 (continued)

```
DRB1*01:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*03:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*04:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPITVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*07:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVMSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*08:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*09:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVMSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*10:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVMSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*11:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*12:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*13:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*14:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*15:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
DRB1*16:01  DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLL  240
*****;*****; *****

DRB1*01:01  FLGAGLFIYFRNQKGHSGLQPTGFSL  266
DRB1*03:01  FLGAGLFIYFRNQKGHSGLQPRGFSL  266
DRB1*04:01  FLGAGLFIYFRNQKGHSGLQPTGFSL  266
DRB1*07:01  FLGAGLFIYFRNQKGHSGLQPTGFSL  266
DRB1*08:01  FLGAGLFIYFRNQKGHSGLQPTGFSL  266
DRB1*09:01  FLGAGLFIYFRNQKGHSGLQPTGFSL  266
DRB1*10:01  FLGAGLFIYFRNQKGHSGLPPTGFSL  266
DRB1*11:01  FLGAGLFIYFRNQKGHSGLQPRGFSL  266
DRB1*12:01  FLGAGLFIYFRNQKGHSGLQPRGFSL  266
DRB1*13:01  FLGAGLFIYFRNQKGHSGLQPRGFSL  266
DRB1*14:01  FLGAGLFIYFRNQKGHSGLQPRGFSL  266
DRB1*15:01  FLGAGLFIYFRNQKGHSGLQPTGFSL  266
DRB1*16:01  FLGAGLFIYFRNQKGHSGLQPTGFSL  266
***** * *****
```

Amino acids 30-124 = $\beta 1$ Amino acids 125-227 = $\beta 2$

Amino acids 228-250 = TM

FIG. 8 MHC Class II DRB3 beta chains

Homo sapiens

DRB3*01:01	MVCLKLPGGSSLAALTVTLMVLSSRLAFAGDTRPRFLELRKSECHFFNGTERVRYLDRYF	60
DRB3-EAX03632	MVCLKLPGGSSLAALTVTLMVLSSRLAFAGDTRPRFLELRKSECHFFNGTERVRYLDRYF	60
DRB3*02:01	MVCLKLPGGSSLAALTVTLMVLSSRLAFAGDTRPRFLELLKSECHFFNGTERVRFLEERHF	60
DRB3*03:01	MVCLKLPGGSSLAALTVTLMVLSSRLAFAGDTRPRFLELLKSECHFFNGTERVRFLEERYF	60
*****:****:		
DRB3*01:01	HNQEEFLRFDSDVGEYRAVTELGRPVAESWNSQKDLLEQKRGVDNYCRHNYGVGESFTV	120
DRB3-EAX03632	HNQEEFLRFDSDVGEYRAVTELGRPVAESWNSQKDLLEQKRGQVDNYCRHNYGVVESFTV	120
DRB3*02:01	HNQEEYARFDSDVGEYRAVRELGRPDAEYWNSQKDLLEQKRGQVDNYCRHNYGVVESFTV	120
DRB3*03:01	HNQEEFVRFDSDVGEYRAVTELGRPVAESWNSQKDLLEQKRGQVDNYCRHNYGVVESFTV	120
*****:*****:*****		
DRB3*01:01	QRRVHPQVTVYPAKTQPLQHHNLLVCSVSGFYPGSIEVRWFRNCQEEKAGVVSTGLIQNG	180
DRB3-EAX03632	QRRVHPQVTVYPAKTQPLQHHNLLVCSVSGFYPGSIEVRWFRNCQEEKAGVVSTGLIQNG	180
DRB3*02:01	QRRVHPQVTVYPAKTQPLQHHNLLVCSVSGFYPGSIEVRWFRNCQEEKAGVVSTGLIQNG	180
DRB3*03:01	QRRVHPQVTVYPAKTQPLQHHNLLVCSVSGFYPGSIEVRWFRNCQEEKAGVVSTGLIING	180
*****:*****:*****		
DRB3*01:01	DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSALTVEWRARSESQAQSKMLSGVGGFVLGLL	240
DRB3-EAX03632	DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSALTVEWRARSESQAQSKMLSGVGGFVLGLL	240
DRB3*02:01	DWTFQTLVMLETFPRSGEVYTCQVEHPSVTSPLTVEWSARSESQAQSKMLSGVGGFVLGLL	240
DRB3*03:01	DWTFQTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESQAQSKMLSGVGGFVLGLL	240
*****:*****:*****		
DRB3*01:01	FLGAGLFIYFRNQKGHSGLQPTGFLS	266
DRB3-EAX03632	FLGAGLFIYFRNQKGHSGLQPTGFLS	266
DRB3*02:01	FLGAGLFIYFRNQKGHSGLQPTGFLS	266
DRB3*03:01	FLGAGLFIYFRNQKGHSGLQPTGFLS	266

Amino acids 1-29 = signal peptide

Amino acids 30-124 = β 1Amino acids 125-227 = β 2

FIG. 9

MHC Class II DRB4 beta chain

Homo sapiens

GenBank NP_068818.4 & ImMunoGeneTics ("IMGT")/HLA Acc No: HLA00908 (DRB4*01:03)

```

1  MVCLKLPGGG CMAALTVTLT VLSSPLALAG DTQPRFLEQA KCECHFLNGT ERVWNLIRYI
61  YNQEEYARYN SDLGEYQAVT ELGRPDAEYW NSQKDLLERR RAEVDITYCRY NYGVVESFTV
121 QRRVQPKVTV YPSKTQPLQH HNLIVCSVNG FYPGSIEVRW FRNGQEEKAG VVSTGLIQNG
181 DWTTFQTLVML ETVPRSGEVY TCQVEHPSMM SPLTVQWSAR SESAQSKMLS GVGGFVLGLL
241 FLGTGLFIYF RNQKGHSGLQ PTGLLS

```

Amino acids 1-29 = signal peptide

Amino acids 30-124 = β 1Amino acids 125-227 = β 2

FIG. 10

MHC Class II DRB5 beta chain

Homo sapiens

GenBank NP_002116 and IMGT/HLA Acc No: HLA00915 (DRB5*01:01)

```

1  MVCLKLPGGG YMAKLTVTLM VLSSPLALAG DTRPRFLQOD KYECHFFNGT ERVRFLHRDI
61  YNQEEDLRFD SDVGEYRAVT ELGRPDAEYW NSQKDFLEDR RAAVDITYCRH NYGVGESFTV
121 QRRVEPKVTV YPARTQTLQH HNLIVCSVNG FYPGSIEVRW FRNSQEEKAG VVSTGLIQNG
181 DWTTFQTLVML ETVPRSGEVY TCQVEHPSVT SPLTVEWRAQ SESAQSKMLS GVGGFVLGLL
241 FLGAGLFIYF KNQKGHSGLH PTGLVS

```

Amino acids 1-29 = signal peptide

Amino acids 30-124 = β 1Amino acids 125-227 = β 2

FIG. 11

MHC Class II DMA alpha chain

Homo sapiens

GenBank NP_006111.2 and IMGT/HLA Acc No: HLA00485 MHC Class II DMA(DMA*01:01)alpha chain

```

1  MGHEQNQGAA LLQMLPLLWL LPHSWAVPEA PTPMWPDDLQ NHTFLHTVYC QDGSPSVGLS
61  EAYDEDQLFF FDFSQNTTRVP RLPEFADWAQ EQGDAPAILF DKEFCEWMIQ QIGPKLDGKI
121 FVSRGFPIAE VFTLKPLEFG KPNTLVCFVS NLFPPMLTVN WQHHSVPVEG FGPTFVSAVD
181 GLSFQAFSYL NTFPEPSDIF SCIVTHEIDR YTAIAYWVPR NALPSDLLEN VLCGVAFGLG
241 VLGIIVGIVL IIFYRKPCSG D

```

Amino acids 1-26 = signal peptide

Amino acids 27-124 = α 1Amino acids 125-217 = α 2

FIG. 12
MHC Class II DMB beta chain

Homo sapiens

GenBank NP_002109.2 and IMGT/HLA Acc No: HLA00489 (DMB*01:03)

```

1  MITFLPLLLG LSLGCTGAGG FVAHVESTCL LDDAGTPKDF TYCISFNKDL LTCWDPEENK
61  MAPCEFGVLN SLANVLSQHL NQKDTLMQRL RNLQNCATH TQPFWGSLTN RTRPPSVQVA
121 KTTPEFTREP VMLACYVWGF YPAEVTITWR KNGKLVMPHS SAHKTAQPNG DWTYQTLSHL
181 ALTPSYGDTY TCVVEHTGAP EPILRDWTPG LSPMQTLKVS VSAVTLGLGL IIFSLGVISW
241 RRAGHSSYTP LPGSNYSEGW HIS

```

Amino acids 1-18 = signal peptide

Amino acids 19-112 = β 1

Amino acids 113-207 = β 2

FIG. 13
MHC Class II DOA alpha chain

Homo sapiens

GenBank NP_002110.1 and 2 and IMGT/HLA Acc No: HLA00494 MHC Class II DOA (DOA*01:01) alpha chain

```

1  MALRAGLVLG FHTLMTLLSP QEAGATKADH MGSYGPAFYQ SYGASGQFTH EFDEEQLFVS
61  DLKKSEAVWR LPEFGDFARF DPQCGLAGIA AIKAHLDILV ERSNRSRAIN VPPRVTVLPK
121 SRVELGQPNL LICIVDNIFF PVINITWLRN GQTVTEGVAQ TSFYSQPDHL FRKFHYLPFV
181 PSAEDVYDCQ VEHWGLDAPL LRHWELQVPI PPPDAMETLV CALGLAIGLV GFLVGTVLII
241 MGTYYSSVPR

```

Amino acids 1-25 = signal peptide

Amino acids 26-110 = α 1

Amino acids 111-204 = α 2

FIG. 14
MHC Class II DOB beta chain

Homo sapiens

GenBank NP_002111.1 and IMGT/HLA Acc No: HLA01098 MHC Class II DOB (DOB*01:01) beta chain

```

1  MSGGWVPWV ALLVNLTRLD SSMTQGTDSP EDFVIQAKAD CYFTNGTEKV QFVVRFIENL
61  EEYVRFDSKV GMFVALTKLG QPDAEQWNSR LDLLERSQA VDGVCRRNYR LGAPFTVGRK
121 VQPEVTVYPE RTPLLHQHNL LHCSVTGFYP GDIKIKWFLN QGEERAGVMS TGPINRGDWT
181 FQTVVMLEMT PELGHVYTCL VDHSSLLSPV SVEWRAQSEY SWRKMLSGIA AFLGLLIFLL
241 VGIVIQLRAQ KGYVRTQMSG NEVSRAVLLP QSC

```

Amino acids 1-26 = signal peptide

Amino acids 27-120 = β 1

Amino acids 121-214 = β 2

FIG. 15
MHC Class II DPA1 alpha chains

Homo sapiens

GenBank NP_001229453.1 and IMGT/HLA Acc No: HLA00499 MHC Class II DPA1(DPA1*01:03) alpha chain

```
1   MRPEDRMFHI RAVILRALSL AFLLSLRGAG AIKADHVSTY AAFVQTHRPT GEFMFEFDED
61  EMFYVDLDKK ETVWHLEEFQ QAFSFEAQGG LANIAILNNN LNTLIQRSNH TQATNDPPEV
121 TVFPKEPVEL GQNTLICH I DKFFPPVLNV TWLCNGELVT EGVAESLFLP RTDYSFHKFH
181 YLTFVPSAED FYDCRVEHWG LDQPLLKHWE AQEPIQMPET TETVLCALGL VLGLVGIIVG
241 TVLIISKSLRS GHDPRAQGTL
```

Homo sapiens

IMGT/HLA Acc No: HLA00504 MHC Class II DPA1:02(DPA1*02:01) alpha chain

```
1   MRPEDRMFHI RAVILRALSL AFLLSLRGAG AIKADHVSTY AAFVQTHRPT GEFMFEFDED
61  EQFYVDLDKK ETVWHLEEFQ RAFSFEAQGG LANIAILNNN LNTLIQRSNH TQANDPPEV
121 TVFPKEPVEL GQNTLICH I DRFFPPVLNV TWLCNGEPVT EGVAESLFLP RTDYSFHKFH
181 YLTFVPSAED FYDCRVEHWG LDQPLLKHWE AQEPIQMPET TETVLCALGL VLGLVGIIVG
241 TVLIISKSLRS GHDPRAQGTL
```

Amino acids 1-28 = signal peptide

Amino acids 29-115 = $\alpha 1$

Amino acids 116-209 = $\alpha 2$

```

DPB1*01:01      MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYVYQGRQECYAFNGTQRFLERYIYN  60
DPB1*02:01      MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYLFQGRQECYAFNGTQRFLERYIYN  60
DPB1*03:01      MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYVYQLRQECYAFNGTQRFLERYIYN  60
DPB1*04:01      MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYLFQGRQECYAFNGTQRFLERYIYN  60
DPB1*06:01      MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYVYQLRQECYAFNGTQRFLERYIYN  60
DPB1*11:01      MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYVYQLRQECYAFNGTQRFLERYIYN  60
DPB1*71:01      MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYLFQGRQECYAFNGTQRFLERYIYN  60
DPB1*104:01     MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYVYQLRQECYAFNGTQRFLERYIYN  60
DPB1*141:01     MMVLQVSAAPRTVALTALLMVLTTSVVQGRATPENYLFQGRQECYAFNGTQRFLERYIYN  60
*****:*****

DPB1*01:01      REEYARFSDSDVGEFRAVTELGRPAAEYWNQSQKDILEEKRAVPDRVCRHNYELDEAVTLQR  120
DPB1*02:01      REEFVRFSDSDVGEFRAVTELGRPDDEYWNQSQKDILEEERAVPDRMCRHNYELGGPMTLQR  120
DPB1*03:01      REEFVRFSDSDVGEFRAVTELGRPDDEYWNQSQKDILEEKRAVPDRVCRHNYELDEAVTLQR  120
DPB1*04:01      REEFARFSDSDVGEFRAVTELGRPAAEYWNQSQKDILEEKRAVPDRMCRHNYELGGPMTLQR  120
DPB1*06:01      REEFVRFSDSDVGEFRAVTELGRPDDEYWNQSQKDILEEERAVPDRMCRHNYELDEAVTLQR  120
DPB1*11:01      RQEYARFSDSDVGEFRAVTELGRPAAEYWNQSQKDILEERRAVPDRMCRHNYELDEAVTLQR  120
DPB1*71:01      REEFVRFSDSDVGEFRAVTELGRPAAEYWNQSQKDILEEERAVPDRMCRHNYELGGPMTLQR  120
DPB1*104:01     REEFVRFSDSDVGEFRAVTELGRPDDEYWNQSQKDILEEKRAVPDRVCRHNYELDEAVTLQR  120
DPB1*141:01     REEFVRFSDSDVGEFRAVTELGRPDDEYWNQSQKDILEEERAVPDRMCRHNYELGGPMTLQR  120
*:*:*****:*****:*****:*****:*****:*****

DPB1*01:01      RVQPKVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*02:01      RVQPRVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*03:01      RVQPKVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*04:01      RVQPRVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*06:01      RVQPKVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*11:01      RVQPKVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*71:01      RVQPRVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*104:01     RVQPKVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVRWFLNGQEETAGVVSTNLIRNGDW  180
DPB1*141:01     RVQPRVNVSPSKKGPLQHNNLLVCHVTDFYPGSIQVQWFLNGQEETAGVVSTNLIRNGDW  180
****:*****:*****:*****:*****:*****

DPB1*01:01      TFQILVMLEMTPOQGDVYICQVEHTSLDSPVTVEWKAQSDSAQSKTLTGAGGFVLGLIIC  240
DPB1*02:01      TFQILVMLEMTPOQGDVYTCQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
DPB1*03:01      TFQILVMLEMTPOQGDVYICQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
DPB1*04:01      TFQILVMLEMTPOQGDVYTCQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
DPB1*06:01      TFQILVMLEMTPOQGDVYICQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
DPB1*11:01      TFQILVMLEMTPOQGDVYICQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
DPB1*71:01      TFQILVMLEMTPOQGDVYTCQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
DPB1*104:01     TFQILVMLEMTPOQGDVYICQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
DPB1*141:01     TFQILVMLEMTPOQGDVYTCQVEHTSLDSPVTVEWKAQSDSARSKTLTGAGGFVLGLIIC  240
*****:*****:*****:*****:*****:*****

```

FIG. 16 (continued)

```
DPB1*01:01  GVGIFMHRRSKKVQRGSA 258
DPB1*02:01  GVGIFMHRRSKKVQRGSA 258
DPB1*03:01  GVGIFMHRRSKKVQRGSA 258
DPB1*04:01  GVGIFMHRRSKKVQRGSA 258
DPB1*06:01  GVGIFMHRRSKKVQRGSA 258
DPB1*11:01  GVGIFMHRRSKKVQRGSA 258
DPB1*71:01  GVGIFMHRRSKKVQRGSA 258
DPB1*104:01 GVGIFMHRRSKKVQRGSA 258
DPB1*141:01 GVGIFMHRRSKKVQRGSA 258
*****
```

Amino acids 1-29 = signal peptide

Amino acids 30-121 = β 1

Amino acids 122-215 = β 2

FIG. 17
MHC Class II DQA1 alpha chain
Homo sapiens
 Amino acids 1-23 = signal peptide
 Amino acids 24-110 = $\alpha 1$
 Amino acids 111-204 = $\alpha 2$

```

DQA1*01:01 MILNKALLLGALALTTVMSPCGGEDIVADHVASCGVNLYQFYGPSGGQYTHEFDGDEEFYV 60
DQA1*01:02 MILNKALLLGALALTTVMSPCGGEDIVADHVASCGVNLYQFYGPSGGQYTHEFDGDEQFYV 60
DQA1*02:01 MILNKALMLGALALTTVMSPCGGEDIVADHVASYGVNLYQSYGPSGGQYTHEFDGDEEFYV 60
DQA1*03:01 MILNKALMLGALALTTVMSPCGGEDIVADHVASYGVNLYQSYGPSGGQYSHEFDGDEEFYV 60
DQA1*04:01 MILNKALLLGALALTTVMSPCGGEDIVADHVASYGVNLYQSYGPSGGQYTHEFDGDEQFYV 60
DQA1*05:01 MILNKALMLGALALTTVMSPCGGEDIVADHVASYGVNLYQSYGPSGGQYTHEFDGDEQFYV 60
DQA1*05:05 MILNKALMLGTLALTTVMSPCGGEDIVADHVASYGVNLYQSYGPSGGQYTHEFDGDEQFYV 60
DQA1*06:01 MILNKALLLGALALTTVMSPCGGEDIVADHVASYGVNLYQSYGPSGGQYTHEFDGDEQFYV 60
*****; **; ***** ***** *****; *****; **

DQA1*01:01 DLERKETAWRPWPEFSKFGGFDPPQALRNMAVAKHNLNIMIKRYNSTAATNEVPEVTVFESK 120
DQA1*01:02 DLERKETAWRWPEFSKFGGFDPPQALRNMAVAKHNLNIMIKRYNSTAATNEVPEVTVFESK 120
DQA1*02:01 DLERKETVWKLPLFHRRL-RFDPQFALTNI AVLKHNLNILIKRSNSTAATNEVPEVTVFESK 119
DQA1*03:01 DLERKETVWQLPLFRRFRFDPQFALTNI AVLKHNLNIVIKRSNSTAATNEVPEVTVFESK 120
DQA1*04:01 DLGRKETVWCLPVLRQF-RFDPQFALTNI AVLKHNLNILIKRSNSTAATNEVPEVTVFESK 119
DQA1*05:01 DLGRKETVWCLPVLRQF-RFDPQFALTNI AVLKHNLSLIKRSNSTAATNEVPEVTVFESK 119
DQA1*05:05 DLGRKETVWCLPVLRQF-RFDPQFALTNI AVLKHNLSLIKRSNSTAATNEVPEVTVFESK 119
DQA1*06:01 DLGRKETVWCLPVLRQF-RFDPQFALTNI AVLKHNLNILIKRSNSTAATNEVPEVTVFESK 119
** ****,* * : ; ** **** ** *; ** ***** ; **** ***** *****

DQA1*01:01 SPVTLGQPNTLICLVDNIFPPVNVITWLSNGQSVTEGVSETSFSLKSDHSFFKISYLTFL 180
DQA1*01:02 SPVTLGQPNTLICLVDNIFPPVNVITWLSNGQSVTEGVSETSFSLKSDHSFFKISYLTFL 180
DQA1*02:01 SPVTLGQPNTLICLVDNIFPPVNVITWLSNGHSVTEGVSETSFSLKSDHSFFKISYLTFL 179
DQA1*03:01 SPVTLGQPNTLICLVDNIFPPVNVITWLSNGHSVTEGVST-SFSLKSDHSFFKISYLTFL 179
DQA1*04:01 SPVTLGQPNTLICLVDNIFPPVNVITWLSNGHSVTEGVSETSFSLKSDHSFFKISYLTFL 179
DQA1*05:01 SPVTLGQPNILICLVDNIFPPVNVITWLSNGHSVTEGVSETSFSLKSDHSFFKISYLTLL 179
DQA1*05:05 SPVTLGQPNILICLVDNIFPPVNVITWLSNGHSVTEGVSETSFSLKSDHSFFKISYLTLL 179
DQA1*06:01 SPVTLGQPNTLICLVDNIFPPVNVITWLSNGHSVTEGVSETSFSLKSDHSFFKISYLTFL 179
***** ***** *****; ***** ***** ***** *****; **

DQA1*01:01 PSAD EYDCKVEHWGLDQPLLKHWEPEIPAPMSELTETVVCALGLSVGLVGVVGTVFII 240
DQA1*01:02 PSAD EYDCKVEHWGLDQPLLKHWEPEIPAPMSELTETVVCALGLSVGLMGIVVGTVFII 240
DQA1*02:01 PSAD EYDCKVEHWGLDEPLLKHWEPEIPAPMSELTETVVCALGLSVGLVGVVGTVLII 239
DQA1*03:01 PSAD EYDCKVEHWGLDEPLLKHWEPEIPTPMSELTETVVCALGLSVGLVGVVGTVLII 239
DQA1*04:01 PSAD EYDCKVEHWGLDEPLLKHWEPEIPAPMSELTETVVCALGLSVGLVGVVGTVFII 239
DQA1*05:01 PSAEESYDCKVEHWGLDKPLLKHWEPEIPAPMSELTETVVCALGLSVGLVGVVGTVFII 239
DQA1*05:05 PSAEESYDCKVEHWGLDKPLLKHWEPEIPAPMSELTETVVCALGLSVGLVGVVGTVFII 239
DQA1*06:01 PSAD EYDCKVEHWGLDEPLLKHWEPEIPAPMSELTETVVCALGLSVGLVGVVGTVFII 239
***,* *****; *****; *****; *****; *****; **

DQA1*01:01 QGLRSVGASRHQGFL 255
DQA1*01:02 QGLRSVGASRHQGFL 255
DQA1*02:01 RGLRSVGASRHQGFL 254
DQA1*03:01 RGLRSVGASRHQGFL 254
DQA1*04:01 RGLRSVGASRHQGFL 254
DQA1*05:01 RGLRSVGASRHQGFL 254
DQA1*05:05 RGLRSVGASRHQGFL 254
DQA1*06:01 RGLRSVGASRHQGFL 254
; *****

```

FIG. 18
MHC Class II DQA2 alpha chain

Homo sapiens GenBank NP_064440.1

```
1   MILNKALLLG ALALTAVMSP CGGEDIVADH VASYGVNFYQ SHGPSGQYTH EFDGDEEFYV
61  DLETKETVWQ LPMFSKFISF DPQSALRNMA VGKHTLEFMM RQSNSTAATN EVPEVTVFSK
121 FPVTLGQPNT LICLVDNIFP PVVNITWLSN GHSVTEGVSE TSFLSKSDHS FFKISYLTFL
181 PSADEIYDCK VEHWGLDEPL LKHWEPEIPA PMSELTETLV CALGLSVGLM GIVVGTVFII
241 QGLRSVGASR HQGLL
```

Amino acids 1-23 = signal peptide

Amino acids 24-110 = α 1

Amino acids 111-204 = α 2

FIG. 19A
MHC Class II DQB1 beta chain

Homo sapiens

GenBank NP_001230890.1 Isoform 2 (DQB1*06:02)

```
1   MSWKKALRIP GDLRVATVTL MLAMLSSLLA EGRDSPEDFV FQFKGMCYFT NGTERVRLVT
61  RYIYNREEYA RFDSDVGIVYR AVTPQGRPDA EYWNSQKEVL EGTRAELDTV CRHNYEVAFR
121 GILQRRVEPT VTISPSRTEA LNHHNLLVCS VTDFYPGQIK VRWFRNDQEE TAGVVSTPLI
181 RRGDWTFQIL VMLEMTFQRG DVYTCHVEHP SLQSPITVEW RAQSESAQSK MLSGVGGEVL
241 GLIFLGLGLI IRQRSQKGPQ GPPPAGLLH
```

Amino acids 1-32 = signal peptide

Amino acids 33-126 = β 1

Amino acids 127-220 = β 2

FIG. 19B

Homo sapiens

GenBank NP_001230891.1 Isoform 1 and IMGT/HLA Acc No: HLA08917 (DQB1*02:01)

```

1   MSWKALRIP GGLRAATVTL MLSMLSTPVA EGRDSPEDFV YQFKGMCYFT NGTERVRLVS
61  RSIYNREEIV RFDSDVGVEFR AVTLLGLPAA EYWNSQKDIL ERKRAAVDRV CRHNYQLELR
121 TTLQRRVEPT VTISPSRTEA LNHHNLLVCS VTDFYPAQIK VRWFRNDQEE TAGVVSTPLI
181 RNGDWTFOIL VMLEMPQRG DVYTCHVEHP SLQSPITVEW RAQSESAQSK MLSGIGGFVL
241 GLIFLGLGLI IHRSQKGLL H

```

Amino acids 1-32 = signal peptide

Amino acids 33-126 = β 1Amino acids 127-220 = β 2

FIG. 19C

Homo sapiens

GenBank AGW82927.2 HLA-DQB1*03:02 (HLA-DQB1*0302)

```

1   MSWKALRIP GGLRVATVTL MLAMLSTPVA EGRDSPEDFV YQFKGMCYFT NGTERVRLVT
61  RYIYNREEYA RFDSDVGVEFR AVTFLGPPAA EYWNSQKEVL ERTRAELDTV CRHNYQLELR
121 TTLQRRVEPT VTISPSRTEA LNHHNLLVCS VTDFYPAQIK VRWFRNDQEE TIGVVSTPLI
181 RNGDWTFOIL VMLEMPQRG DVYTCHVEHP SLQNPITVEW RAQSESAQSK MLSGIGGFVL
241 GLIFLGLGLI IHRSQKGLL H

```

Amino acids 1-32 = signal peptide

Amino acids 33-126 = β 1Amino acids 127-220 = β 2

Amino acids 33-220 (bolded and underlined represent an exemplary HLA-DQB1 fragment for incorporation into a TMAPP)

FIG. 20A

MHC Class II DQB2 beta chain

Homo sapiens

GenBank NP_001185787.1 MHC Class II DQB2 beta chain Isoform 2

```

1   MALQIPGGFW AAAVTVMLVM LSTPVAEARD FPKDFLVQFK GMICYFTNGTE RVRGVARYIY
61  NREEYGRFDS DVGEFQAVTE LGRSIEDWNN YKDFLEQERA AVDKVCRHNY EAELRTTLQR
121 QVEPTVTISP SRTEALNHHN LLVCSVTDFY PAQIKVRWFR NDQEETAGVV STSLIRNGDW
181 TFQILVMLEI TPQRGDIYTC QVEHPSLQSP ITVEWRPRGP PPAGLLH

```

Amino acids 1-32 = signal peptide

Amino acids 33-126 = β 1Amino acids 127-215 = β 2

FIG. 20B*Homo sapiens*

GenBank NP_001287719 MHC Class II DQB2 beta chain Isoform 1

```
1   MALQIPGGFW AAAVTVMLVM LSTPVAEARD FPKDFLVQFK GMCYFTNGTE RVRGVARYIY
61  NREEYGRFDS DVGEFQAVTE LGRSIEDWNN YKDFLEQERA AVDKVCRHNY EAE LR TTLQR
121 QVEPTVTISP SRTEALNHHN LLVCSVTDFY PAQIKVRWFR NDQEETAGVV STSLIRNGDW
181 TFQILVMLEI TPQRGDIYTC QVEHPSLQSP ITVEWRAQSE SAQSKMLSGI GGFVLGLIFL
241 GLGLIIRHRG QKGPRGPPPA GLLH
```

Amino acids 1-32 = signal peptide

Amino acids 33-126 = β 1Amino acids 127-215 = β 2

Figure 21A
GenBank 3S7G_A
Homo sapiens IgG1 Fc
227 aa

1 dkthtccpcp apellggpsv flfppkpkdt lmsrtpevt cvvvdvshed pevknwyvd
61 gvevhnaktk preeqynsty rvsvltvlh qdwlngkeyk ckvsnkappa piektiskak
121 gqprepvyt lppsrdeltk nqsltcclvk gfypsdiave wesngqpenn ykttppvlds
181 dgsfflyskl tvdksrwqgg nvfscsvmhe alhnhytqks lslspgk

GenBank AAN76044
Homo sapiens IgG2 Fc (amino acids 99-325)
227 aa

1 stkgpsvfpl apcsrstses taalgcclvkd yfpepvtvsw nsgaltsgvh tfpavliqssg
61 lyslssvvtv pssnfgtqty tcnvdhkpsn tkvdktkverk ccvecpcca ppvagpsvfl
121 fppkpkdtlm isrtpevtcv vvdvshedpe vqfnwyvdgv evhnaktkpr eeqfnstfir
181 vsvltvvhqg wlngkeykck vsnkglpapi ektisktkgq prepqvytlp psreemtknq
241 vsltcclvkgf ypsdiavewe sngqpennyk ttpmldsdg sfflyskltv dksrwqqgnv
301 fscsvmheal hnhytqksls lspgk

GenBank AAW65947
Homo sapiens IgG3 Fc (amino acids 19-246)
238 aa

1 hkpsntkvdk rvelktplgd tthtcpcpa pellggpsvf lfppkpkdtl misrtpevtc
61 vvvdvshedp evkfnwyvdg vevhnaktkp reeqynstyr vsvltvlhq dwlngkeykc
121 kvsnkappa iektiskakg qprepvytl ppsrdeltkn qvsltcclvk gfypsdiave
181 esngqpenny ktppvldsds gsfflysklt vdksrwqqgn vscsvmhea lnhhlytqksl
241 slspgk

Figure 21B

GenBank AKA52770

Homo sapiens IgD Fc (amino acids 162-383)

222 aa

1 ptkapdvfpi isgcrhpkdn spvvlacilit gynhtsvtvt wymgtqspq rtfpeiqrdr
61 syymtssqls tplqwrqge ykcvvqhtas kskkeifrw pspkqassv ptaqpqaegs
121 lakattapat trntgrggee kkekekeeq eeretktpec pshtqplgvy lltpavqdlw
181 lrdkatftcf vvgdldkdh ltwevagkvp tggveeglle rhngsqsqh srllprslw
241 nagtsvtcti nhpslppqrl malrepaaqa pvklslnila ssdppeaasw llcevsqfsp
301 pnillmwled qrevntsgfa parppqprs ttfwawsvlr vpappspqpa tytctvvhed
361 srlllnasrs levsyvtldhg pmk

GenBank 0308221A

Homo sapiens IgM Fc

276 aa

1 vtstltikzs dwlgesmftc rvdhrgltfq qnassmcpvd qdtairvfai ppsfasiflt
61 kstklitclvt dlitybsvti swtreengav kthtnisesh pnatfsavge asicedbdws
121 gerftctvth tdlpsplkqt isrpkgvalh rpbvylppa rzzlnlresa titclvtgfs
181 padvfvevmq rgeplspqky vtsapmpepq apgryfahsi ltvseeeewnt ggtytctvah
241 ealpnrvter tvdkstgkpt lynvslvmsd tagtcty

Figure 21C

GenBank P01876

Homo sapiens IgA Fc (amino acids 120-353)

234 aa

```

1 asptspkvfp lsclstqpdg nvviacvlvqg ffpqeplsvt wsesgggvta rnfpssqdas
61 gdlyttssql tlpatqclag ksvtchvkhy tnpsqdvtp cpvpstptp spstptpsp
121 scchprlslh rpaledlllg seanltctlt glrdasgvtf twtpssgksa vqppperdlc
181 gcysvssvlp gcaepwnhvk tftctaaype sktpiltatls ksgntfrpev hllpppseel
241 alnelvtltc largfspkdv lvrwlqgsqe lprekyltwa srqepsqgtt tfavtsilrv
301 aaedwkkqdt fscmvqheal plaftqktid rlagkpthvn vsvmaevdg tcy

```

GenBank 1F6A_B

Homo sapiens IgE Fc (amino acids 6-222)

212 aa

```

1 adpcdsnprg vsaylsrpsp fdlfirkcpt itclvvdlap skgtvnltws rasgkpvnhs
61 trkeekqrng tltvtstlpv gtrdwieget yqcrvthphi pralmrsttk tsgpraapev
121 yafatpewpg srdkrtlacl ignfmpedis vqwlhnevql pdarhsttqp rktkgsgfiv
181 fsrlevtrae weqdeficr avheaaspsq tvqravsvnp gk

```

GenBank P01861

Homo sapiens IgG4 Fc (amino acids 100-327)

228 aa

```

1 astkgpsvfp lapcsrstse staaigclvk dyfpepvtvs wnsгалtsgv htfpavlgss
61 glyslssvvt vpssslgtkt ytcnvdhkps ntkvdkrves kygppcpscp afe1lgpsv
121 flfppkpkdt lmisrtpevt cvvvdvsqed pevqfnwyvd gvevhnaktk preeqfnsty
181 rvsvltvlh qdwlngkeyk ckvsnkglps siektiskak gqprepqvyt lppsqeemtk
241 nqvsltclvk gfypsdiave wesngqpenn ykttppvlds dgsfflysr1 tvdksrwqeg
301 nvfscsvmhe alnhnytqks ls1slgk

```

FIG. 21DWT Human IgG1 Fc Sequence:

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RWVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
 ESNQGPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

FIG. 21EHuman IgG1 Fc Mutant: L234F/L235E/P331S (Triple Mutant "TM")

DKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RWVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
 ESNQGPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

FIG. 21FHuman IgG1 Fc Mutant: N297A

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTY
 RWVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
 ESNQGPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

FIG. 21GHuman IgG1 Fc Mutant: L234A/L235A ("LALA")

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
 YRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

Residue numbered according to EU index (Kabat Numbering)

FIG. 22A

DRA*0101 (wild-type)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:9)

FIG. 22B

DRA*0101 (E3C)

IK[□]EHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:203)

FIG. 22C

DRA*0101 (E4C)

IK[□]EHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:204)

FIG. 22D

DRA*0101 (F12C)

IKEEHVIIQAE[□]YLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:205)

FIG. 22E

DRA*0101 (G28C)

IKEEHVIIQAEFYLNPDQSGEFMFDFD[**C**]DEIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:206)

FIG. 22F

DRA*0101 (D29C)

IKEEHVIIQAEFYLNPDQSGEFMFDFD[**C**]EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:10)

FIG. 22G

DRA*0101 (I72C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD[**E**]EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLE[**C**]MTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:11)

FIG. 22H

DRA*0101 (K75C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD[**E**]EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMT[**C**]RSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:12)

FIG. 22I

DRA*0101 (T80C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNY[C]PITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:207)

FIG. 22J

DRA*0101 (P81C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYT[C]ITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:13)

FIG. 22K

DRA*0101 (I82C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTP[C]ITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:14)

FIG. 22L

DRA*0101 (T93C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVL[C]NSPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:208)

FIG. 22M

DRA*0101 (N94C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLT[C]SPVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:209)

FIG. 22N

DRA*0101 (S95C)

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTN[C]PVELREPNVLICFIDK
FTPPVVNVVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET (SEQ ID NO:210)

FIG. 22O

PD-L1

FTVTVPKDLVYVVEYGSNM TIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEE
DLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKR
ITVKVNAPYNKINQRILVVD PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTT
TTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNE
R (SEQ ID NO:99)

FIG. 23A

DRB1*0401 (wild-type)

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTLVM
LETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQSKM (SEQ ID NO:30)

FIG. 23B

DRB1*0401 (P5C)

GDTRP[CR]FLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTLVM
LETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQSKM (SEQ ID NO:35)

FIG. 23C

DRB1*0401 (F7C)

GDTRPR[CL]EQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTLVM
LETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQSKM (SEQ ID NO:211)

FIG. 23D

DRB1*0401 (Q10C)

GDTRPRFLE[CV]KHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGDWFQTLVM
LETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQSKM (SEQ ID NO:212)

FIG. 23E

DRB1*0401 (N19C)

GDTRPRFLEQVKHECHFF[C]GTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGDWTFQTLVM
LETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:213)

FIG. 23F

DRB1*0401 (G20C)

GDTRPRFLEQVKHECHFFN[C]TERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGDWTFQTLVM
LETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:214)

FIG. 23G

DRB1*0401 (N33C)

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFY[H]QEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGDWTFQTLVM
LETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:30)

FIG. 23H

DRB1*0401 (G151C)

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQN[C]DWTFQTLVM
LETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:36)

FIG. 23I

DRB1*0401 (D152C)

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNC[**C**]WTFQTLVM
LETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:215)

FIG. 23J

DRB1*0401 (W153C)

GDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEEYVRFDSDVGEYRAVTELG
RPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKT
QPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG VVSTGLIQNGD[**C**]TFQTLVM
LETVPRSGEVYTCQVEHPSLTSP LTV EWRARSESAQSKM (SEQ ID NO:37)

FIG. 24A

3893

FTVTVPKDLVYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEE
DLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKR
ITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTT
TTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNE
RGGGGSGGGGSGGGGSGGGGSIKEEHVHQAEFYLNPDQSGEFMDFDGDDEI
FHVDMAKKETVWRLEEFGRFASFEAOGALANIAVDKANLEIMTCRSNYTPI
TNPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTTGVSET
VFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPL
PETGGSAAGGDKTHTCPPCPAPEAAGGPSVFLFPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQ
KSLSLSPG (SEQ ID NO:216)

PDL1 – underlined

(G4S)4 linker (SEQ ID NO:75)– bold

DRA*0101 (K75C) – bold and underlined

GGSAAAGG linker (SEQ ID NO:83)– underlined and italicized

IgG1 Fc (L234A; L235A) – italicized

FIG. 24B

(X_n)CGGGSGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQE
EYVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGE
SFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPPASIEVRWFRNGQEEKTG
VVSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESA
QSKM (SEQ ID NO:217)

(X_n) -- autoimmune-associate epitope

CGGGSGGGSGGGGS linker (SEQ ID NO:218)– bold

DRB1*0401 – underlined

FIG. 24C

(X_n)GCGGSGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQE
EYVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGE
SFTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYPPASIEVRWFRNGQEEKTG
VVSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPPLTVEWRARSESA
QSKM (SEQ ID NO:218)

(X_n) -- autoimmune-associate epitope

GCGGSGGGGSGGGGS linker (SEQ ID NO:219)– bold

DRB1*0401 – underlined

FIG. 24D

(X_n)GGCGSGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQE
EYVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGE
SFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPPASIEVRWFRNGQEEKTG
VYSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPPLTVEWRARSESA
QSKM (SEQ ID NO:220)

(X_n) -- autoimmune-associate epitope

GGCGSGGGGSGGGGS linker (SEQ ID NO:128)– bold

DRB1*0401 – underlined

FIG. 24E

(X_n)GGGCSGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQE
EYVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGE
SFTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYPPASIEVRWFRNGQEEKTG
VVSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPSTVEWRARSESA
QSKM (SEQ ID NO:221)

(X_n) -- autoimmune-associate epitope

GGGCSGGGGSGGGGS linker (SEQ ID NO:222)– bold

DRB1*0401 – underlined

FIG. 24F

(X_n)GGGGCGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQE
EYVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGE
SFTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPPASIEVRWFRNGQEEKTG
VYSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPSTVEWRARSESA
QSKM (SEQ ID NO:223)

(X_n) -- autoimmune-associate epitope

GGGGCGGGGSGGGGS linker (SEQ ID NO:224)– bold

DRB1*0401 – underlined

FIG. 24G

FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEE
DLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKR
ITVKVNAPYNKINQRILVVDPTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTT
TTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNE
RGGGGSGGGGSGGGGSGGGGSGGGGSIKEEHVHQAEFYLNPDQSGEFMFDFDGDEI
FHVDMAKKETVWRLEEFGRFASFEAOGALANIAVDKANLECMTKRSNYTPI
TNPPEVTVLTNSPVELREPNVLICFIDKFTPPVVNVTWLRNGKPVTTGVSET
VFLPREDHLFRKFHYLPFLPSTEDVYDCRVEHWGLDEPLLKHWEFDAPSPL
PETGGSAAGGDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQ
KSLSLSPG (SEQ ID NO:225)

PDL1 -- underlined

(G4S)₄ linker (SEQ ID NO:75)– bold

DRA*0101 (I72C) – bold and underlined

GGSAAGG linker (SEQ ID NO:83)– underlined and italicized

IgG1 Fc (L234A; L235A) – italicized

FIG. 24H

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMT**CR**SNYTPITNVPPEVTVL TNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPETGGGGSGGGGSGGGGSGGGGSFTVTVPKDL
YVVEYGSNM TIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHG EEDLKVOHSSY
RQARLLKDQLSLGNAALOITDVKLQDAGVYRCMISYGGADYKRITVKVNAPY
NKINQRILVVD PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEK
LFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERGGGGSGG
GGSGGGGSGGGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHN
HYTQKSLSLSPG (SEQ ID NO:226)

hDRA*0101 α chain (K75C) – underlined
(G4S)_n linker (SEQ ID NO:75)– bold
PD-L1 – double underlined
IgG1 Fc (LALA) – italicized

FIG. 24I

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMT**CR**SNYTPITNVPPEVTVLTNSPVELREPNVLCFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPETGGSAAAGGDKTHTCPPCPAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSP**GGGGGSGGGGSGGGGSGGGGSGGGG**SFTVT
VPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKV
QHSSYRQRRARLLKDKQSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVK
VNAPYNKINQRILVVDPTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNS
KREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNER

(SEQ ID NO:227)

hDRA*0101 α chain (K75C) -- underlined
(G4S)4 (SEQ ID NO:75)– bold and underlined
hIgG1 (LALA) -- italicized
PD-L1 – double underlined

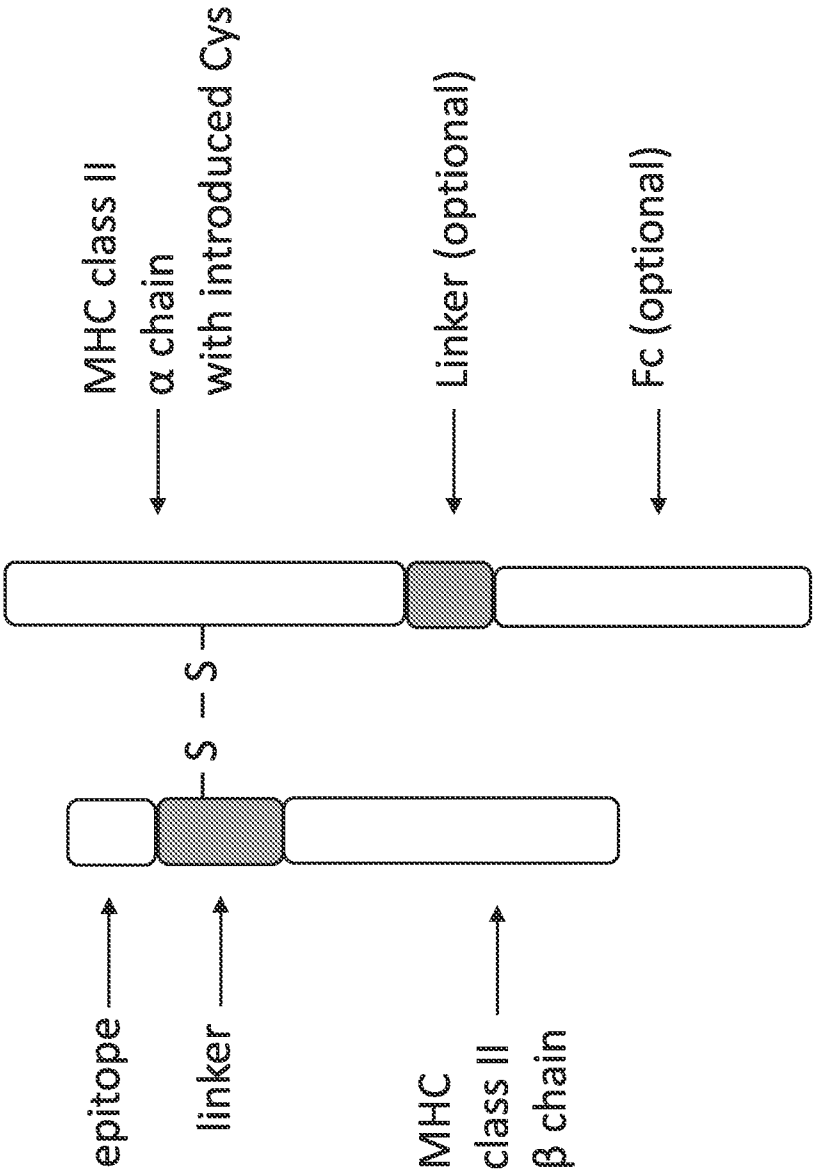


FIG. 25A

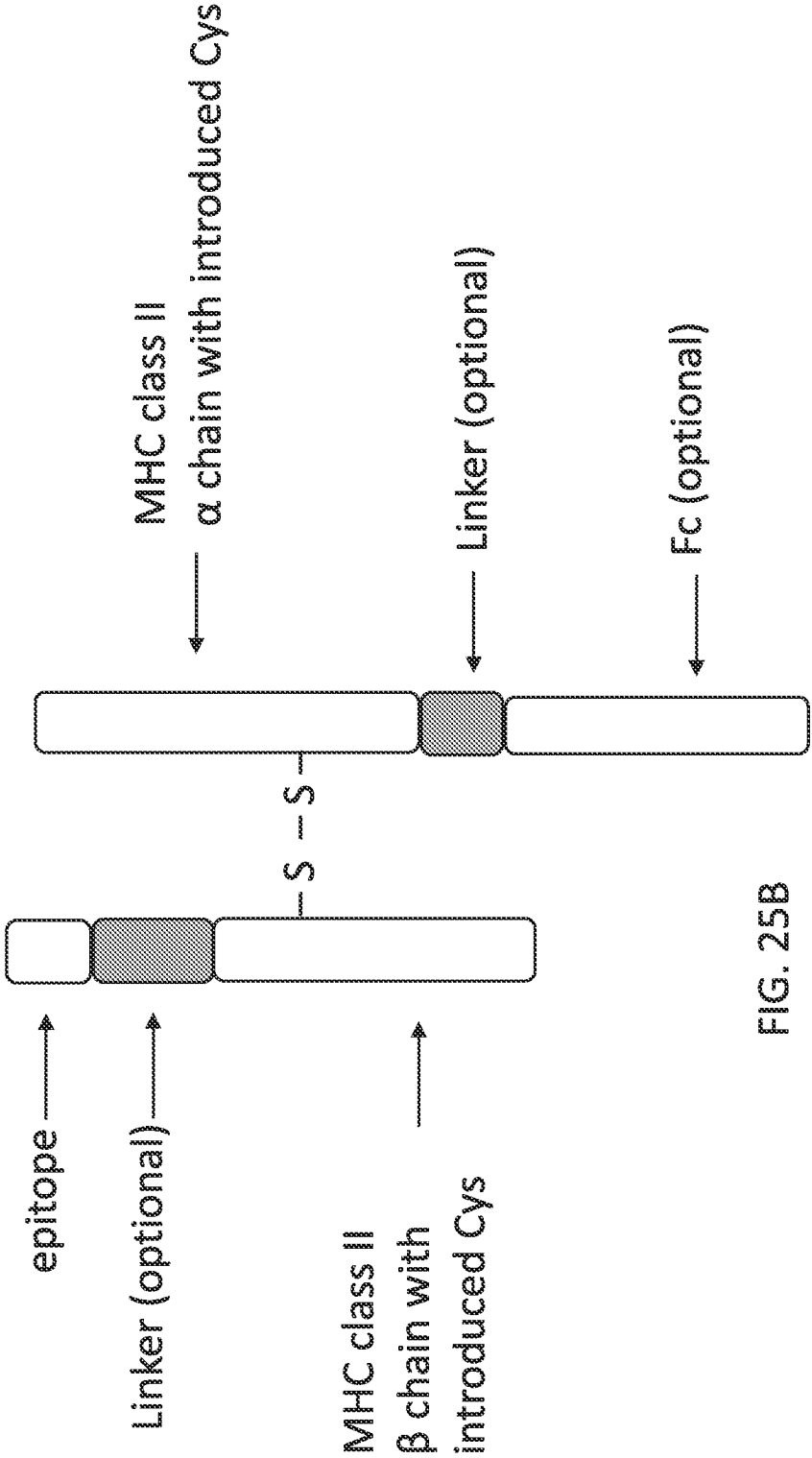


FIG. 25B

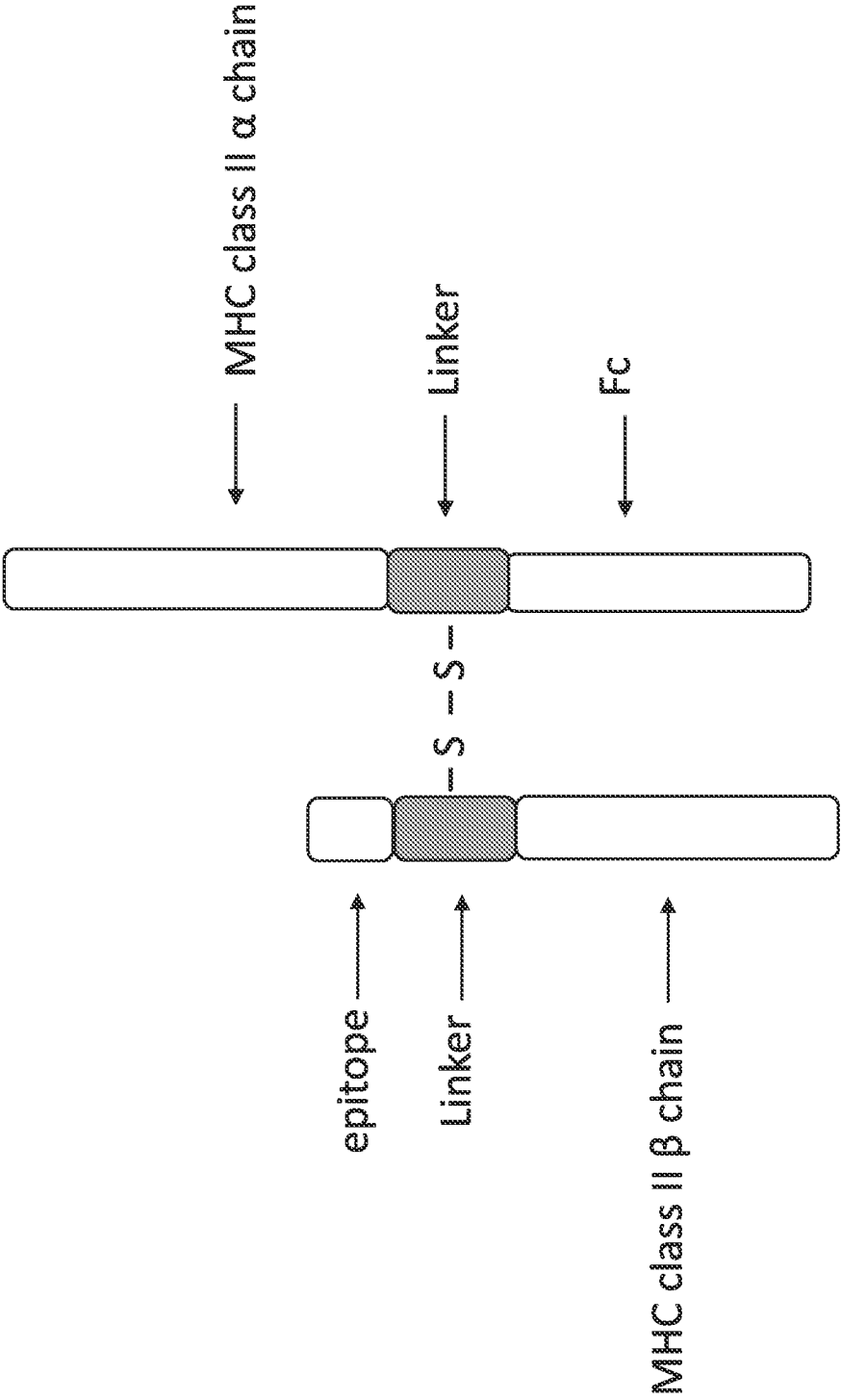


FIG. 25C

FIG. 26A

2983

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTCITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET**GGSAAGGDKTHTC**PPCPAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:228)

DRA1 MHC class II α chain (P81C)

GGSAAGG linker – bold

hIgG1 Fc (LALA) – italicized

FIG. 26B

X_nGGGGSGGGGSGGGSGDTRPRCLEQVKHECHFFNGTERVRFLDRYFYHQEE
YVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEOKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYFASIEVRWFRNGQEEKTG
VSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSES
SAQSKM (SEQ ID NO:229)

(X_n) – autoimmune disease-associated peptide(G4S)_n linker (SEQ ID NO:74)– bold

hDRB1*0401 (F7C) – underlined

FIG. 26C

X_nGGGGSGGGGSGGGGSGDTR**CR**FLEQVKHECHFFNGTERVRFLDRYFYHQEE
YVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVPYPAKTQPLQHNNLLVCSVNGFYFASIEVRWFRNGQEEKTG
VSTGLIQNGDWTFTQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:230)

(X_n) -- autoimmune disease-associated peptide
(G4S)_n linker (SEQ ID NO:74) -- bold
DRB1*0401 (P5C) -- underlined

FIG. 26D

X_nGGGGSGGGGSGGGGSGDTRPR**F**FLEQVKHECHFFNGTERVRFLDRYFY**C**QEE
YVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVPYPAKTQPLQHNNLLVCSVNGFYFASIEVRWFRNGQEEKTG
VSTGLIQNGDWTFTQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:231)

(X_n) -- autoimmune disease-associated peptide
(G4S)_n linker (SEQ ID NO:74) -- bold
DRB1*0401 (H33C) -- underlined

FIG. 26E

2984

IKECHVIIQAEFYLNPDQSGEFMFDFDGDGDEIFHVDMAKKETVWRLEEFGRFASFE
 AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
 FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
 HWGLDEPLLKHWEFDAPSPLPETGGSAAAGGDKTHTCPPCPAPEAAGGPSVFLFP
 PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
 VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW
 QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:232)

hDRA1 MHC class II α chain (E4C) – underlined
 GGSAAAGG linker (SEQ ID NO:83)– bold
 hIgG1 Fc (LALA) – italicized

FIG. 26F

X_nGGGGSGGGGSGGGSGDTRPRFLEQVKHECHFHCGTERVRFLDRYFYHQEE
 YVRFSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
 FTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYPPASIEVRWFRNGQEEKTG
 VSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSAQ
 SKM (SEQ ID NO:233)

(X_n) – autoimmune disease-associated peptide
 (G4S)_n linker (SEQ ID NO:74)– bold
 hDRB1*0401 MHC class II β chain (N19C) – underlined

FIG. 26G

X_nGGGGSGGGSGGGSGDTRPRFLEOVKHECHFFN**C**TERVRFLDRYFYHQEE
YVRFSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYPAIEVRWFRNGQEEKTG
VSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:234)

(X_n) -- autoimmune disease-associated peptide
 (G4S)_n linker -- bold
 hDRB1*0401 MHC class II β chain (G20C) – underlined

FIG. 26H

2985

IKEEHVIIQAEFYLNPDQSGEFMFDFDGDIEIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVL**C**NSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPETGGSAAAGGDKTHTCPPCPAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:235)

GGSAAGG linker (SEQ ID NO:83)– bold
 hDRA1 MHC class II α chain (T93C) – underlined
 IgG1 Fc (LALA) – italicized

FIG. 26I

X_nGGGGSGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEE
YVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYFASIEVRWFRNGQEEKTGV
VSTGLIQNGDWTH**C**ITLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:236)

(X_n) – autoimmune disease-associated peptide
(G4S)_n linker (SEQ ID NO:74)– bold
hDRB1*0401 MHC class II β chain (Q156C) – underlined

FIG. 26J

X_nGGGGSGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEE
YVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYFASIEVRWFRNGQEEKTGV
VSTGLIQNGD**C**ITFOTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQS
KM (SEQ ID NO:237)

(X_n) – autoimmune disease-associated peptide
(G4S)_n linker (SEQ ID NO:74)– bold
hDRB1*0401 MHC class II β chain (W153C) – underlined

FIG. 26K

3018

IKEEHVIIQAE[C]YLNPDQSGEFMFDFDGDGDEIFHVDMAKKETVWRLEEFGRFASFE
 AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
 FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
 HWGLDEPLLKHWEFDAPSPLPET**GGSAAGGDKTHTCPPCPAPEAAGGPSVFLFP**
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:238)

GGSAAGG linker – bold

hDRA1 MHC class II α chain (F12C) – underlined

IgG1 Fc (LALA) – italicized

FIG. 26L

X_n**GGGGSGGGGSGGGSGDTRPRFLE[C]VKHECHFFNGTERVRFLDRYFYHQEE**
YVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEOKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYFASIEVRWFRNGQEEKTG
VSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSES
SAQSKM (SEQ ID NO:239)

(X_n) – autoimmune disease-associated peptide(G4S)_n linker (SEQ ID NO:74) – boldhDRB1*0401 MHC class II β chain (Q10C) – underlined

FIG. 26M

3019

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
 AQGALANIAVDKANLEIMTKRSNY**C**PITNVPPEVTVL TNSPVELREPNVLCFIDK
 FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
 HWGLDEPLLKHWEFDAPSPLPETGG**SAAAGGDKTHTCP**PCAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:240)

hDRA1 MHC class II α chain (T80C) -- underlined
 GGSAAAGG linker (SEQ ID NO:83)-- bold
 hIgG1 Fc (LALA) italicized

FIG. 26N

3020

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
 AQGALANIAVDKANLEIMTKRSNY**T**CITNVPPEVTVL TNSPVELREPNVLCFIDK
 FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
 HWGLDEPLLKHWEFDAPSPLPETGG**SAAAGGDKTHTCP**PCAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:241)

hDRA1 MHC class II α chain (I82C) -- underlined
 GGSAAAGG linker (SEQ ID NO:83)-- bold
 hIgG1 Fc (LALA) italicized

FIG. 26O

X_nGGGGSGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFY**C**QEE
YVRFDSVDGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVNGFYPASIEVRWFRNGQEEKTG
VSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:231)

(X_n) -- autoimmune disease-associated peptide
 (G4S)_n linker (SEQ ID NO:74)– bold
 hDRB1*0401 MHC class II β chain (H33C) – underlined

FIG. 26P

3021

IKEEHVIIQAEFYLNPDQSGEFMFDFD**C**DEIFHVDMAKKETVWRLEEFGRFASFE
AQALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLCFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET**GG**SAAAGGDKTHTCPPCPAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:242)

hDRA1 MHC class II α chain (G28C) – underlined
 GGSAAAGG linker (SEQ ID NO:83)– bold
 hIgG1 Fc (LALA) italicized

FIG. 26Q

X_nGGGGSGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEE
YVRFSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYFASIEVRWFRNGQEEKTG
VSTGLIONCDWTFOTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:243)

(X_n) – autoimmune disease-associated peptide
(G4S)_n linker (SEQ ID NO:74)– bold
hDRB1*0401 MHC class II β chain (G151C) – underlined

FIG. 26R

X_nGGGGSGGGGSGGGSGDTRPRFLEQVKHECHFFNGTERVRFLDRYFYHQEE
YVRFSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHNNLLVCSVNGFYFASIEVRWFRNGQEEKTG
VSTGLIONGCDWTFOTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:244)

(X_n) – autoimmune disease-associated peptide
(G4S)_n linker (SEQ ID NO:74)– bold
hDRB1*0401 MHC class II β chain (D152C) – underlined

FIG. 26S

3022

IKEEHVIIQAEFYLNPDQSGEFMFDFDGCEIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET**GGSAAGGDKTHTCPPCAPEAAGGPSVFLFP**
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:245)

hDRA1 MHC class II α chain (D29C) – underlined
 GGSAAAGG linker (SEQ ID NO:83)– bold
 hIgG1 Fc (LALA) italicized

FIG. 26T

3023

IKEEHVIIQAEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTCSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET**GGSAAGGDKTHTCPPCAPEAAGGPSVFLFP**
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:246)

hDRA1 MHC class II α chain (N94C) – underlined
 GGSAAAGG linker (SEQ ID NO:83)– bold
 hIgG1 Fc (LALA) italicized

FIG. 26U

X_nGGGGSGGGGSGGGSGDTRPRFLEOVKHECHFFNGTERVRFLDRYFYHQEE
YVRFSDVGEYRAVTELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGES
FTVQRRVYPEVTVYPAKTQPLQHHNLLVCSVCGFYPASIEVRWFRNGQEEKTG
VSTGLIQNGDWTFQTLVMLETVPRSGEVYTCQVEHPSLTSPLTVEWRARSESAQ
SKM (SEQ ID NO:247)

(X_n) -- autoimmune disease-associated peptide
 (G4S)_n linker (SEQ ID NO:74)– bold
 hDRB1*0401 MHC class II β chain (N120C) – underlined

FIG. 26V

3024

IKEEHVIIQAEFYLNPDQSGEFMFDFDGD EIFHVDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNCFPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPETGGSAAGGDKTHTCPPCPAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSQSV MHEALHNHYTQKSLSLSPG (SEQ ID NO:248)

hDRA1 MHC class II α chain (S95C) – underlined
 GGSAAAGG linker (SEQ ID NO:83)– bold
 hIgG1 Fc (LALA) italicized

FIG. 26W

3025

IKCEHVIIQAEFYLNPDQSGEFMFDFDGD~~EIFH~~VDMAKKETVWRLEEFGRFASFE
AQGALANIAVDKANLEIMTKRSNYTPITNVPPEVTVLTNSPVELREPNVLICFIDK
FTPPVVNVTWLRNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDVYDCRVE
HWGLDEPLLKHWEFDAPSPLPET**GG**SAAAGGDKTHTCPPCPAPEAAGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:249)

hDRA1 MHC class II α chain (E3C) – underlined

GGSAAGG linker (SEQ ID NO:83)– bold

hIgG1 Fc (LALA) italicized

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/49486

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 39/00, C07K 14/705, C07K 14/725, C12N 15/85 (2021.01)

CPC - C07K 14/7051, A61K 35/17, A61P 37/02, C07K 2319/00, C07K 14/70539, A61K 2039/605, A61K 2039/64, C12N 2510/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2020/0172595 A1 (Cue Biopharma, Inc.) 04 June 2020 (04.06.2020) Claim 1, Claim 2, Claim 9, Claim 10, para [0154], [0165]	1-2, 40-41, 43/(40-41)
-		-----
Y		3-4, 42, 43/42
Y	US 2018/0207228 A1 (ALK-Abello A/S) 26 July 2018 (26.07.2018) abstract, para [0853]	3-4, 42, 43/42

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 November 2021

Date of mailing of the international search report

DEC 22 2021

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/49486

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☒ forming part of the international application as filed:
☒ in the form of an Annex C/ST.25 text file.
☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/49486

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 5-39, 44-67
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.