CLAIMS

WHAT IS CLAIMED IS:

~~1. A complex comprising: one or more human leukocyte antigens (HLAs), wherein said one or more HLAs are inhibited from eliciting a T cell response when said complex is interrogated by one or more T cells.~~

~~2. The complex of claim 1, wherein said complex comprises, in N-terminus to C-terminus order,~~ a segment comprising a peptide, one or more linkers, and a segment comprising a human HLA class 1 heavy chain sequence, wherein said human HLA class 1 heavy chain sequence comprises HLA-C~~.~~

~~3. The complex of claim 2, wherein said peptide does not elicit a T cell response when said peptide is interrogated by one or more T cells.~~

~~4. The complex of claim 2 or 3, wherein said peptide is incapable of activating said one or more T cells.~~

~~5.~~1. ~~The complex of any one of claims 2 to 4, wherein said peptide is capable of binding to a receptor of said one or more T cells~~, and wherein said one or more linkers comprises a conformation configured to not block one or more killer-cell immunoglobulin-like receptor binding sites on said human HLA class 1 heavy chain sequence; and wherein said human HLA class 1 heavy chain sequence comprises one or more mutations as compared to an endogenous HLA of the same type, wherein said mutations occur at one or more of amino acid residues 115, 122, 128, 194, 197, 198, 212, 214, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 243, 245, 248, 262, or any combination thereof~~binding is insufficient to activate said one or more T cells~~.

~~6.~~2. The complex of claim 1~~any one of claims 2 to 5~~, wherein said peptide is coupled~~binds~~ to one or more HLA binding groove domain residues of said human HLA class 1 heavy chain sequence.

~~7.~~3. The complex of claim 1 or~~any one of claims~~ 2~~ to 6~~, wherein said peptide modulates a conformation of said human HLA class 1 heavy chain sequence.

~~8. The complex of claim 7, wherein said conformation prevents said one or more T cells from binding to said human HLA class 1 heavy chain sequence.~~

~~9.~~4. The complex of any one of claims 1~~2~~ to 3~~8~~, wherein said HLA-C is synthetic.~~peptide comprises greater than or equal to 8, 9, 10, 11, 12, 13, or 14 amino acids.~~

~~10.~~ The complex of any one of claims 1~~2~~ to 4~~9~~, wherein a linker of said one or more linkers are disposed between said peptide and said human HLA class 1 heavy chain sequence, ~~comprises one or more class 1 HLAs.~~

~~11. The complex of any one of claims 2 to 10, wherein said human HLA class 1 heavy chain sequence comprises HLA-A, HLA-B, HLA-C, or any combination thereof.~~

~~12. The complex of claim 11, wherein said human HLA class 1 heavy chain sequence comprise multiple versions of HLA-A, HLA-B, HLA-C, or any combination thereof.~~

~~13. The complex of any one of claims 2 to 12, wherein said human HLA class 1 heavy chain sequence comprises said HLA-A, wherein said HLA-A is displaced between said HLA-B and said HLA-C.~~

~~14. The complex of any one of claims 2 to 13, wherein said complex further comprises one or more linkers between said peptide~~ and ~~said human HLA class 1 heavy chain sequence.~~

~~15.~~5. ~~The complex of claim 14,~~ wherein said one or more linkers are configured to resist proteolytic cleavage.

~~16.~~6. The complex of claim 5~~14 or 15~~, wherein said ~~one or more linkers comprise a conformation configured to not block one or more killer cell immunoglobulin-like receptor (KIR) binding sites on said~~ human HLA class 1 heavy chain sequence is inhibited from eliciting a T-cell response when said complex is interrogated by one or more T cells.~~.~~

~~17.~~7. The complex of any one of claims 1~~2~~ to 6~~16~~, wherein said peptide is coupled to said complex by a disulfide bond.

~~18.~~8. The complex of any one of claims 1~~2~~ to 7~~17~~, wherein said complex further comprises one or more immune checkpoint agonists.

~~19.~~9. The complex of claim 8~~18~~, wherein said one or more immune checkpoint agonists comprise CD47, PD-L1, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, NOX2, PD-1, TIM-3, VISTA, SIGLEC7, or a combination thereof.

~~20. The complex of any one of claims 12 to 919, wherein said human HLA class 1 heavy chain sequence comprises HLA-E or a fragment thereof, HLA-F or a fragment thereof, HLA-G or a fragment thereof, or any combination thereof.~~

~~21. The complex of claim 20, wherein at least one of said HLA-E or said fragment thereof, HLA-F or said fragment thereof, HLA-G or said fragment thereof, or any combination thereof is inhibited from eliciting a T-cell response when said complex is interrogated by one or more T-cells.~~

~~22. The complex of any one of claims 1 to 21, wherein said complex further comprises a regulatory peptide.~~

~~23. The complex of claim 22, wherein said regulatory peptide is an apoptosis-inducing peptide.~~

~~24. The complex of any one of claims 1 to 23, wherein said complex further comprises an epitope configured to allow for detection of said complex.~~

~~25. The complex of claim 24, wherein said epitope comprises 3,5-dinitrosalicylic acid.~~

~~26. The complex of any one of claims 1 to 24, wherein said complex comprises a human β2-microglobulin sequence.~~

~~27.~~10. ~~The complex of any one of claims 14 to 25~~, wherein a linker of said one or more linkers is disp~~os~~~~lac~~ed between said peptide and ~~a~~said human β2-microglobulin sequence, between ~~a~~said human β2-microglobulin sequence and said human HLA class 1 heavy chain sequence, or both.

~~28.~~11. The complex of any one of claims ~~1~~14 to 10~~27~~, wherein a linker of said one or more linkers comprises a sequence at least about 70%, 80%, 90%, or 99% identical to any one of SEQ ID NOs: 48-54.

~~29. The complex of any one of claims 1~~14 to 11~~28~~, wherein said ~~complex comprises, in N-terminus to C-terminus order,~~

~~a. said peptide;~~

~~b. a first linker of said one or more linkers;~~

~~c. said human β2-microglobulin sequence;~~

~~d. a second linker of said one or more linkers; and~~

~~e. said human HLA class 1 heavy chain sequence.~~

~~30. A complex comprising one or more human leukocyte antigens (HLAs), wherein said one or more HLAs are inhibited from eliciting a T cell response when said complex is interrogated by one or more T cells, and wherein said complex comprises,~~

~~a. a first linker; and~~

~~b. a segment comprising a~~ human HLA class 1 heavy chain sequence ~~is engineered to;~~

~~wherein said first linker comprises a conformation configured to not block one or more killer cell immunoglobulin-like receptor (KIR) binding sites on said human HLA class 1 heavy chain sequence.~~

~~31. The complex of claim 30, further comprising a peptide, wherein said peptide is configured or selected for being incapable of activating said one or more T cells.~~

~~32. The complex of either claim 30 or 31, wherein said configuration is further configured to resist proteolytic cleavage.~~

~~33. The complex of any one of claims 30 to 32, wherein said complex further comprises a human β2-microglobulin and an additional linker between said human β2-microglobulin sequence and said human HLA class 1 heavy chain sequence.~~

~~34. The complex of claim 33, wherein said additional linker comprises a conformation configured to resist proteolytic cleavage.~~

~~35. The complex of either claim 33, wherein said additional linker is further configured to not block one or more killer cell immunoglobulin-like receptor (KIR) binding sites on said human HLA class 1 heavy chain sequence.~~

~~36. The complex of any one of claims 30 to 35, wherein said first linker comprises a sequence at least about 70%, 80%, 90%, or 99% identical to any one of SEQ ID NOs: 48-54 or said additional linker comprises a sequence at least about 70%, 80%, 90%, or 99% identical to any one of SEQ ID NOs: 48-54.~~

~~37.~~12. ~~The complex of any one of claims 1 to 36, wherein said one or more human leukocyte antigens (HLAs) comprise one or more mutations, wherein said one or more mutations~~ inhibit ~~said one or more HLAs from eliciting~~ a T-cell response when said complex is interrogated by one or more CD8 cells.

~~38. The complex of claim 37, wherein said one or more mutations comprises a mutation of one or more of amino acid residues 115, 122, 128, 194, 197, 198, 212, 214, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 243, 245, 248, 262, or any combination thereof.~~

13. The complex of any one of claims 1 to 12~~38~~, wherein said complex further comprises a synthetic HLA-E~~one~~ or fragment thereof.

~~39.~~14. The complex of claim 13, wherein said synthetic HLA-E~~more proteins~~ or fragment~~s~~ thereof comprises one or more mutations as compared to ~~that inhibit~~ an endogenous HLA-E or equivalent fragment thereof.~~immune response by the complement system.~~

~~40. The complex of claim 39, wherein said one or more proteins or fragments thereof are selected from CD48, CD59, or a combination thereof.~~

~~41.~~ The complex of any one of claims 1~~2~~ to 14~~40~~, wherein said peptide comprises an amino acid sequence comprising nine~~a second~~ amino acid residues~~residue selected from L, M, S, I, F, T, V~~, and ~~Y.~~

~~42. The complex of claim 41, wherein said second amino acid residue is selected from T, V, and Y.~~

~~43.~~15. ~~The complex of claim 41 or 42,~~ wherein said peptide comprises, in N-terminus to C-terminus order: ~~a last amino acid residue selected from V, I, F, W, Y, L, R, and K.~~

~~44. an~~The complex of claim 43, wherein said last amino acid residue is selected from Y, L, R, and K.

~~45.~~a. ~~The complex of any one of claims 2 to 40, wherein said peptide comprises a second~~ amino acid residue selected from E, P, L, Q, A, R, H, S, T, V, M, D, and K at a second position of said amino acid sequence; and ~~.~~

~~46. an~~The complex of claim 45, wherein said second amino acid residue is selected from E, P, L, Q, A, R, and H.

~~47. The complex of claim 45 or 46, wherein said peptide comprises a last~~ amino acid residue selected from V, ~~L, F, A,~~ I, F~~Y, M~~, W, Y, L, R~~P~~, and K at a ninth position~~R.~~

~~48. The complex~~ of ~~claim 47, wherein~~ said ~~last~~ amino acid sequence~~residue is selected from V, L, and F.~~

~~49. The complex of any one of claims 2 to 40, wherein said peptide comprises a second amino acid residue selected from A, Y, S, T, V, I, L, F, Q, R, N, and W.~~

~~50. The complex of claim 49, wherein said second amino acid residue is selected from A and Y.~~

~~51. The complex of claim 49 or 50, wherein said peptide comprises a last amino acid residue selected from L, V, M, F, Y, and I.~~

~~52.~~b. ~~The complex of claim 51, wherein said last amino acid residue is L~~.

~~53.~~16. A nucleic acid molecule encoding the complex of any one of claims 1-15 ~~to 52~~.

17. An engineered vector comprising the ~~The~~ nucleic acid molecule of claim 16.

~~54.~~18. The engineered vector of claim 18~~53~~, wherein said vector is ~~nucleic acid molecule comprises~~ a plasmid, adenovirus, adeno-associated virus (AAV), lentivirus, retrovirus, or transposon.~~deletion in the endogenous HLA locus.~~

~~55. An isolated cell comprising said The nucleic acid molecule of claim 54, wherein said deletion comprises a deletion in the endogenous HLA-A, HLA-B, or HLA-C locus, or any combination thereof.~~

~~56.~~19. ~~The~~ nucleic acid molecule of claim 16, or said vector of claim 17~~54~~ or 18.~~55, wherein said deletion is complete deletion of the endogenous HLA locus.~~

20. The isolated cell of claim 19, wherein said isolated cell is a stem cell.

21. The isolated cell of claim 20, wherein said stem cell is an embryonic stem cell, a hematopoietic stem cell, a mesenchymal stem cell, or an induced pluripotent stem cell.

~~57. The nucleic acid molecule of any one of claims 53 to 56, wherein said nucleic acid molecule further comprises a sequence encoding a human HLA class 1 heavy chain sequence.~~

~~58. The nucleic acid molecule of claim 57, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises an HLA-A sequence, an HLA-B sequence, an HLA-C sequence, or any combination thereof.~~

~~59. The nucleic acid molecule of claim 57 or 58, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises multiple alleles of an HLA-A sequence, an HLA-B sequence, an HLA-C sequence, or any combination thereof.~~

~~60. The nucleic acid molecule of claim 58 or 59, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises an HLA-A sequence, wherein said HLA-A sequence is displaced between said HLA-B sequence and said HLA-C sequence.~~

~~61. The nucleic acid molecule of any one of claims 57 to 59, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises fewer than 1700 base pairs (bp).~~

~~62. The nucleic acid molecule of any one claims 57 to 61, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises fewer than 500 bp.~~

~~63. The nucleic acid molecule of any one of claims 57 to 62, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises fewer than 250 bp.~~

~~64. The nucleic acid molecule of any one of claims 57 to 63, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises fewer than 150 bp.~~

~~65. The nucleic acid molecule of any one of claims 58 to 64, wherein said HLA-A sequence, HLA-B sequence, HLA-C sequences, or combination thereof comprises one or more flanking sequences.~~

~~66. The nucleic acid molecule of claim 65, wherein said one or more flanking sequences comprise an endogenous HLA sequence.~~

~~67. The nucleic acid molecule of claim 65 or 66, wherein said one or more flanking sequences are specific to one or more promoters.~~

~~68. The nucleic acid molecule of claim 67, wherein said promoters comprise an HLA-A promoter, HLA-B promoter, HLA-C promoter, or combination thereof.~~

~~69. The nucleic acid molecule of any one of claims 57 to 68, wherein said sequence encoding a human HLA class 1 heavy chain sequence does not comprise at least a portion of said HLA-A sequence, HLA-B sequence, HLA-C sequence, or combination thereof.~~

~~70. The nucleic acid molecule of any one of claims 53 to 69, wherein said nucleic acid molecule further comprises a sequence encoding a human β2-microglobulin peptide.~~

~~71. The nucleic acid molecule of any one of claims 53 to 70, wherein said nucleic acid molecule further comprises a sequence encoding a peptide.~~

~~72. The nucleic acid molecule of claim 71, wherein said peptide does not elicit a T-cell response when said peptide is interrogated by one or more T-cells.~~

~~73. The nucleic acid molecule of claim 71 or 72, wherein said peptide is incapable of activating said one or more T-cells.~~

~~74. The nucleic acid molecule of any one of claims 71 to 73, wherein said peptide is capable of binding to a receptor of said one or more T-cells, and wherein said binding is insufficient to activate said one or more T-cells.~~

~~75. The nucleic acid molecule of any one of claims 71 to 74, wherein said peptide binds to one or more HLA binding-groove domain residues of said human HLA class 1 heavy chain sequence.~~

76. The nucleic acid molecule of any one of claims 71 to 73, wherein said first peptide modulates a conformation of said human HLA class 1 heavy chain sequence.

77. The nucleic acid molecule of claim 76, wherein said conformation prevents said one or more T cells from binding said human HLA class 1 heavy chain sequence.

78. The nucleic acid molecule of any one of claims 71 to 77, wherein said peptide comprises greater than or equal to 8, 9, 10, 11, 12, 13, or 14 amino acids.

79. The nucleic acid molecule of any one of claims 53 to 78, wherein said nucleic acid molecule further comprises one or more sequences encoding one or more linkers between said sequence encoding said peptide and said sequence encoding said human HLA class 1 heavy chain sequence.

80. The nucleic acid molecule of claim 79, wherein said one or more linkers are configured to resist proteolytic cleavage.

81. The nucleic acid molecule of claim 79 or 80, wherein said one or more linkers comprise a conformation configured to not block one or more killer cell immunoglobulin-like receptor (KIR) binding sites on said human HLA class 1 heavy chain sequence.

82. The nucleic acid molecule of any one of claims 79 to 81, wherein a sequence of said one or more sequences encoding one or more linkers is displaced between said sequence encoding said peptide and said sequence encoding said human β2-microglobulin peptide, between said sequence encoding said human β2-microglobulin peptide and said sequence encoding said human HLA class 1 heavy chain sequence, or both.

83. The nucleic acid molecule of any one of claims 79 to 82, wherein a linker of said one or more linkers comprises a sequence at least about 70%, 80%, 90%, or 99% identical to any one of SEQ ID NOs: 48-54.

84. The nucleic acid molecule of any one of claims 53 to 83, wherein said nucleic acid molecule further comprises a sequence encoding one or more immune checkpoint agonists.

85. The nucleic acid molecule of claim 84, wherein said one or more immune checkpoint agonists comprise CD47, PD-L1, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, NOX2, PD-1, TIM-3, VISTA, SIGLEC7, or combination thereof.

86. The nucleic acid molecule of claim 85, wherein said nucleic acid molecule further comprises a sequence encoding one or more knocked out proteins corresponding to a receptor of said one or more immune checkpoint agonists.

87. The nucleic acid molecule of any one of claims 57 to 86, wherein said sequence encoding said human HLA class 1 heavy chain sequence comprises an HLA-E sequence or a fragment thereof, an HLA-F sequence or a fragment thereof, an HLA-G sequence or a fragment thereof, or any combination thereof.

88. The nucleic acid molecule of claim 87, wherein at least one of said HLA-E sequence or said fragment thereof, HLA-F sequence or said fragment thereof, HLA-G sequence or said fragment thereof, or any combination thereof is inhibited from eliciting a T-cell response when said human HLA class 1 heavy chain sequence is interrogated by one or more T-cells.

89. The nucleic acid molecule of claim 87 or 88, wherein said nucleic acid molecule further comprises a sequence encoding one or more knocked out proteins corresponding class II, major histocompatibility complex, transactivator (CIITA).

90. The nucleic acid molecule of any one of claims 53 to 89, wherein said nucleic acid molecule further comprises a sequence encoding a regulatory peptide.

91. The nucleic acid molecule of claim 90, wherein said regulatory peptide is an apoptosis-inducing peptide.

92. The nucleic acid molecule of any one of claims 53 to 91, wherein said nucleic acid molecule further comprises a sequence encoding an epitope configured to allow for detection of said complex.

93. The nucleic acid molecule of claim 92, wherein said epitope comprises 3,5-dinitrosalicylic acid.

94. The nucleic acid molecule of any one of claims 53 to 93, wherein said nucleic acid molecule further comprises a sequence encoding one or more knocked out proteins.

95. The nucleic acid molecule of claim 94, wherein said one or more knocked out proteins are selected from blood group A antigen and blood group B antigen.

96. The nucleic acid molecule of any one of claims 53 to 95, wherein said nucleic acid molecule comprises,

a. said sequence encoding said peptide;

b. a first sequence encoding a first linker of said one or more sequences encoding one or more linkers;

c. said sequence encoding said human β2-microglobulin peptide;

d. a second sequence encoding a second linker of said one or more sequences encoding one or more linkers; and

e. said sequence encoding said human HLA class 1 heavy chain sequence.

97. A nucleic acid molecule comprising a sequence encoding a complex comprising one or more Class 1 human leukocyte antigen (HLA) proteins, wherein said one or more Class 1 HLA proteins are inhibited from eliciting a T-cell response when said complex is interrogated by one or more T-cells, and wherein said nucleic acid molecule comprises,

a. a sequence encoding a peptide, wherein said peptide is incapable of activating said one or more T-cells;

b. a first sequence encoding a first linker; and

c. a sequence encoding one or more Class 1 HLA proteins;

wherein said first linker comprises a conformation configured to not block one or more killer-cell immunoglobulin-like receptor (KIR) binding sites on said human HLA class 1 heavy chain sequence, and wherein said conformation is further configured to resist proteolytic cleavage.

98. The nucleic acid molecule of claim 97, wherein said nucleic acid molecule further comprises a sequence encoding a human β2-microglobulin peptide between said sequence encoding said linker and said sequence encoding said human HLA class 1 heavy chain sequence.

99. The nucleic acid molecule of claim 98, wherein said nucleic acid molecule further comprises an additional sequence encoding an additional linker between said sequence encoding said human β2-microglobulin peptide and said sequence encoding said human HLA class 1 heavy chain sequence, wherein said additional linker comprises a conformation configured to resist proteolytic cleavage.

100. The nucleic acid molecule of claim 99, wherein said additional linker is further configured to not block one or more killer-cell immunoglobulin-like receptor (KIR) binding sites on said human HLA class 1 heavy chain sequence.

101. The nucleic acid molecule of any one of claims 97 to 100, wherein said first linker comprises a sequence at least about 70%, 80%, 90%, or 99% identical to any one of SEQ ID NOs: 48-54 or said additional linker comprises a sequence at least about 70%, 80%, 90%, or 99% identical to any one of SEQ ID NOs: 48-54.

102. The nucleic acid molecule of any one of claims 57 to 101, wherein said sequence encoding a human HLA class 1 heavy chain sequence comprises one or more mutations, wherein said one or more mutations inhibit said human HLA class 1 heavy chain sequence from eliciting a T cell response when said human HLA class 1 heavy chain sequence is interrogated by one or more CD8 cells.

103. The nucleic acid molecule of claim 102, wherein said one or more mutations comprises a mutation of one or more of amino acid residues 115, 122, 128, 194, 197, 198, 212, 214, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 243, 245, 248, 262, or any combination thereof.

104. The nucleic acid molecule of any one of 53 to 103, wherein said nucleic acid molecule further comprises a sequence encoding one or more proteins or fragments thereof that inhibit an immune response by the complement system.

105. The nucleic acid molecule of claim 104, wherein said one or more proteins or fragments thereof are selected from CD48, CD59, or a combination thereof.

~~106. A method for generating the nucleic acid molecule of any one of claims 53 to 105, comprising displacing a sequence encoding a region configured to receive a sequence comprising said deletion in the HLA locus, a sequence encoding said human HLA class 1 heavy chain sequence, or any combination thereof.~~

~~107.~~22. A method of generating an immune incompetent cell, comprising administering said complex of any one of claims 1-15, ~~to 52~~ or said nucleic acid molecule of claim 16, or said vector of claim 17 or 18~~any one claims 53 to 105~~ to a cell.

~~108.~~ The method of claim 22~~107, wherein said nucleic acid molecule of claims 53 to 105 is delivered to said cell's genome.~~

~~109. The method of claim 107, wherein said cell is incubated with said complex of any one of claims 1 to 52.~~

~~110.~~23. ~~The method of any one of claims 107 to 109~~, wherein said cell is a stem cell.

~~111.~~24. The method of claim 23~~110~~, wherein said stem cell is an embryonic stem cell, a hematopoietic~~Induced Pluripotent~~ stem cell, a mesenchymal stem cell, or an induced pluripotent stem cell. ~~(iPSC).~~

~~112.~~25. A therapeutically effective amount of said nucleic acid molecule of claim 16 or said isolated cell of any one of claims 19-21, for use in ~~A method of~~ treating a disease or disorder in a subject in need thereof~~, comprising administering a therapeutically effective amount of said nucleic acid molecule of any one of claims 53 to 105 or said immune incompetent cell of any one of claims 107 to 111 to said subject~~.

~~113. The method of claim 112, wherein said disease is an autoimmune disease.~~

~~114. The method of claim 112, wherein said disease is a cancer.~~

~~115. The method of claim 112, wherein said disease is a degenerative disease.~~

~~116. A method of inhibiting a human leukocyte antigen (HLA) comprising contacting said HLA with a peptide that does not comprise T cell receptor binding residues or fragments.~~

~~117. The method of claim 116, wherein said peptide binds to one or more HLA binding groove domain residues of said HLA.~~

~~118. The method of claim 116 or 117, wherein said peptide modulates a conformation of said HLA.~~

~~119. The method of any one of claims 116 to 118, wherein said conformation prevents a T cell from binding said HLA.~~

~~120. The method of any one of claims 116 to 119, wherein said peptide comprises greater than or equal to 8, 9, 10, 11, 12, 13, or 14 amino acids.~~

~~121. The method of any one of claims 116 to 120, wherein said HLA is synthetic.~~