Claims

1. A variant HLA-DRB protein comprising:

an amino acid sequence at least 95% identical to a sequence encoded by a native allele of HLA-DRB1, HLA-DRB3, HLA-DRB4, or HLA-DRB5; and

at least one amino acid residue at an amino acid position of the amino acid sequence being different than an amino acid residue at the amino acid position of the sequence encoded by the native HLA allele, wherein the amino acid position is at or near Pocket 1 of an antigen binding cleft and the variant HLA-DRB protein has altered binding affinity for at least one peptide antigen compared to a protein encoded by the native HLA allele.

2. The variant HLA-DRB protein of claim 1, wherein the amino acid position is position 85 or position 86 of the amino acid sequence.

3. The variant HLA-DRB protein of any one of claims 1-2, wherein the at least one amino acid residue at an amino acid position of the amino acid sequence is valine, methionine, or leucine.

4. A nucleic acid coding for the variant HLA-DRB protein according to any one of claims 1-3.

5. An engineered hematopoietic cell comprising the nucleic acid of claim 4.

6. Use of the variant HLA-DRB protein of any one of claims 1-3, the engineered hematopoietic cell of claim 5, or the nucleic acid of claim 4 in the manufacture of a medicament for the treatment of an autoimmune disease.

7. A method of treating a subject suffering from or at risk of developing an autoimmune disease, comprising:

identifying a susceptible HLA allele of an HLA gene within an HLA complex of the subject, wherein the susceptible HLA allele is associated with susceptibility to the autoimmune disease;

isolating a plurality of CD34+ immune cells from the subject;

modifying the HLA complex of the CD34+ immune cells to create engineered CD34+

immune cells, wherein the engineered CD34+ immune cells do not express the susceptible HLA allele, and express an engineered HLA allele, wherein a protein encoded for by the engineered HLA allele differs from a protein encoded for by the susceptible HLA allele by presence of an occlusion within a pocket of an antigen binding cleft of the protein encoded for by the engineered HLA allele, and alters binding affinity for at least one self-peptide as compared to a protein coded for by the susceptible HLA allele;

isolating a plurality of the engineered CD34+ immune cells;

administering the isolated, engineered CD34+ immune cells to the subject; and thereby treating the subject suffering from or at risk of developing the autoimmune disease.

8. The method of claim 7, wherein the HLA allele is selected from HLA-DRB1, HLA-DRB3, HLA-DRB4, and HLA-DRB5.

9. The method of claim 7, wherein the pocket is pocket 1.

10. The method of any one of claims 7-9, wherein the amino acid substitution replaces the amino acid at position 86 with an amino acid selected from valine, methionine, and leucine.

11. A method of modifying an HLA allele associated with an autoimmune disease, comprising:

identifying an HLA gene associated with an autoimmune disease;

identifying a susceptible HLA allele of the identified HLA gene, wherein the susceptible HLA allele is associated with susceptibility to the autoimmune disease;

identifying a resistant HLA allele of the identified HLA gene, wherein the resistant HLA allele is associated with resistance to the autoimmune disease;

identifying one or more target amino acid positions within a binding cleft of an HLA protein encoded for by the susceptible HLA allele, wherein the target amino acid position has a first identity and the target amino position in the HLA protein encoded by the resistant HLA allele has a different, second identity;

modifying the susceptible HLA allele to encode an HLA protein with the target amino acid position having the second identity and with altered binding affinity for at least one self-peptide as compared to biding affinity of a HLA protein encoded for by the susceptible HLA allele for the at least one self-peptide; and thereby

modifying an HLA allele associated with an autoimmune disease.

12. The method of claim 11, wherein the autoimmune disease is selected from celiac disease, Type 1 diabetes, rheumatoid arthritis, ankylosing spondylitis, and multiple sclerosis.

13. The method of any one of claims 10-11, wherein the HLA gene codes for HLA-A, HLA-B, or HLA-C.

14. A method of treating a subject suffering from or at risk of developing an autoimmune disease, comprising:

identifying a susceptible HLA allele of the subject, wherein the susceptible HLA allele is associated with susceptibility to the autoimmune disease;

isolating a plurality of CD34+ immune cells from the subject;

modifying the plurality of CD34+ immune cells to create a plurality of engineered CD34+ immune cells, wherein the engineered CD34+ immune cells do not express the susceptible HLA allele, and express an engineered HLA allele, wherein the engineered HLA allele differs from a HLA protein encoded for by the susceptible HLA allele by an identity of at least one target amino acid in an antigen binding cleft, and wherein the HLA protein encoded for by the engineered HLA allele possess altered binding affinity for at least one self-peptide as compared to a protein coded for by the susceptible HLA allele;

isolating the plurality of the engineered CD34+ immune cells; and administering the plurality of isolated, engineered CD34+ immune cells to the subject; and thereby treating the subject suffering from or at risk of developing the autoimmune disease.

15. The method of claim 14, wherein the autoimmune disease is type 1 diabetes, and the HLA allele encoding the engineered HLA protein is selected from DQB1*02:01_A57D and DQB1*03:02_A57D.

16. The method of claim 14, wherein the autoimmune disease is ankylosing spondylitis, and the HLA allele encoding the engineered HLA protein is HLA- B*27:05_D116H.

17. The method of claim 14, wherein the autoimmune disease is multiple sclerosis, and the HLA allele encoding the engineered HLA protein is selected from DRB1*15:01_F47Y, DRB1*15:01_A71R, DRB1*15:01_V86L, and DRB1*15:01_V86F.

18. The method of claim 14, wherein the autoimmune disease is celiac disease, and wherein the HLA allele encoding engineered HLA protein is selected from DQB1*02:01_K71E and DQB1*02:01_K71T.

19. The method of claim 14, wherein the autoimmune disease is neuromyelitis optica, and the HLA allele encoding the engineered HLA protein is selected from DRB1*03:01_V86L and DRB1*03:01_V86M.