Claims

1. An engineered HLA-DRB1 protein comprising:

an amino acid sequence at least 95% identical to a sequence encoded by a native allele of HLA-DRB1; 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-DRB1 allele, wherein the amino acid position is at or near Pocket 1 of an antigen binding cleft and the engineered HLA-DRB1 protein has altered binding affinity for at least one self-peptide as compared to a protein encoded by the native HLA-DRB1 allele.

2. The engineered HLA-DRB1 protein of claim 1, wherein the amino acid position is position 85 or position 86 of the amino acid sequence.

3. The engineered HLA-DRB1 protein of claim 1 or 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. The engineered HLA-DRB1 protein of claim 3, wherein the at least one amino acid residue at an amino acid position of the amino acid sequence is valine.

5. The engineered HLA-DRB1 protein of claim 3, wherein the at least one amino acid residue at an amino acid position of the amino acid sequence is methionine.

6. The engineered HLA-DRB1 protein of claim 3, wherein the at least one amino acid residue at an amino acid position of the amino acid sequence is leucine.

7. A nucleic acid coding for the engineered HLA-DRB1 protein according to any one of claims 1 to 6.

8. An engineered hematopoietic cell comprising the nucleic acid of claim 7.

9. Use of the engineered HLA-DRB1 protein of any one of claims 1 to 6, the engineered hematopoietic cell of claim 8, or the nucleic acid of claim 7 in the manufacture of a medicament for the treatment or prevention of an autoimmune disease, wherein the autoimmune disease is selected from rheumatoid arthritis, neuromyelitis optica, and multiple sclerosis.

10. Use of an engineered CD34+ immune cell in the manufacture of a medicament for the treatment or prevention of an autoimmune disease in a subject having, or at risk of developing, the autoimmune disease, wherein the autoimmune disease is selected from rheumatoid arthritis, neuromyelitis optica, and multiple sclerosis, and wherein:

the subject has a susceptible HLA-DRB1 allele associated with susceptibility to the autoimmune disease;

the engineered CD34+ immune cell expresses an engineered HLA-DRB1 protein that differs from a protein encoded by the susceptible HLA-DRB1 allele by the presence of an amino acid residue that occludes Pocket 1 of an antigen binding cleft of the engineered HLA-DRB1 protein, and has altered binding affinity for at least one self-peptide as compared to the protein encoded by the susceptible HLA-DRB1 allele; and

the engineered CD34+ immune cell is engineered from a plurality of CD34+ immune cells isolated from the subject.

11. The use of claim 10, wherein the amino acid residue that occludes Pocket 1 of the antigen binding cleft is at position 85 or position 86.

12. The use of claim 10 or 11, wherein the amino acid residue that occludes Pocket 1 of the antigen binding cleft is a valine, methionine, or leucine at position 86.

13. A method of preparing an engineered HLA-DRB1 allele for use in connection with an autoimmune disease, wherein the autoimmune disease is selected from rheumatoid arthritis, neuromyelitis optica, and multiple sclerosis, the method comprising:

identifying an HLA-DRB1 gene associated with the autoimmune disease;

identifying a susceptible HLA-DRB1 allele of the identified HLA-DRB1 gene, wherein the susceptible HLA-DRB1 allele is associated with susceptibility to the autoimmune disease;

identifying one or more target amino acids at or near Pocket 1 of an antigen binding cleft of an HLA-DRB1 protein encoded by the susceptible HLA allele; and

modifying the susceptible HLA-DRB1 allele to encode an engineered HLA-DRB1 protein wherein the one or more target amino acids are substituted with one or more different amino acids such that the engineered HLA-DRB1 protein has altered binding affinity for at least one self-peptide as compared to the binding affinity of an HLA-DRB1 protein encoded by the susceptible HLA-DRB1 allele for the at least one self-peptide.

14. Use of an engineered CD34+ immune cell in the manufacture of a medicament for the treatment or prevention of an autoimmune disease in a subject having, or at risk of developing the autoimmune disease, wherein the autoimmune disease is selected from rheumatoid arthritis, neuromyelitis optica, and multiple sclerosis, and wherein:

the engineered CD34+ immune cell expresses an engineered HLA-DRB1 protein encoded by an engineered HLA-DRB1 allele and not a protein encoded by the susceptible HLA-DRB1 allele wherein the susceptible HLA-DRB1 allele is associated with susceptibility to the autoimmune disease;

the engineered HLA-DRB1 protein differs from an HLA-DRB1 protein encoded by the susceptible HLA-DRB1 allele by at least one target amino acid at or near Pocket 1 of an antigen binding cleft, and has altered binding affinity for at least one self-peptide as compared to the HLA-DRB1 protein encoded by the susceptible HLA-DRB1 allele; and

the engineered CD34+ immune cell is engineered from a plurality of CD34+ immune cells isolated from the subject.

15. The use or method of any one of claims 9-14, wherein the autoimmune disease is multiple sclerosis.

16. The use or method of any one of claims 9-15, wherein the autoimmune disease is multiple sclerosis, and the HLA-DRB1 allele encoding the engineered HLA-DRB1 protein is selected from DRB1*15:01_F47Y, DRB1*15:01_A71R, DRB1*15:01_V86L, and DRB1*15:01_V86F.

17. The use or method of claim 16, wherein the HLA-DRB1 allele encoding the engineered HLA-DRB1 protein is DRB1*15:01_F47Y or DRB1*15:01_A71R.