

WHAT IS CLAIMED IS:

1. An antibody capable of binding, with a human major histocompatibility complex (MHC)-restricted specificity, a MHC being complexed with an HLA-restricted peptide tumor antigen or autoimmune antigen, said antibody having a binding specificity dictated by at least 4 amino acid residues in said HLA-restricted peptide such that at least 70 % reduction in binding of said antibody to said complex is observed when each of said at least 4 amino acid residues is substituted by alanine as determined by FACS of cells loaded with said HLA-restricted peptide comprising said substitution, said at least 4 amino acid residues not being anchor residues.
2. An antibody capable of binding, with a human major histocompatibility complex (MHC)-restricted specificity, a MHC being complexed with an HLA-restricted peptide antigen, said antibody having a binding specificity dictated by at least 4 amino acid residues in said HLA-restricted peptide such that at least 70 % reduction in binding of said antibody to said complex is observed when each of said at least 4 amino acid residues is substituted by alanine as determined by FACS of cells loaded with said HLA-restricted peptide comprising said substitution, said at least 4 amino acid residues not being anchor residues and further wherein the antibody does not bind HLA-restricted peptide antigens presented on normal essential tissues, wherein said HLA-restricted peptide antigen is not from LMP-2A polypeptide.
3. An antibody capable of binding, with a human major histocompatibility complex (MHC)-restricted specificity, a HLA-A2/TyrD369-377 peptide complex, said antibody having a binding specificity dictated by at least 4 amino acid residues in said TyrD369-377 peptide such that at least 70 % reduction in binding of said antibody to said complex is observed when each of said at least 4 amino acid residues is substituted by alanine as determined by FACS of cells loaded with said peptide comprising said substitution, said at least 4 amino acid residues not being anchor residues.

4. The antibody of any one of claims 1-3, wherein said at least 70 % reduction in binding is at least 90 % reduction in binding observed when at least 1 amino acid residue of said at least 4 amino acid residues comprises said substitution or wherein said at least 70 % reduction in binding is at least 90 % reduction in binding observed when each of at least 2 amino acid residues of said at least 4 amino acid residues comprise said substitutions or wherein said at least 4 amino acid residues comprise 5 amino acid residues such that at least 70 % reduction in binding of said antibody to said complex is observed when each of at least 4 amino acid residues of said 5 amino acids residues is substituted by alanine and wherein at least 30 % reduction in binding of said antibody to said complex is observed when a fifth amino acid of said 5 amino acids is substituted by alanine.
5. The antibody of any one of claims 1, 3-4, wherein said antibody does not bind to HLA-presented peptides, which are present in essential tissues as determined by FACS analysis of cells loaded with said HLA-presented peptides, said HLA-presented peptides having at least one amino acid substitution as compared to said HLA-restricted peptide antigen in an amino acid residue which is not one of said at least 4 amino acid residues.
6. An antibody capable of binding, with a human major histocompatibility complex (MHC)-restricted specificity, a MHC being complexed with an HLA-restricted peptide antigen, wherein said antibody does not bind to HLA-presented peptides, which are present in essential tissues as determined by FACS analysis of cells loaded with said HLA-presented peptides, said HLA-presented peptides having at least one amino acid substitution as compared to said HLA-restricted peptide antigen in an amino acid residue not critical for binding said peptide antigen, as determined by as determined by FACS of cells loaded with said HLA-restricted peptide comprising an alanine substitution.
7. The antibody of any one of claims 2, 4 and 6, wherein said HLA-restricted peptide antigen is not from LMP-2A polypeptide.
8. The antibody of any one of claims 1-7:

- (i) having a binding affinity below 20 nanomolar to a single chain human major histocompatibility complex (MHC) complexed with said HLA-restricted peptide antigen, as determined by surface plasmon resonance assay;
- (ii) capable of binding said HLA-restricted peptide antigen when naturally presented on cells, as determined by FACS
- (iii) not binding an *in-silico* predicted HLA-restricted peptide.

9. The antibody of any one of claims 1, 6-8, wherein said MHC is class I MHC.

10. The antibody of any one of claims 6-9, wherein said at least one amino acid substitution comprises 1-4 amino acid substitutions.

11. An isolated polynucleotide comprising a nucleic acid sequence encoding the antibody of any one of claims 1-10.

12. A method for selecting highly selective TCR-like antibody with the optimal fine specificity towards a specific MHC being complexed with an HLA-restricted peptide antigen, the method comprising:

- (a) providing an antibody capable of binding, with a human major histocompatibility complex (MHC)-restricted specificity, a MHC being complexed with an HLA-restricted peptide antigen, wherein said binding is with a predetermined affinity;
- (b) determining binding of the antibody to peptides similar to said HLA-restricted peptide antigen having been mutated with alanine/glycine/valine/leucine in amino acids other than anchor residues so as to identify amino acids which are critical for binding of said antibody to said HLA-restricted peptide;
- (c) determining binding of the antibody to *in silico*-predicted and/or validated HLA-presented peptides which are present on at least one normal essential tissue, said HLA-presented peptides comprising 1-4 amino acid substitutions as compared to said HLA-restricted peptide;

wherein said determining binding of said antibody to said peptides of (a) and (b) is by FACS analysis of cells loaded with said peptides or by functional assay, said antibody being qualified if said binding of (b) is undetectable by said FACS analysis.

13. The method of claim 12, wherein said HLA-presented peptides which are present on at least one essential tissue have at least one amino acid substitution as compared to said HLA-restricted peptide antigen in an amino acid residue not critical for binding said peptide antigen.

14. The method of any one of claims 12 or 13, further comprising determining binding of the antibody to normal cells, which do not present said HLA-restricted peptide but are positive for said HLA.

15. The method of any one of claims 12-14, wherein said predetermined affinity is below 20 nM.