CLAIMS

1. A computer-implemented method of designing an antibody that will bind to a target epitope, comprising:

a) identifying one or more hotspot residues that will each bind to a corresponding one of one or more hotspot sites on the target epitope, each hotspot residue comprising a hotspot sub-structure comprising one or more hotspot sub-structure characteristic atoms;

b) selecting from a database of antibody structures one or more candidate antibody structures, each candidate antibody structure having one or more matching residues each comprising a matching residue sub-structure comprising one or more matching residue sub-structure characteristic atoms, wherein the selection is performed such that the relative positions of the matching residue sub-structure characteristic atoms within the antibody structure and the relative positions of the hotspot sub-structure characteristic atoms when bound to the target epitope are such that at least three of the matching residue sub-structure characteristic atoms can be superimposed computationally on a corresponding at least three hotspot sub-structure characteristic atoms with a spatial deviation between each pair of superimposed characteristic atoms averaged over all pairs being less than a predetermined threshold; and

c) generating a designed antibody by modifying one of the candidate antibody structures, the modifying comprising replacing at least one of the matching residues with a different residue such that a predicted affinity between the designed antibody and the target epitope is higher than a predicted affinity between the candidate antibody structure and the target epitope or outputting one of the candidate antibody structures as a designed antibody structure in the case where each of the matching residues is already a residue of the same amino acid as the hotspot residue which the matching residue matches.

2. The method of claim 1, wherein the predetermined threshold is 2.0 Angstroms.

3. The method of claim 1 or 2, wherein in step (c) the modifying comprises replacing each of at least one of the matching residues with a residue of the same amino acid as the hotspot residue which the matching residue matches.

4. The method of any one of claims 1-3, wherein:

the alpha carbon atom of at least one of the matching residues is in one of the pairs of superimposed characteristic atoms.

5. The method of claim 4, wherein:

the pairs of superimposed characteristic atoms comprise the alpha carbon and at least one of the backbone carbon atom derived from the carboxyl group, the backbone nitrogen, the backbone oxygen, and the beta carbon of the side chain of each of at least one of the matching residues.

6. The method of claim 4, wherein:

the pairs of superimposed characteristic atoms comprise the alpha carbon and at least two of the backbone carbon atom derived from the carboxyl group, the backbone nitrogen, the backbone oxygen, and the beta carbon of the side chain of each of at least one of the matching residues.

7. The method of any one of claims 1-6, wherein:

the one or more matching residues consists of a single matching residue only.

8. The method of claim 7, wherein the at least three of the matching residue sub-structure characteristic atoms that can be superimposed on the corresponding at least three hotspot sub-structure characteristic atoms comprise the alpha atom of the matching residue and at least two of the backbone carbon derived from the carboxyl group of the matching residue, the backbone nitrogen of the matching residue, the backbone oxygen of the matching residue, and the beta carbon of the side chain of the matching residue.

9. The method of any one of claims 1-6, wherein the one or more matching residues consists of a first matching residue and a second matching residue.

10. The method of claim 9, wherein the first matching residue comprises at least two of the matching residue sub-structure characteristic atoms that can be superimposed on the corresponding hotspot sub-structure characteristic atoms and the second matching residue comprises at least one of the matching residue sub-structure characteristic atoms that can be superimposed on the corresponding hotspot sub-structure atoms.

11. The method of any one of claims 1-6, wherein the one or more matching residues consists of a first matching residue, a second matching residue and a third matching residue.

12. The method of claim 11, wherein each of the first matching residue, second matching residue and third matching residue comprises three of the matching residue sub-structure characteristic atoms that can be superimposed on the corresponding hotspot sub-structure characteristic atoms.

13. The method of claim 12, wherein said three of the matching residue sub-structure characteristic atoms comprises the alpha carbon atom, the backbone carbon atom and the backbone nitrogen atom.

14. The method of any one of claims 1-13, wherein the generating of the designed antibody further comprises iteratively swapping each of one or more of the CDR loops of the candidate antibody structure with CDR loops from a database of CDR loops to increase a predicted affinity between the candidate antibody structure and the target epitope.

15. A method of manufacturing an antibody, comprising:
designing an antibody using the method of any one of claims 1-14; and
manufacturing the antibody thus designed.