

connected to the MHC class II $\alpha 1$ domain or the MHC class II $\beta 1$ domain by a disulfide bond formed between a cysteine amino acid associated with the antigenic peptide and a cysteine amino acid of the MHC class II $\alpha 1$ domain or the MHC class II $\beta 1$ domain. In certain embodiments, the cysteine amino acid of the MHC class II $\alpha 1$ domain or the MHC class II $\beta 1$ domain is within 10 amino acids of a residue that forms a part of an MHC class II binding groove. In certain embodiments, the cysteine residue of the MHC class II $\alpha 1$ domain or the MHC class II $\beta 1$ domain is within 3 amino acids of a residue that forms a part of an MHC class II binding groove. In certain embodiments, the cysteine amino acid of the MHC class II $\alpha 1$ domain or the MHC class II $\beta 1$ domain has been introduced into the naturally occurring sequence of the MHC class II $\alpha 1$ domain or the MHC class II $\beta 1$ domain. In certain embodiments, the isolated heterodimer is for use in treating an individual diagnosed or suspected of having an autoimmune disease. In certain embodiments, the isolated heterodimer is encoded by a polynucleotide encoding the first or the second polypeptide described herein. In certain embodiments, a host cell comprises the polynucleotide. In certain embodiments, the polynucleotide is stably integrated into the genome. In certain embodiments, at least one heterodimer is conjugated to a nanoparticle to form a heterodimer-nanoparticle conjugate, wherein the nanoparticle is non-liposomal and/or has a solid core. In certain embodiments, the solid core is a gold, iron, or iron oxide core. In certain embodiments, the solid core has a diameter of less than 100 nanometers. In certain embodiments, the at least one heterodimer is covalently linked to the nanoparticle. In certain embodiments, the at least one heterodimer is covalently linked to the nanoparticle through a linker comprising polyethylene glycol (PEG). In certain embodiments, the polyethylene glycol is functionalized with maleimide. In certain embodiments, polyethylene glycol is less than 5 kD. In certain embodiments, a pharmaceutical composition comprising the heterodimer-nanoparticle conjugate is formed with a pharmaceutical excipient, stabilizer, or diluent. In certain embodiments, the isolated heterodimer or the pharmaceutical composition is for use in a method of treating an autoimmune disease or inflammatory condition. In certain embodiments, a method of treating an autoimmune disease or inflammatory condition comprises administering to an individual the isolated heterodimer-nanoparticle conjugate or the pharmaceutical composition.

[0027a] Provided herein, in another aspect, is an isolated heterodimer described herein for use in therapy.

[0027b] Provided herein, in another aspect, is a use of an isolated heterodimer described herein in the manufacture of a medicament for treating an individual diagnosed with or suspected of being afflicted with an autoimmune disease.

[0027c] Provided herein, in another aspect, is a polynucleotide encoding the first or the second

polypeptide described herein.

[0027d] Provided herein, in another aspect, is a host cell comprising the polynucleotide sequence described herein.

[0027e] Provided herein, in another aspect, is a pharmaceutical composition comprising the heterodimer-nanoparticle conjugate described herein and a pharmaceutical excipient, stabilizer, or diluent.

[0027f] Provided herein, in another aspect, is a heterodimer-nanoparticle conjugate described herein or a pharmaceutical composition described herein for use in therapy.

[0027g] Provided herein, in another aspect, is a use of a heterodimer-nanoparticle conjugate described herein or a pharmaceutical composition described herein in the manufacture of a medicament for treating an autoimmune disease or inflammatory condition.

[0028] In another aspect, described herein, is a method of preparing a heterodimer comprising a first polypeptide and a second polypeptide, wherein the first polypeptide and the second polypeptide meet at an interface, wherein the interface of the first polypeptide comprises an engineered protuberance which is positionable in an engineered cavity in the interface of the second polypeptide; and (i) the first polypeptide comprises an MHC class II $\alpha 1$ domain, an MHC class II $\alpha 2$ domain, or a combination thereof; and the second polypeptide comprises an

CLAIMS

WHAT IS CLAIMED IS:

1. An isolated heterodimer comprising at least one first polypeptide and at least one second polypeptide, wherein the first polypeptide and the second polypeptide meet at an interface, wherein the interface of the first polypeptide comprises an engineered protuberance which is positionable in an engineered cavity in the interface of the second polypeptide; and
 - (i) the first polypeptide comprises an MHC class II α 1 domain, an MHC class II α 2 domain, or a combination thereof; and the second polypeptide comprises an MHC class II β 1 domain, an MHC class II β 2 domain, or a combination thereof; or
 - (ii) the first polypeptide comprises an MHC class II β 1 domain, an MHC class II β 2 domain, or a combination thereof; and the second polypeptide comprises an MHC class II α 1 domain, an MHC class II α 2 domain, or a combination thereof.
2. The isolated heterodimer of claim 1, wherein the protuberance comprises one or more non-naturally occurring amino acid residues.
3. The isolated heterodimer of claim 1 or 2, wherein the protuberance comprises one or more amino acids selected from phenylalanine, arginine, tyrosine, tryptophan, and cysteine.
4. The isolated heterodimer of any one of claims 1 to 3, wherein the first or second polypeptide of the isolated heterodimer comprises an amino acid sequence that is at least 80% identical to the amino acid sequence set forth in **SEQ ID NO: 53**.
5. The isolated heterodimer of claim 4, wherein the first or second polypeptide of the isolated heterodimer comprises an amino acid sequence at least 80% identical to the amino acid sequence set forth in **SEQ ID NO: 54**.
6. The isolated heterodimer of claim 1, wherein the first or second polypeptide of the isolated heterodimer comprises a C_H3 domain, and the C_H3 domain comprises at least one mutation selected from the list consisting of S354C, T366W, and both S354C and T366W (EU numbering).
7. The isolated heterodimer of claim 1, wherein the cavity comprises a non-naturally occurring amino acid residue.
8. The isolated heterodimer of claims 1 or 7, wherein the cavity comprises one or more amino acids selected from alanine, serine, threonine, valine, and cysteine.

9. The isolated heterodimer of any one of claims 1, 7, or 8, wherein the first or second polypeptide of the isolated heterodimer comprises an amino acid sequence that is at least 80% identical to the amino acid sequence set forth in **SEQ ID NO: 51**.
10. The isolated heterodimer of claim 9, wherein the first or second polypeptide of the isolated heterodimer comprises an amino acid sequence at least 80% identical to the amino acid sequence set forth in **SEQ ID NO: 52**.
11. The isolated heterodimer of claim 1, wherein the first or second polypeptide of the isolated heterodimer comprises a C_H3 domain, and the C_H3 domain comprises at least one mutation selected from the list consisting of Y349C, T366S, L368A, Y407V (EU numbering), and combinations thereof.
12. The isolated heterodimer of any one of claims 1 to 11, wherein one or both of the first polypeptide or the second polypeptide does not comprise a heterologous dimerization domain.
13. The isolated heterodimer of any one of claims 1 to 11, wherein one or both of the first polypeptide or the second polypeptide does not comprise a leucine zipper.
14. The isolated heterodimer of any one of claims 1 to 11, wherein one or both of the first polypeptide or the second polypeptide does not comprise a site specific biotinylation site.
15. The isolated heterodimer of any one of claims 1 to 14, further comprising an autoimmune disease-relevant antigen.
16. The isolated heterodimer of claim 15, wherein the disease-relevant antigen comprises a polypeptide at least 11 amino acids in length.
17. The isolated heterodimer of claim 15 or 16, wherein the autoimmune disease-relevant antigen is connected to the MHC class II α 1 domain or the MHC class II β 1 domain by a flexible linker.
18. The isolated heterodimer of any one of claims claim 15 to 17, wherein the antigen is covalently connected to the MHC class II α 1 domain or the MHC class II β 1 domain by a disulfide bond formed between a cysteine amino acid associated with the antigenic peptide and a cysteine amino acid of the MHC class II α 1 domain or the MHC class II β 1 domain.
19. The isolated heterodimer of claim 18, wherein the cysteine amino acid of the MHC class II α 1 domain or the MHC class II β 1 domain is within 10 amino acids of a residue that forms a part of an MHC class II binding groove.
20. The isolated heterodimer of claim 19, wherein the cysteine residue of the MHC class II α 1 domain or the MHC class II β 1 domain is within 3 amino acids of a residue that forms a part of the MHC class II binding groove.

21. The isolated heterodimer of any one of claims 18 to 20, wherein the cysteine amino acid of the MHC class II α 1 domain or the MHC class II β 1 domain has been introduced into the naturally occurring sequence of the MHC class II α 1 domain or the MHC class II β 1 domain.
22. The isolated heterodimer of any one of claims 1 to 21 for use in therapy.
23. Use of the isolated heterodimer of any one of claims 1 to 21 in the manufacture of a medicament for treating an individual diagnosed with or suspected of being afflicted with an autoimmune disease.
24. A polynucleotide encoding the first or the second polypeptide of any one of claims 1 to 21.
25. A host cell comprising the polynucleotide sequence of claim 24.
26. The host cell of claim 25, wherein the polynucleotide is stably integrated into the genome.
27. The isolated heterodimer of any one of claims 1 to 21, wherein at least one heterodimer is conjugated to a nanoparticle to form a heterodimer-nanoparticle conjugate, wherein the nanoparticle is non-liposomal and/or has a solid core.
28. The heterodimer-nanoparticle conjugate of claim 27, wherein the solid core is a gold, iron, or iron oxide core.
29. The heterodimer-nanoparticle conjugate of claims 27 or 28, wherein the solid core has a diameter of less than 100 nanometers.
30. The heterodimer-nanoparticle conjugate of any one of claims 27 to 29, wherein the at least one heterodimer is covalently linked to the nanoparticle.
31. The heterodimer-nanoparticle conjugate of claim 30, wherein the at least one heterodimer is covalently linked to the nanoparticle through a linker comprising polyethylene glycol (PEG).
32. The heterodimer-nanoparticle conjugate of claim 31, wherein the polyethylene glycol is functionalized with maleimide.
33. The heterodimer-nanoparticle conjugate of claim 32, wherein the polyethylene glycol is less than 5 kD.
34. A pharmaceutical composition comprising the heterodimer-nanoparticle conjugate of any one of claims 27 to 33, and a pharmaceutical excipient, stabilizer, or diluent.
35. A heterodimer-nanoparticle conjugate of any one of claims 27 to 33 or the pharmaceutical composition of claim 34 for use in therapy.

36. Use of a heterodimer-nanoparticle conjugate of any one of claims 27 to 33 or the pharmaceutical composition of claim 34 in the manufacture of a medicament for treating an autoimmune disease or inflammatory condition.

37. A method of preparing a heterodimer comprising a first polypeptide and a second polypeptide, wherein

the first polypeptide and the second polypeptide meet at an interface, wherein the interface of the first polypeptide comprises an engineered protuberance which is positionable in an engineered cavity in the interface of the second polypeptide; and

- (i) the first polypeptide comprises an MHC class II α 1 domain, an MHC class II α 2 domain, or a combination thereof; and the second polypeptide comprises an MHC class II β 1 domain, an MHC class II β 2 domain, or a combination thereof; or
- (ii) the first polypeptide comprises an MHC class II β 1 domain, an MHC class II β 2 domain, or a combination thereof; and the second polypeptide comprises an MHC class II α 1 domain, an MHC class II α 2 domain, or a combination thereof;

comprising the steps of:

- (iii) culturing a host cell comprising a nucleic acid encoding the first polypeptide and second polypeptide including the interfaces thereof, wherein the nucleic acid encoding the interface of the first polypeptide has been altered from nucleic acid encoding an original interface of the first polypeptide to encode the protuberance, the nucleic acid encoding the interface of the second polypeptide has been altered from nucleic acid encoding an original interface of the second polypeptide to encode the cavity, or both, and wherein the culturing is such that the first polypeptide and second polypeptide are expressed; and

- (iv) recovering and purifying the heterodimer from the host cell culture.

38. A method of preparing a heterodimer comprising a first polypeptide and a second polypeptide, wherein

the first polypeptide and the second polypeptide meet at an interface, wherein the interface of the first polypeptide comprises an engineered protuberance which is positionable in an engineered cavity in the interface of the second polypeptide; and

- (i) the first polypeptide comprises an MHC class II α 1 domain, an MHC class II α 2 domain, or a combination thereof; and the second polypeptide comprises an MHC class II β 1 domain, an MHC class II β 2 domain, or a combination thereof; or
- (ii) the first polypeptide comprises an MHC class II β 1 domain, an MHC class II β 2 domain, or a combination thereof; and the second polypeptide comprises an MHC class II α 1 domain, an MHC class II α 2 domain, or a combination thereof;

comprising the steps of:

- (iii) culturing a first host cell comprising a nucleic acid encoding the first polypeptide;
- (iv) culturing a second host cell comprising a nucleic acid encoding the second polypeptide;
- (v) recovering the first and second polypeptides from the host cell cultures; and
- (vi) forming the heterodimer by incubating the first and second polypeptides together;

wherein the nucleic acid encoding the interface of the first polypeptide has been altered from nucleic acid encoding an original interface of the first polypeptide to encode the protuberance, the nucleic acid encoding the interface of the second polypeptide has been altered from nucleic acid encoding an original interface of the second polypeptide to encode the cavity, or both.

- 39. The method of claims 37 or 38, wherein the nucleic acid encoding the first polypeptide and the second polypeptide is stably integrated into the genome of the host cell.
- 40. The method of claim 37, wherein the host cell comprises a Chinese hamster ovary (CHO) cell.
- 41. The method of claim 38, wherein the first and second host cells comprise a Chinese hamster ovary (CHO) cell.
- 42. The method of any one of claims 37 to 41, wherein recovering the polypeptides from the host cell culture or host cell cultures comprises applying a liquid comprising the heterodimer to liquid chromatography column.
- 43. The method of claim 42, wherein the liquid chromatography column comprises Protein A, Protein G, Protein L, or any combination thereof.