

WHAT IS CLAIMED IS:

1. A multimeric binding molecule comprising two, five, or six bivalent binding units or variants or fragments thereof,
 wherein each binding unit comprises two IgA or IgM heavy chain constant regions or
 5 multimerizing fragments or variants thereof, each associated with a binding domain,
 wherein three to twelve of the binding domains are programmed cell death protein 1 (PD-1)-binding domains that specifically and agonistically bind to PD-1,
 wherein the binding molecule can activate PD-1-mediated signal transduction in a cell at a higher potency than an equivalent amount of a bivalent IgG antibody or fragment thereof
 10 comprising two of the same PD-1-binding domains, which also specifically binds to and agonizes PD-1.
2. The multimeric binding molecule of claim 1, wherein the three to twelve PD-1-binding domains comprise a heavy chain variable region (VH) and a light chain variable region (VL), wherein:
 - 15 (a) the VH and VL comprise six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL of SEQ ID NO: 1 and SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, SEQ
 20 ID NO: 7 and SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14, SEQ ID NO: 25 and SEQ ID NO: 26, SEQ ID NO: 27 and SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, SEQ ID NO: 31 and SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34, or SEQ ID NO: 49 and SEQ ID NO: 50, respectively with zero,
 25 one, or two single amino acid substitutions in one or more of the HCDRs or LCDRs;
 - (b) the VH and VL comprise six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs
 30 of an antibody comprising the VH of any one of SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and the VL of any one of SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, or SEQ

ID NO: 22 with zero, one, or two single amino acid substitutions in one or more of the HCDRs or LCDRs;

- (c) the VH and VL comprise amino acid sequences at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 1 and SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14, SEQ ID NO: 25 and SEQ ID NO: 26, SEQ ID NO: 27 and SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, SEQ ID NO: 31 and SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34, or SEQ ID NO: 49 and SEQ ID NO: 50, respectively; or
- (d) the VH comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to of any one of SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and the VL comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to of any one of SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, or SEQ ID NO: 22.

3. The multimeric binding molecule of claim 2, wherein the VH and VL comprise six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the CDRs of an antibody comprising the VH and VL of SEQ ID NO: 1 and SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, SEQ ID NO: 13 and SEQ ID NO: 14, and SEQ ID NO: 25 and SEQ ID NO: 26, respectively with zero, one, or two single amino acid substitutions in one or more of the HCDRs or LCDRs.

4. The multimeric binding molecule of claim 1, which is a dimeric binding molecule comprising two bivalent IgA or IgA-like binding units and a J chain or functional fragment or variant thereof, wherein each binding unit comprises two IgA heavy chain constant regions or multimerizing fragments or variants thereof, each comprising an IgA Cα3 domain and an IgA tailpiece domain.

5. The multimeric binding molecule of claim 4, wherein:

- (a) each IgA heavy chain constant region or multimerizing fragment or variant thereof further comprises a C α 1 domain, a C α 2 domain, an IgA hinge region, or any combination thereof;
- (b) the IgA heavy chain constant regions or multimerizing fragments thereof are human IgA constant regions; and/or
- (c) each binding unit comprises two IgA heavy chains each comprising a VH situated amino terminal to the IgA constant region or multimerizing fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.
6. The multimeric binding molecule of claim 1, which is a pentameric or a hexameric binding molecule comprising five or six bivalent IgM binding units, respectively, wherein each binding unit comprises two IgM heavy chain constant regions or multimerizing fragments thereof each associated with a PD-1-binding domain, wherein each IgM heavy chain constant region comprises an IgM C μ 4 and IgM tailpiece domain.
7. The multimeric binding molecule of claim 6, wherein:
- (a) the IgM heavy chain constant regions or fragments or variants thereof each further comprise a C μ 1 domain, a C μ 2 domain, a C μ 3 domain, or any combination thereof;
- (b) the IgM heavy chain constant region is a human IgM constant region.
- (c) each binding unit comprises two IgM heavy chains each comprising a VH situated amino terminal to the IgM constant region or fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.
8. The multimeric binding molecule of claim 6, wherein the IgM constant region comprises:
- (a) SEQ ID NO: 35, SEQ ID NO: 36, or a multimerizing fragment thereof;
- (b) a substitution relative to a wild-type human IgM constant region at position 310, 311, 313, and/or 315 of SEQ ID NO: 35 or SEQ ID NO: 36; or

- (c) two or more substitutions relative to a wild-type human IgM constant region at positions 46, 209, 272, or 440 of SEQ ID NO: 35 or SEQ ID NO: 36.

9. The multimeric binding molecule of claim 6, which is pentameric, and further comprises a J-chain or functional fragment or variant thereof.

- 5 10. The multimeric binding molecule of claim 9, wherein the J-chain or functional fragment or variant thereof is a variant J-chain comprising one or more single amino acid substitutions, deletions, or insertions relative to a wild-type J-chain that can affect serum half-life of the multimeric binding molecule; and wherein the multimeric binding molecule comprising the variant J-chain exhibits an increased serum half-life upon administration to an
10 animal relative to a reference multimeric binding molecule that is identical except for the one or more single amino acid substitutions, deletions, or insertions, and is administered in the same way to the same animal species.

11. The multimeric binding molecule of claim 9, wherein the J-chain or functional fragment thereof comprises:

- 15 (a) an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the mature wild-type human J-chain (SEQ ID NO: 41);
- (b) an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the mature wild-type human J-chain (SEQ ID NO: 41), wherein
20 the amino acid corresponding to Y102 of SEQ ID NO: 41 is substituted with alanine (A);
- (c) an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the mature wild-type human J-chain (SEQ ID NO: 41), wherein the J-chain is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 42; or
- 25 (d) an amino acid substitution at the amino acid position corresponding to amino acid N49, amino acid S51, or both N49 and S51 of the mature human J-chain (SEQ ID NO: 41), wherein a single amino acid substitution corresponding to position S51 of SEQ ID NO: 41 is not a threonine (T) substitution.

12. The multimeric binding molecule of claim 9, wherein the J-chain or functional fragment or variant thereof further comprises a heterologous polypeptide, wherein the heterologous polypeptide is fused to the J-chain or functional fragment or variant thereof via a peptide linker comprising at least 5 amino acids, but no more than 25 amino acids.

5 13. The multimeric binding molecule of claim 12, wherein the heterologous polypeptide is fused to the N-terminus of the J-chain or fragment or variant thereof, the C-terminus of the J-chain or fragment or variant thereof, or to both the N-terminus and C-terminus of the J-chain or fragment or variant thereof.

10 14. The multimeric binding molecule of claim 12, wherein the heterologous polypeptide comprises an antigen binding domain, and wherein:

- (a) the antigen binding domain of the heterologous polypeptide is an antibody or antigen-binding fragment thereof;
- (b) the antigen binding domain of the heterologous polypeptide is an antigen-binding fragment of an antibody, and the antigen-binding fragment comprises an Fab fragment, an Fab' fragment, an F(ab')₂ fragment, an Fd fragment, an Fv fragment, a single-chain Fv (scFv) fragment, a disulfide-linked Fv (sdFv) fragment, or any combination thereof;
- (c) the antigen binding domain of the heterologous polypeptide is an antigen-binding fragment of an antibody, and the antigen-binding fragment is a scFv fragment; and/or
- (d) the antigen binding domain of the heterologous polypeptide is an antigen-binding fragment of an antibody, and the antigen binding domain binds ICOS Ligand (ICOSLG), ICOS (CD278), Interleukin 6 (IL6), CD28, CD3, CD80, CD86, Tumor Necrosis Factor Alpha (TNFα), or Fibroblast Activation Protein (FAP).

15. A composition comprising the multimeric binding molecule of any one of claims 1 to 14.

16. A polynucleotide comprising a nucleic acid sequence that encodes a polypeptide subunit of the binding molecule of any one of claims 1 to 14.

17. The polynucleotide of claim 16, wherein the polypeptide subunit comprises an IgM heavy chain constant region and at least an antibody VH portion of the PD-1-binding domain of the multimeric binding molecule; or comprises a light chain constant region and an antibody VL portion of the PD-1-binding domain of the multimeric binding molecule.
- 5 18. A composition comprising a polynucleotide comprising a nucleic acid sequence that encodes an IgM heavy chain constant region and at least an antibody VH portion of the PD-1-binding domain of the multimeric binding molecule of any one of claims 1 to 14, and a polynucleotide comprising a nucleic acid sequence that encodes a light chain constant region and an antibody VL portion of the PD-1-binding domain of the multimeric
10 binding molecule of any one of claims 1 to 14, wherein the polynucleotides are on separate vectors or on a single vector.
19. The composition of claim 18, further comprising a polynucleotide comprising a nucleic acid sequence encoding a J chain, or a functional fragment thereof, or a functional variant thereof.
- 15 20. The vector or the vectors of claim 19.
21. A host cell comprising the composition of claim 18, wherein the host cell can express the binding molecule, or a subunit thereof.
22. A method of producing the binding molecule, comprising culturing the host cell of claim 21, and recovering the binding molecule.
- 20 23. A method for treating an autoimmune disorder, an inflammatory disorder, or a combination thereof in a subject in need of treatment comprising administering to the subject an effective amount of the multimeric binding molecule of any one of claims 1 to 14, wherein the multimeric binding molecule exhibits greater potency than an equivalent amount of a monomeric or dimeric binding molecule binding to the same binding partner.
- 25 24. A method for preventing transplantation rejection in a subject, comprising administering to the subject an effective amount of the multimeric binding molecule of any one of claims 1 to 14, wherein the multimeric binding molecule exhibits greater potency than an equivalent amount of a monomeric or dimeric binding molecule binding to the same binding partner, and wherein the subject is a transplantation recipient.
- 30 25. The method of claim 23, wherein the subject is human.