

fusions, however, a limited as an IgG fusion protein can only be expressed as a monomer or a dimer, limiting efficacy in some situations. Indeed, monomeric forms of the TNF receptor Fc fusion protein had greatly reduced TNF α inhibitory activity as compared to the dimer (Pepel, K., *et al*, *J. Exp. Med.* 174:1483-1489 (1991)).

[0005] Many reports have described polymerized therapeutic protein-Fc fusions through a variety of methods. In one report, IgG Fc regions were engineered to facilitate hexamerization of a malaria antigen-IgG fusion, but effector function of the IgG fusion portions were altered, and the molecules were not immunogenic when used to immunize animals, in contrast to the corresponding monomeric fusion proteins (Mekhaie, DN, *et al.*, *Scientific Reports* 1, Doi: 10.1038/srep00124 (2011)). In another study, the human PD-L1 ectodomain was fused to wild-type human IgM constant region and expressed either with or without human J-chain and was tested in *in vitro* flow cytometry and plate-based immunoassays, but the ability of the constructs to induce signal transduction in PD-1-expressing cells was not tested (Ammann, JU., *et al*, *Eur. J. Immunol* 42:1354-1356 (2012)).

[0006] There remains a need for higher avidity Fc fusion therapeutics that maintain the stability and serum half-life characteristics of IgG Fc fusion proteins.

SUMMARY

[0007] This disclosure provides a multimeric binding molecule that includes two, five, or six bivalent binding units or variants or fragments thereof where each binding unit includes two IgA or IgM heavy chain constant regions or multimerizing fragments or variants thereof, each fused to a binding polypeptide or fragment thereof that specifically binds to a binding partner expressed on the surface of a cell, where the binding polypeptide is not an antibody or antigen-binding fragment of an antibody, and where binding of the binding polypeptide to the binding partner modulates signal transduction in the cell.

[0007a] In one aspect, the present disclosure provides a multimeric binding molecule comprising five, six, or two bivalent binding units or variants or fragments thereof, wherein each binding unit comprises two IgM or IgA heavy chain constant regions or multimerizing fragments or variants thereof, each fused to a binding polypeptide or fragment thereof that specifically binds to a binding partner expressed on the surface of a cell, wherein the binding polypeptide is not an antibody or antigen-binding fragment of an antibody, and wherein binding of the binding polypeptide to the binding partner modulates

signal transduction in the cell; wherein at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or twelve of the binding polypeptides bind to and modulate signal transduction of the same binding partner; and wherein the binding molecule can induce or inhibit signal transduction in the cell at a higher potency than an equivalent amount of a monovalent or divalent binding molecule with one or two binding polypeptides binding to the same binding partner.

[0007b] In another aspect, the present disclosure provides a multimeric binding molecule comprising five, six, or two bivalent binding units or variants or fragments thereof, wherein each binding unit comprises two IgM or IgA heavy chain constant regions or multimerizing fragments or variants thereof, each fused to binding polypeptide, wherein at least three of the binding polypeptides comprise a receptor ectodomain that specifically binds to a binding partner comprising a ligand or receptor-binding fragment thereof, wherein the receptor ectodomain is not an antibody or antigen-binding fragment of an antibody, and wherein binding of the receptor ectodomain to the ligand can modulate signal transduction in a cell that expresses the receptor; wherein at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or twelve of the receptor ectodomains bind to the same ligand; and wherein the binding molecule can modulate signal transduction at a higher potency than an equivalent amount of a monomeric or dimeric binding molecule with one or two receptor ectodomains binding to the same ligand.

[0007c] In certain examples at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or twelve of the binding polypeptides bind to and modulate signal transduction of the same binding partner. Moreover, in certain examples the binding molecule can induce or inhibit signal transduction in the cell at a higher potency than an equivalent amount of a monovalent or divalent binding molecule with one or two binding polypeptides binding to the same binding partner.

[0008] This disclosure further provides a multimeric binding molecule that includes two, five, or six bivalent binding units or variants or fragments thereof where each binding unit includes two IgA or IgM heavy chain constant regions or multimerizing fragments or variants thereof, each fused to binding polypeptide, where at least three of the binding polypeptides include a receptor ectodomain that specifically binds to a binding partner that includes a ligand or receptor-binding fragment thereof, where the receptor ectodomain is not an antibody or antigen-binding fragment of an antibody, and where binding of the

receptor ectodomain to the ligand can modulate signal transduction in a cell that expresses the receptor. In certain examples at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or twelve of the receptor ectodomains bind to the same ligand. Moreover, in certain examples the binding molecule can modulate signal transduction at a higher potency than an equivalent amount of a monomeric or dimeric binding molecule with one or two receptor ectodomains binding to the same ligand.

[0009] In certain of the binding multimeric binding molecules provided by the disclosure, each binding unit includes two IgA heavy chain constant regions or multimerizing fragments or variants thereof that each include an IgA C α 3 domain and an IgA tailpiece domain and where the multimeric binding molecule further includes a J-chain or functional fragment or variant thereof. In certain examples, each IgA heavy chain constant region or multimerizing fragment or variant thereof further includes an IgA C α 2 domain situated N-terminal to the IgA C α 3 and IgA tailpiece domains. For example, the heavy chain constant regions of the multimeric binding molecule can include amino acids 125 to 353 of SEQ ID NO: 24, or amino acids 113 to 340 of SEQ ID NO: 25. In certain examples, each IgA heavy chain constant region or multimerizing fragment or variant thereof further includes an IgA hinge region situated N-terminal to the IgA C α 2 domain. For example, the heavy chain constant regions of the multimeric binding molecule can include amino acids 102 to 353 of SEQ ID NO: 24, or amino acids 102 to 340 of SEQ ID NO: 25.

[0010] In certain of the binding multimeric binding molecules provided by the disclosure, each binding unit includes two IgM heavy chain constant regions or multimerizing fragments or variants thereof that each include an IgM C μ 4 domain and an IgM tailpiece domain. In certain examples, each IgM heavy chain constant region or multimerizing fragment or variant thereof further includes an IgM C μ 3 domain situated N-terminal to the IgM C μ 4 and IgM tailpiece domains. In certain examples, each IgM heavy chain constant region or multimerizing fragment or variant thereof further includes an IgM C μ 2 domain situated N-terminal to the IgM C μ 3 domain. For example, the heavy chain constant regions of the multimeric binding molecule can include the amino acid sequence SEQ ID NO: 3. In other examples, each IgM heavy chain constant region or multimerizing fragment or variant thereof includes the amino acid sequence SEQ ID NO: 4, which confers upon the multimeric binding molecule reduced complement-dependent cytotoxicity (CDC) activity relative to a corresponding binding molecule that includes the wild type multimerizing fragment of the human IgM constant region of SEQ ID NO: 3. In certain examples where

each IgM heavy chain constant region or multimerizing fragment or variant thereof includes an IgM C μ 3 domain situated N-terminal to the IgM C μ 4 and IgM tailpiece domains, each IgM heavy chain constant region or multimerizing fragment or variant thereof further includes an IgG hinge region or functional variant thereof situated N-terminal to the IgM C μ 3 domain. In certain examples the IgG hinge region is a variant human IgG1 hinge region fused to a multimerizing fragment of the human IgM constant region that includes the C μ 3, C μ 4, and TP domains. For example, the multimerizing hinge-IgM constant region fragment can include the amino acid sequence SEQ ID NO: 6, or the amino acid sequence SEQ ID NO: 7, the latter sequence including a C μ 3 region that confers the binding molecules with reduced CDC activity relative to a corresponding binding molecule that includes the multimerizing hinge-IgM fragment of SEQ ID NO: 6.

[0011] In certain examples an IgM-Fc-based multimeric binding molecule provided by this disclosure is pentameric and further includes a J-chain or functional fragment or variant thereof. The J-chain or functional fragment or variant thereof is a variant J-chain can include one or more single amino acid substitutions, deletions, or insertions relative to a wild-type J-chain that can, *e.g.*, affect serum half-life of the multimeric binding molecule. For example, in certain examples, the multimeric binding molecule exhibits an increased serum half-life upon administration to an 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. In certain examples, the J-chain or functional fragment or variant thereof includes an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the wild-type human J-chain (SEQ ID NO: 15). In certain examples, the amino acid corresponding to Y102 of SEQ ID NO: 15 is substituted with alanine (A), serine (S), or arginine (R). In certain examples, the amino acid corresponding to Y102 of SEQ ID NO: 15 is substituted with alanine (A). In certain examples, the J-chain is a variant human J-chain that includes the amino acid sequence SEQ ID NO: 16. In certain examples the J-chain or functional fragment thereof includes an amino acid substitution at the amino acid position corresponding to amino acid N49, amino acid S51, or both N49 and S51 of the human J-chain (SEQ ID NO: 15), provided that the single amino acid substitution corresponding to position S51 of SEQ ID NO: 15 is not a threonine (T) substitution. In certain examples, the position corresponding to N49 of SEQ ID NO: 15 is substituted with alanine (A), glycine (G), threonine (T), serine (S) or aspartic acid (D). In certain examples, the position corresponding to N49 of SEQ ID NO: 15 is substituted with alanine (A). In

certain examples, the J-chain is a variant human J-chain and includes the amino acid sequence SEQ ID NO: 17. In certain examples, the position corresponding to S51 of SEQ ID NO: 15 is substituted with alanine (A) or glycine (G). In certain examples, the position corresponding to S51 of SEQ ID NO: 15 is substituted with alanine (A). In certain examples, the J-chain is a variant human J-chain and includes the amino acid sequence SEQ ID NO: 18.

[0012] In certain examples where a multimeric binding molecule provided by this disclosure includes a J-chain or functional fragment or variant thereof, the J-chain or functional fragment or variant thereof can further include a heterologous polypeptide, where the heterologous polypeptide is directly or indirectly fused to the J-chain or functional fragment or variant thereof, e.g., via a peptide linker that can include at least 5 amino acids, but no more than 25 amino acids. In certain examples the peptide linker consists of GGGGS (SEQ ID NO: 19), GGGGSGGGGS (SEQ ID NO: 20), GGGGSGGGGSGGGGS (SEQ ID NO: 21), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 22), or GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 23). In certain examples, the heterologous polypeptide can be 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 identical or non-identical heterologous polypeptides can be to both the N-terminus and C-terminus of the J-chain or fragment or variant thereof. In certain examples, the heterologous polypeptide can influence the absorption, distribution, metabolism and/or excretion (ADME) of the multimeric binding molecule. In certain examples, the heterologous polypeptide can include an antigen binding domain, e.g., an antibody or antigen-binding fragment thereof, where the antigen-binding fragment can be a Fab fragment, a 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. In certain examples, the antigen-binding fragment is a scFv fragment.

[0013] In certain examples an IgA-Fc-based binding molecule as provide herein can include four identical binding polypeptides. In certain examples an IgM-Fc-based binding molecule as provided herein can be pentameric and can include ten identical binding polypeptides. In certain examples an IgM-Fc-based binding molecule as provided herein can be pentameric and can include twelve identical binding polypeptides.

[0014] In certain of the binding multimeric binding molecules provided by the disclosure, each binding polypeptide is a ligand or receptor-binding fragment thereof, a cytokine or receptor-binding fragment thereof, a growth factor or receptor binding fragment thereof, a

neurotransmitter or receptor binding fragment thereof, a peptide or protein hormone or receptor binding fragment thereof, an immune checkpoint modulator ligand or receptor-binding fragment thereof, or a receptor-binding fragment of an extracellular matrix protein. The ligand or receptor-binding fragment thereof can include, but is not limited to, a chemokine, a complement protein, a fibroblast growth factor (FGF) family ligand, an immune checkpoint modulator ligand, an epidermal growth factor (EGF), an interferon, a tumor necrosis factor superfamily (TNFSF) ligand, a vascular endothelial growth factor (VEGF) family ligand, a transforming growth factor- β superfamily (TGF β sf) ligand, any receptor-binding fragment thereof, or any combination thereof. In certain examples where the binding polypeptide includes a TNFSF ligand or receptor-binding fragment thereof, the TNFSF ligand can include, but is not limited to, TRAIL, OX40 ligand, CD40 ligand, a glucocorticoid-induced tumor necrosis factor receptor ligand (GITRL), 4-1BB ligand, any receptor binding fragment thereof, or any combination thereof. In certain examples where the binding polypeptide includes an immune checkpoint modulator ligand protein or receptor-binding fragment thereof, the immune checkpoint modulator protein can include CD86 or a receptor-binding fragment thereof, CD80 or a receptor-binding fragment thereof, PD-L1 or a receptor-binding fragment thereof, or any combination thereof.

[0015] In an exemplary example, the binding polypeptide includes a receptor-binding fragment of human PD-L1, e.g., amino acids 19 to 127 of SEQ ID NO: 8, which contains the V-type domain of human PD-L1, or SEQ ID NO: 9, which contains the V-type and C2-type domains of human PD-L1. In an exemplary example, a multimeric binding molecule provided by the disclosure includes ten or twelve copies of a polypeptide including the amino acid sequence SEQ ID NO: 11 or SEQ ID NO: 13 and can further include a variant J-chain including the amino acid sequence SEQ ID NO: 16. A binding molecule according to this exemplary example can be an agonist of PD-1.

[0016] In certain examples, the binding partner can be a cell-surface receptor protein or an immune checkpoint modulator.

[0017] In certain examples where the binding polypeptide includes a receptor ectodomain, the binding polypeptide can include, but is not limited to, a ligand-binding fragment of a tumor necrosis factor superfamily receptor (TNFrSF), a ligand-binding fragment of an immune checkpoint modulator receptor, ligand-binding fragment of a TGF β receptor, or any combination thereof. For example, a TNFrSF receptor fragment can include, but is not limited to, a ligand-binding fragment of death domain containing receptor-4 (DR4), death

domain containing receptor-5 (DR5), OX-40, CD40, 4-1BB, glucocorticoid-induced tumor necrosis factor receptor (GITR), or any combination thereof. As a further example, an immune checkpoint modulator receptor ectodomain can include, but is not limited to a ligand-binding fragment of PD-1, a ligand-binding fragment of CTLA4, a ligand-binding fragment of LAG3, a ligand-binding fragment of CD28, a ligand-binding fragment of immunoglobulin-like domain containing receptor 2 (ILDR2), a ligand-binding fragment of T-cell immunoglobulin mucin family member 3 (TIM-3), or any combination thereof. As a further example, a TGF β receptor can include, but is not limited to a ligand binding fragment of a TGF β R-1, a TGF β R-2, a TGF β R3, or any combination thereof.

[0018] In another aspect, the disclosure further provides an isolated polynucleotide that includes a nucleic acid sequence that encodes a subunit of a multimeric binding molecule as provided herein, where each subunit includes an IgA or IgM heavy chain constant region or multimerizing fragment or variant thereof fused to a binding polypeptide or fragment thereof that specifically binds to a binding partner, or a receptor ectodomain that specifically binds to a ligand. Further disclosed in another aspect is a vector that includes the provided polynucleotide. In a further aspect, the present disclosure provides a host cell that includes the provided vector or polynucleotide. In certain examples, the provided host cell can further include an isolated polynucleotide that includes a nucleic acid sequence encoding a J-chain or functional fragment or variant thereof as provided by the disclosure.

[0018a] In a further aspect, the present disclosure provides the multimeric binding molecule as described herein for use in therapy, 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.

[0018b] In a further aspect, the present disclosure provides the use of the multimeric binding molecule as described herein in the manufacture of a medicament for treating an autoimmune disorder, an inflammatory disorder, or a combination thereof in a subject in need of treatment, 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.

[0018c] In a further aspect, the present disclosure provides the use of the multimeric binding molecule as described herein in the manufacture of a medicament for preventing transplantation rejection in a transplantation recipient, 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.

[0019] The disclosure further provides a method for treating an autoimmune disorder, an inflammatory disorder, or a combination thereof in a subject in need of treatment where the method includes administering to the subject an effective amount of a multimeric binding molecule as provided herein, where the multimeric binding molecule exhibits greater potency than an equivalent amount of a monomeric or dimeric binding molecule binding to the same binding partner.

[0020] The disclosure further provides a method for preventing transplantation rejection in a transplantation recipient, where the method includes administering to the subject an effective amount of the multimeric binding molecule as provided herein, where the multimeric binding molecule exhibits greater potency than an equivalent amount of a monomeric or dimeric binding molecule binding to the same binding partner.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0021] **FIGURE 1A** shows a prototype hexameric binding molecule that has six IgM-derived binding units each having two IgM-derived heavy chain fragments that include a C μ 2 domain, a C μ 3 domain, and a C μ 4-tp domain, where the IgM derived heavy chain fragments are fused to the C-terminus of a ligand or receptor binding polypeptide.

[0022] **FIGURE 1B** shows a prototype pentameric binding molecule that has five IgM-derived binding units each having two IgM-derived heavy chain fragments that include a C μ 2 domain, a C μ 3 domain, and a C μ 4-tp domain, where the IgM derived heavy chain fragments are fused to the C-terminus of binding polypeptide, and where the pentameric binding molecule further includes a modified J-chain bearing optional N-and C-terminal fusions of heterologous polypeptides, *e.g.*, scFv antibody binding domains.

[0023] **FIGURE 2** shows a prototype pentameric binding molecule has five IgM-derived binding units each having two IgM-derived heavy chain fragments that have a C μ 2 domain, a C μ 3 domain, and a C μ 4-tp domain, where the IgM derived heavy chain fragments are fused to the C-terminus of binding polypeptide, where the binding polypeptides are receptor ectodomains, and where the pentameric binding molecule further includes a modified J-chain bearing optional N-and C-terminal fusions of heterologous polypeptides, *e.g.*, scFv antibody binding domains.

[0024] **FIGURE 3A-C** shows the structures of the PD-L1 binding molecules produced according to Example 1. **FIGURE 3A:** PD-L1-IgM; **FIGURE 3B:** PD-L1-H-IgM; **FIGURE 3C:** PD-L1-Fc.

[0025] **FIGURE 4** is a graph showing the ability of various PD-L1 binding molecules to stimulate PD-1 activity in reporter Jurkat T-cells.

WHAT IS CLAIMED IS:

1. A multimeric binding molecule comprising five, six, or two bivalent binding units or variants or fragments thereof,

wherein each binding unit comprises two IgM or IgA heavy chain constant regions or multimerizing fragments or variants thereof, each fused to a binding polypeptide or fragment thereof that specifically binds to a binding partner expressed on the surface of a cell, wherein the binding polypeptide is not an antibody or antigen-binding fragment of an antibody, and wherein binding of the binding polypeptide to the binding partner modulates signal transduction in the cell;

wherein at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or twelve of the binding polypeptides bind to and modulate signal transduction of the same binding partner; and

wherein the binding molecule can induce or inhibit signal transduction in the cell at a higher potency than an equivalent amount of a monovalent or divalent binding molecule with one or two binding polypeptides binding to the same binding partner.

2. A multimeric binding molecule comprising five, six, or two bivalent binding units or variants or fragments thereof,

wherein each binding unit comprises two IgM or IgA heavy chain constant regions or multimerizing fragments or variants thereof, each fused to binding polypeptide, wherein at least three of the binding polypeptides comprise a receptor ectodomain that specifically binds to a binding partner comprising a ligand or receptor-binding fragment thereof, wherein the receptor ectodomain is not an antibody or antigen-binding fragment of an antibody, and wherein binding of the receptor ectodomain to the ligand can modulate signal transduction in a cell that expresses the receptor;

wherein at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or twelve of the receptor ectodomains bind to the same ligand; and

wherein the binding molecule can modulate signal transduction at a higher potency than an equivalent amount of a monomeric or dimeric binding molecule with one or two receptor ectodomains binding to the same ligand.

3. The multimeric binding molecule of claim 1 or claim 2, wherein each binding unit comprises two IgA heavy chain constant regions or multimerizing fragments or variants thereof, each comprising:

- (a) an IgA C α 3 domain and an IgA tailpiece domain;
- (b) an IgA C α 3 domain, an IgA tailpiece domain, and an IgA C α 2 domain situated N-terminal to the IgA C α 3 and IgA tailpiece domains;
- (c) an IgA C α 3 domain, an IgA tailpiece domain, an IgA C α 2 domain situated N-terminal to the IgA C α 3 and IgA tailpiece domains, and an IgA hinge region situated N-terminal to the IgA C α 2 domain;
- (d) amino acids 125 to 353 of SEQ ID NO: 24;
- (e) amino acids 113 to 340 of SEQ ID NO: 25;
- (f) amino acids 102 to 353 of SEQ ID NO: 24; or
- (g) amino acids 102 to 340 of SEQ ID NO: 25,

and wherein the multimeric binding molecule further comprises a J-chain or functional fragment or variant thereof.

4. The multimeric binding molecule of claim 1 or claim 2, wherein each binding unit comprises two IgM heavy chain constant regions or multimerizing fragments or variants thereof, each comprising:

- (a) an IgM C μ 4 domain and an IgM tailpiece domain;
- (b) an IgM C μ 4 domain, an IgM tailpiece domain, and an IgM C μ 3 domain situated N-terminal to the IgM C μ 4 and IgM tailpiece domains;
- (c) an IgM C μ 4 domain, an IgM tailpiece domain, an IgM C μ 3 domain situated N-terminal to the IgM C μ 4 and IgM tailpiece domains, and an IgM C μ 2 domain situated N-terminal to the IgM C μ 3 domain;
- (d) an IgM C μ 4 domain, an IgM tailpiece domain, an IgM C μ 3 domain situated N-terminal to the IgM C μ 4 and IgM tailpiece domains, an IgM C μ 2 domain

situated N-terminal to the IgM C μ 3 domain, and an IgG hinge region or functional variant thereof situated N-terminal to the IgM C μ 3 domain;

- (e) SEQ ID NO: 3;
- (f) SEQ ID NO: 4, wherein the multimeric binding molecule comprising SEQ ID NO: 4 has reduced complement-dependent cytotoxicity (CDC) activity relative to a corresponding binding molecule comprising the wild type multimerizing fragment of the human IgM constant region of SEQ ID NO: 3;
- (g) SEQ ID NO: 6; or
- (h) SEQ ID NO: 7, and wherein the multimeric binding molecule comprising SEQ ID NO: 7 has reduced CDC activity relative to a corresponding binding molecule comprising the multimerizing hinge-IgM fragment of SEQ ID NO: 6.

5. The multimeric binding molecule of claim 4, which is pentameric, and further comprises a J-chain or functional fragment or variant thereof.

6. The multimeric binding molecule of claim 5, 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 exhibits an increased serum half-life upon administration to an 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 to be administered in the same way to the same animal species, and wherein the J-chain or functional fragment thereof comprises: an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the wild-type human J-chain (SEQ ID NO: 15).

- 7. The multimeric binding molecule of claim 6, wherein:
 - (a) the amino acid corresponding to Y102 of SEQ ID NO: 15 is substituted with alanine (A), serine (S), or arginine (R);
 - (b) the amino acid corresponding to Y102 of SEQ ID NO: 15 is substituted with alanine (A); or

- (c) the J-chain is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 16.

8. The multimeric binding molecule of claim 6, wherein the J-chain or functional fragment thereof comprises an amino acid substitution at the amino acid position corresponding to amino acid N49, amino acid S51, or both N49 and S51 of the human J-chain (SEQ ID NO: 15), wherein:

- (a) a single amino acid substitution corresponding to position S51 of SEQ ID NO: 15 is not a threonine (T) substitution;
- (b) the position corresponding to N49 of SEQ ID NO: 15 is substituted with alanine (A), glycine (G), threonine (T), serine (S) or aspartic acid (D);
- (c) the position corresponding to N49 of SEQ ID NO: 15 is substituted with alanine (A);
- (d) the J-chain is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 17;
- (e) the position corresponding to S51 of SEQ ID NO: 15 is substituted with alanine (A) or glycine (G);
- (f) the position corresponding to S51 of SEQ ID NO: 15 is substituted with alanine (A); or
- (g) the J-chain is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 18.

9. The multimeric binding molecule of any one of claims 3, 5, or 7 to 8, wherein the J-chain or functional fragment or variant thereof further comprises a heterologous polypeptide, wherein the heterologous polypeptide is directly fused to the J-chain or functional fragment or variant thereof or indirectly fused via a peptide linker comprising at least 5 amino acids, but no more than 25 amino acids to the J-chain or functional fragment or variant thereof, and 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. The multimeric binding molecule of claim 9, wherein the heterologous polypeptide:

- (a) 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;
- (b) can influence the absorption, distribution, metabolism and/or excretion (ADME) of the multimeric binding molecule;
- (c) comprises an antigen binding domain;
- (d) is an antibody or antigen-binding fragment thereof;
- (e) is an antigen-binding fragment of an antibody, and wherein 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; and/or
- (f) is an antigen-binding fragment of an antibody, and wherein the antigen-binding fragment is a scFv fragment.

11. The multimeric binding molecule of claim 3, comprising four identical binding polypeptides.

12. The multimeric binding molecule of any one of claims 4 to 10, which is pentameric and comprises ten identical binding polypeptides or hexameric and comprises twelve identical binding polypeptides.

13. The multimeric binding molecule of any one of claims 1 or 3 to 12, wherein each binding polypeptide is a ligand or receptor-binding fragment thereof, a cytokine or receptor-binding fragment thereof, a growth factor or receptor-binding fragment thereof, a neurotransmitter or receptor-binding fragment thereof, a peptide or protein hormone or receptor-binding fragment thereof, an immune checkpoint modulator ligand or receptor-binding fragment thereof, or a receptor-binding fragment of an extracellular matrix protein.

14. The multimeric binding molecule of claim 13, wherein the ligand or receptor-binding fragment thereof comprises a chemokine, a complement protein, a fibroblast growth factor (FGF) family ligand, an immune checkpoint modulator ligand, an epidermal growth

factor (EGF), an interferon, a tumor necrosis factor superfamily (TNFSF) ligand, a vascular endothelial growth factor (VEGF) family ligand, a transforming growth factor- β superfamily (TGF β sf) ligand, any receptor-binding fragment thereof, or any combination thereof.

15. The multimeric binding molecule of claim 14, wherein the binding polypeptide comprises a TNFSF ligand, and wherein the TNFSF ligand comprises TRAIL, OX40 ligand, CD40 ligand, a glucocorticoid-induced tumor necrosis factor receptor ligand (GITRL), 4-1BB ligand, any receptor-binding fragment thereof, or any combination thereof.

16. The multimeric binding molecule of claim 13, wherein the binding polypeptide comprises an immune checkpoint modulator ligand protein or receptor-binding fragment thereof and wherein the immune checkpoint modulator protein comprises CD86 or a receptor-binding fragment thereof, CD80 or a receptor-binding fragment thereof, PD-L1 or a receptor-binding fragment thereof, or any combination thereof.

17. The multimeric binding protein of claim 16, wherein the binding polypeptide comprises:

- (a) a receptor-binding fragment of human PD-L1;
- (b) amino acids 19 to 127 of SEQ ID NO: 8, which contains the V-type domain of human PD-L1; or
- (c) SEQ ID NO: 9, which contains the V-type and C2-type domains of human PD-L1.

18. The multimeric binding molecule of claim 1, comprising ten or twelve copies of a polypeptide comprising the amino acid sequence SEQ ID NO: 11 or SEQ ID NO: 13; or comprising ten or twelve copies of a polypeptide comprising the amino acid sequence SEQ ID NO: 11 or SEQ ID NO: 13 and further comprising a variant J-chain comprising the amino acid sequence SEQ ID NO: 16.

19. The multimeric binding molecule of claim 17 or claim 18, which is an agonist of PD-1.

20. The multimeric binding molecule of any one of claims 1 or 3 to 19, wherein the binding partner is cell-surface receptor protein or an immune checkpoint modulator.

21. The multimeric binding molecule of any one of claims 2 to 12, wherein the receptor ectodomain comprises a ligand-binding fragment of a tumor necrosis factor

superfamily receptor (TNFrSF), a ligand-binding fragment of an immune checkpoint modulator receptor, ligand-binding fragment of a TGF β receptor, or any combination thereof.

22. The multimeric binding molecule of claim 21, wherein:

- (a) the TNFrSF receptor fragment comprises a ligand-binding fragment of death domain containing receptor-4 (DR4), death domain containing receptor-5 (DR5), OX-40, CD40, 4-1BB, glucocorticoid-induced tumor necrosis factor receptor (GITR), or any combination thereof;
- (b) the immune checkpoint modulator receptor ectodomain comprises a ligand-binding fragment of PD-1, a ligand-binding fragment of CTLA4, a ligand-binding fragment of LAG3, a ligand-binding fragment of CD28, a ligand-binding fragment of immunoglobulin-like domain containing receptor 2 (ILDR2), a ligand-binding fragment of T-cell immunoglobulin mucin family member 3 (TIM-3), or any combination thereof; or
- (c) the TGF β receptor comprises a TGF β R-1, a TGF β R-2, a TGF β R3, or any combination thereof.

23. An isolated polynucleotide comprising a nucleic acid sequence that encodes a subunit of the multimeric binding molecule of any one of claims 1 to 22, wherein each subunit comprises an IgA or IgM heavy chain constant region or multimerizing fragment or variant thereof fused to a binding polypeptide or fragment thereof that specifically binds to a binding partner, or a receptor ectodomain that specifically binds to a ligand.

24. A vector comprising the polynucleotide of claim 23.

25. A host cell comprising the vector of claim 24.

26. The multimeric binding molecule of any one of claims 16 to 22 for use in therapy, 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.

27. Use of the multimeric binding molecule of any one of claims 16 to 22 in the manufacture of a medicament for treating an autoimmune disorder, an inflammatory disorder, or a combination thereof in a subject in need of treatment, 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.

28. Use of the multimeric binding molecule of any one of claims 16 to 22 in the manufacture of a medicament for preventing transplantation rejection in a transplantation recipient, 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.