

WHAT IS CLAIMED IS:

1. A multimeric binding molecule comprising two or five bivalent binding units or multimerizing variants or fragments thereof and a modified J-chain,
wherein each binding unit comprises two IgA or IgM heavy chain constant regions or multimerizing variants or fragments thereof, each associated with an antigen-binding domain for a total of four or ten antigen-binding domains,
wherein at least three of the antigen-binding domains of the binding molecule specifically bind to a target antigen, and
wherein the modified J-chain comprises (a) a J-chain or functional fragment or variant thereof ("J"), and (b) an immunostimulatory agent ("ISA"), wherein J and the ISA are associated as a fusion protein.
2. The multimeric binding molecule of claim 1, wherein the ISA comprises a cytokine or receptor-binding fragment or variant thereof.
3. The multimeric binding molecule of claim 2, wherein the cytokine or fragment or variant thereof comprises IL-15 or IL-2, or a receptor-binding fragment or variant thereof.
4. The multimeric binding molecule of any one of claims 1 to 3, wherein the ISA comprises (a) an interleukin-15 (IL-15) protein or receptor-binding fragment or variant thereof ("I"), and (b) an interleukin-15 receptor- α (IL-15R α) fragment comprising the sushi domain or a variant thereof capable of associating with I ("R"), wherein J and at least one of I and R are associated as a fusion protein, and wherein I and R can associate to function as the ISA.
5. The multimeric binding molecule of any one of claims 1 to 4, wherein J is a wild-type human J-chain and comprises the amino acid sequence SEQ ID NO: 2 or a functional fragment or variant thereof.
6. The multimeric binding molecule of any one of claims 1 to 5, wherein J is a variant J-chain or fragment thereof 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 administered in the same way to the same animal species.

7. The multimeric binding molecule of claim 6, wherein the J comprises 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: 2).

8. The multimeric binding molecule of claim 7, wherein the amino acid corresponding to Y102 of SEQ ID NO: 2 is substituted with alanine (A), serine (S), or arginine (R).

9. The multimeric binding molecule of claim 8, wherein the amino acid corresponding to Y102 of SEQ ID NO: 2 is substituted with alanine (A).

10. The multimeric binding molecule of claim 9, wherein J is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 3 ("J*") or amino acids 1-137 of SEQ ID NO: 86.

11. The multimeric binding molecule of any one of claims 1 to 10, wherein J is a variant J-chain or fragment thereof comprising one or more single amino acid substitutions, deletions, or insertions relative to a wild-type J-chain that reduces glycosylation of the J-chain.

12. The multimeric binding molecule of claim 11, wherein the J comprises an amino acid substitution at the amino acid position corresponding to amino acid N49 of the mature wild-type human J-chain (SEQ ID NO: 2).

13. The multimeric binding molecule of claim 12, wherein the amino acid corresponding to N49 of SEQ ID NO: 2 is substituted with aspartic acid (D).

14. The multimeric binding molecule of any one of claims 4 to 13, wherein I comprises the mature human IL-15 amino acid sequence of SEQ ID NO: 4 or a receptor-binding variant or fragment thereof.

15. The multimeric binding molecule of claim 14, wherein the receptor-binding variant comprises at least one, but no more than ten, single amino acid insertions, deletions, or substitutions, and wherein the single amino acid insertions, deletions, or substitutions reduce the affinity of the IL-15 variant for its receptor.

16. The multimeric binding molecule of claim 15, wherein I comprises one, two, three, four, five, six, seven, or eight amino acid substitutions.

17. The multimeric binding molecule of claim 16, wherein the amino acid substitutions are at one or more of positions corresponding to N1, N4, D8, D30, D61, E64, N65, N72, or Q108 of SEQ ID NO: 4.

18. The multimeric binding molecule of claim 17, wherein the amino acid substitutions comprise one or more of substitutions N1D, N4D, D8N, D30N, D61N, E64Q, N65D, N72D, or Q108E in SEQ ID NO: 4.

19. The multimeric binding molecule of claim 18, wherein I comprises SEQ ID NO: 4 except for:

- (a) a single amino acid substitution at a position selected from the group consisting of N1D, N4D, D8N, D30N, D61N, E64Q, N65D, N72D, and Q108E;
- (b) two amino acid substitutions at positions selected from the group consisting of N4D/N65D and N1D/N65D; or
- (c) three amino acid substitutions at positions D30N/E64Q/N65D.

20. The multimeric binding molecule of claim 19, wherein I comprises the amino acid sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, or SEQ ID NO: 68.

21. The multimeric binding molecule of claim 14, wherein the receptor-binding variant comprises at least one, but no more than ten, single amino acid insertions, deletions, or substitutions, and wherein the single amino acid insertions, deletions, or substitutions reduce the glycosylation of the IL-15 variant.

22. The multimeric binding molecule of claim 21, wherein I comprises one, two, three, four, five, six, seven, or eight amino acid substitutions.

23. The multimeric binding molecule of claim 22, wherein the amino acid substitutions are at one or more of positions corresponding to N71, S73, N79, or N112 of SEQ ID NO: 4.

24. The multimeric binding molecule of claim 23, wherein the amino acid substitutions comprise one or more of substitutions N71D, S73I, N79D, or N112D in SEQ ID NO: 4.

25. The multimeric binding molecule of claim 24, wherein I comprises SEQ ID NO: 4 except for one or more amino acid substitutions at a position selected from the group consisting of N71D, S73I, N79D, and N112D.

26. The multimeric binding molecule of claim 25, wherein I comprises the amino acid sequence of amino acids 246-361 of SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, or SEQ ID NO: 90.

27. The multimeric binding molecule of any one of claims 4 to 26, wherein R comprises the amino acid sequence SEQ ID NO: 5 or a variant or fragment thereof that is capable of associating with human IL-15.

28. The multimeric binding molecule of any one of claims 4 to 20, wherein R consists essentially of or consists of the amino acid sequence SEQ ID NO: 5 or a variant thereof that is capable of associating with human IL-15.

29. The multimeric binding molecule of any one of claims 4 to 28, wherein J and I are associated as a fusion protein.

30. The multimeric binding molecule of any one of claims 4 to 28, wherein J and R are associated as a fusion protein.

31. The multimeric binding molecule of any one of claims 4 to 30, wherein J, I, and R are associated as a fusion protein.

32. The multimeric binding molecule of claim 31, wherein J, I, and R are fused via linkers.

33. The multimeric binding molecule of claim 32, wherein the linkers are the same or different.

34. The multimeric binding molecule of claim 32 or claim 33, wherein at least one linker comprises, consists essentially of, or consists of the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO: 78).

35. The multimeric binding molecule of claim 32 or claim 33, wherein at least one linker comprises, consists essentially of, or consists of the amino acid sequence GGS GGGGSGGGGSGGGGSLQ (SEQ ID NO: 79).

36. The multimeric binding molecule of any one of claims 6 to 35, wherein J is J*, and wherein the modified J-chain is arranged from N-terminus to C-terminus as J*-R-I, J*-I-R, I-R-J*, R-I-J*, R-J*-I, I-J*-R, I-J*, or J*-I, wherein “-” is a linker.

37. The multimeric binding molecule of claim 36, wherein the modified J-chain comprises the amino acid sequence SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID

NO: 26, SEQ ID NO: 77, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, or SEQ ID NO: 90.

38. The multimeric binding molecule of claim 36, wherein the modified J-chain is arranged from N-terminus to C-terminus as J*-R-I.

39. The multimeric binding molecule of claim 38, wherein the modified J-chain comprises the amino acid sequence SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 77, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, or SEQ ID NO: 90.

40. The multimeric binding molecule of any one of claims 1 to 3, wherein the ISA comprises a variant of human IL-2 ("IL2v") that does not bind to the α -subunit of the IL-2 receptor.

41. The multimeric binding molecule of claim 40, wherein IL2v comprises the amino acid sequence SEQ ID NO: 31.

42. The multimeric binding molecule of claim 41, wherein the modified J-chain comprises the amino acid sequence SEQ ID NO: 32.

43. The multimeric binding molecule of any one of claims 4 to 42, wherein the modified J-chain further comprises an antigen-binding domain of an antibody fused thereto.

44. The multimeric binding molecule of claim 43, wherein the antigen-binding domain binds to a target on an immune effector cell.

45. The multimeric binding molecule of claim 44, wherein the immune effector cell is a CD8⁺ T cell.

46. The multimeric binding molecule of claim 45, wherein the antigen binding domain is a single-chain Fv (scFv) antibody fragment that specifically binds to CD3epsilon (CD3 ϵ).

47. The multimeric binding molecule of claim 46, wherein the modified J-chain comprises SEQ ID NO: 19.

48. The multimeric binding molecule of any one of claims 1 to 47, which is pentameric and comprises five binding units, wherein each binding unit comprises two IgM heavy chain constant regions or multimerizing variants or fragments thereof.

49. The multimeric binding molecule of any one of claims 1 to 47, which is dimeric and comprises two binding units or multimerizing variants or fragments thereof,

wherein each binding unit comprises two IgA heavy chain constant regions or multimerizing variants or fragments thereof.

50. The multimeric binding molecule of any one of claims 1 to 49, wherein the target antigen comprises a tumor-associated antigen or a target that modulates a T cell response or NK cell response.

51. The multimeric binding molecule of claim 50, wherein the target antigen comprises a target that modulates a T cell response or an NK cell response.

52. The multimeric binding molecule of claim 51, wherein the target inhibits CD8+ T cell or NK cell activity.

53. The multimeric binding molecule of claim 52, wherein the target comprises an inhibitory immune checkpoint protein, and wherein the antigen-binding domains antagonize the target, thereby stimulating CD8+ T cells or NK cells.

54. The multimeric binding molecule of claim 53, wherein the inhibitory immune checkpoint protein comprises a programmed cell death-1 protein (PD-1), a programmed cell death ligand-1 protein (PD-L1), a lymphocyte-activation gene 3 protein (LAG3), a T-cell immunoglobulin and mucin domain 3 protein (TIM3), a cytotoxic T-lymphocyte-associated protein 4 (CTLA4), a B- and T-lymphocyte attenuator protein (BTLA), a V-domain Ig suppressor of T-cell activation protein (VISTA), a T-cell immunoreceptor with Ig and ITIM Domains protein (TIGIT), a Killer-cell Immunoglobulin-like Receptor protein (KIR), a B7-H3 protein, a B7-H4 protein, or any combination thereof.

55. The multimeric binding molecule of claim 54, wherein the inhibitory immune checkpoint protein comprises PD-L1, and wherein the antigen-binding domain comprises a heavy chain variable region (VH) comprising the amino acid sequence SEQ ID NO: 33, SEQ ID NO: 91, SEQ ID NO: 92, or SEQ ID NO: 93 and a light chain variable region (VL) comprising the amino acid sequence SEQ ID NO: 34 or SEQ ID NO: 94.

56. The multimeric binding molecule of claim 54, wherein the inhibitory immune checkpoint protein comprises PD-L1, and wherein the antigen-binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL) 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: 75 and SEQ ID NO: 76, SEQ ID NO: 96 and SEQ ID NO: 97, SEQ ID NO: 98 and SEQ ID NO: 99, SEQ ID NO: 100 and SEQ ID NO: 101, SEQ ID NO: 102 and SEQ ID NO:

103, SEQ ID NO: 104 and SEQ ID NO: 105, SEQ ID NO: 106 and SEQ ID NO: 107, SEQ ID NO: 108 and SEQ ID NO: 109, SEQ ID NO: 110 and SEQ ID NO: 111, SEQ ID NO: 112 and SEQ ID NO: 113, SEQ ID NO: 114 and SEQ ID NO: 115, SEQ ID NO: 116 and SEQ ID NO: 117, SEQ ID NO: 118 and SEQ ID NO: 119, SEQ ID NO: 120 and SEQ ID NO: 121, SEQ ID NO: 122 and SEQ ID NO: 123, SEQ ID NO: 124 and SEQ ID NO: 125, SEQ ID NO: 126 and SEQ ID NO: 127, SEQ ID NO: 128 and SEQ ID NO: 129, SEQ ID NO: 130 and SEQ ID NO: 131, SEQ ID NO: 132 and SEQ ID NO: 133, SEQ ID NO: 134 and SEQ ID NO: 135, SEQ ID NO: 136 and SEQ ID NO: 137, SEQ ID NO: 138 and SEQ ID NO: 139, SEQ ID NO: 140 and SEQ ID NO: 141, SEQ ID NO: 142 and SEQ ID NO: 143, SEQ ID NO: 144 and SEQ ID NO: 145, SEQ ID NO: 146 and SEQ ID NO: 147, SEQ ID NO: 148 and SEQ ID NO: 149, SEQ ID NO: 150 and SEQ ID NO: 151, SEQ ID NO: 152 and SEQ ID NO: 153, SEQ ID NO: 154 and SEQ ID NO: 155, SEQ ID NO: 156 and SEQ ID NO: 157, SEQ ID NO: 158 and SEQ ID NO: 159, SEQ ID NO: 160 and SEQ ID NO: 161, SEQ ID NO: 162 and SEQ ID NO: 163, SEQ ID NO: 164 and SEQ ID NO: 165, SEQ ID NO: 166 and SEQ ID NO: 167, SEQ ID NO: 168 and SEQ ID NO: 169, SEQ ID NO: 170 and SEQ ID NO: 171, SEQ ID NO: 172 and SEQ ID NO: 173, SEQ ID NO: 174 and SEQ ID NO: 175, SEQ ID NO: 176 and SEQ ID NO: 177, SEQ ID NO: 178 and SEQ ID NO: 179, SEQ ID NO: 180 and SEQ ID NO: 181, SEQ ID NO: 182 and SEQ ID NO: 183, SEQ ID NO: 184 and SEQ ID NO: 185, SEQ ID NO: 186 and SEQ ID NO: 187, SEQ ID NO: 188 and SEQ ID NO: 189, SEQ ID NO: 190 and SEQ ID NO: 191, SEQ ID NO: 192 and SEQ ID NO: 193, SEQ ID NO: 194 and SEQ ID NO: 195, SEQ ID NO: 196 and SEQ ID NO: 197, SEQ ID NO: 198 and SEQ ID NO: 199, SEQ ID NO: 200 and SEQ ID NO: 201, SEQ ID NO: 202 and SEQ ID NO: 203, SEQ ID NO: 204 and SEQ ID NO: 205, SEQ ID NO: 206 and SEQ ID NO: 207, SEQ ID NO: 208 and SEQ ID NO: 209, SEQ ID NO: 210 and SEQ ID NO: 211, SEQ ID NO: 212 and SEQ ID NO: 213, SEQ ID NO: 214 and SEQ ID NO: 215, SEQ ID NO: 216 and SEQ ID NO: 217, SEQ ID NO: 218 and SEQ ID NO: 219, SEQ ID NO: 220 and SEQ ID NO: 221, or SEQ ID NO: 222 and SEQ ID NO: 223, respectively with zero, one, or two single amino acid substitutions in one or more of the HCDRs or LCDRs.

57. The multimeric binding molecule of claim 54 or claim 56, wherein the inhibitory immune checkpoint protein comprises PD-L1, and wherein the antigen-binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL) wherein the VH and VL comprise amino acid sequences at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to the mature VH and VL amino acid sequences

comprising SEQ ID NO: 75 and SEQ ID NO: 76, SEQ ID NO: 96 and SEQ ID NO: 97, SEQ ID NO: 98 and SEQ ID NO: 99, SEQ ID NO: 100 and SEQ ID NO: 101, SEQ ID NO: 102 and SEQ ID NO: 103, SEQ ID NO: 104 and SEQ ID NO: 105, SEQ ID NO: 106 and SEQ ID NO: 107, SEQ ID NO: 108 and SEQ ID NO: 109, SEQ ID NO: 110 and SEQ ID NO: 111, SEQ ID NO: 112 and SEQ ID NO: 113, SEQ ID NO: 114 and SEQ ID NO: 115, SEQ ID NO: 116 and SEQ ID NO: 117, SEQ ID NO: 118 and SEQ ID NO: 119, SEQ ID NO: 120 and SEQ ID NO: 121, SEQ ID NO: 122 and SEQ ID NO: 123, SEQ ID NO: 124 and SEQ ID NO: 125, SEQ ID NO: 126 and SEQ ID NO: 127, SEQ ID NO: 128 and SEQ ID NO: 129, SEQ ID NO: 130 and SEQ ID NO: 131, SEQ ID NO: 132 and SEQ ID NO: 133, SEQ ID NO: 134 and SEQ ID NO: 135, SEQ ID NO: 136 and SEQ ID NO: 137, SEQ ID NO: 138 and SEQ ID NO: 139, SEQ ID NO: 140 and SEQ ID NO: 141, SEQ ID NO: 142 and SEQ ID NO: 143, SEQ ID NO: 144 and SEQ ID NO: 145, SEQ ID NO: 146 and SEQ ID NO: 147, SEQ ID NO: 148 and SEQ ID NO: 149, SEQ ID NO: 150 and SEQ ID NO: 151, SEQ ID NO: 152 and SEQ ID NO: 153, SEQ ID NO: 154 and SEQ ID NO: 155, SEQ ID NO: 156 and SEQ ID NO: 157, SEQ ID NO: 158 and SEQ ID NO: 159, SEQ ID NO: 160 and SEQ ID NO: 161, SEQ ID NO: 162 and SEQ ID NO: 163, SEQ ID NO: 164 and SEQ ID NO: 165, SEQ ID NO: 166 and SEQ ID NO: 167, SEQ ID NO: 168 and SEQ ID NO: 169, SEQ ID NO: 170 and SEQ ID NO: 171, SEQ ID NO: 172 and SEQ ID NO: 173, SEQ ID NO: 174 and SEQ ID NO: 175, SEQ ID NO: 176 and SEQ ID NO: 177, SEQ ID NO: 178 and SEQ ID NO: 179, SEQ ID NO: 180 and SEQ ID NO: 181, SEQ ID NO: 182 and SEQ ID NO: 183, SEQ ID NO: 184 and SEQ ID NO: 185, SEQ ID NO: 186 and SEQ ID NO: 187, SEQ ID NO: 188 and SEQ ID NO: 189, SEQ ID NO: 190 and SEQ ID NO: 191, SEQ ID NO: 192 and SEQ ID NO: 193, SEQ ID NO: 194 and SEQ ID NO: 195, SEQ ID NO: 196 and SEQ ID NO: 197, SEQ ID NO: 198 and SEQ ID NO: 199, SEQ ID NO: 200 and SEQ ID NO: 201, SEQ ID NO: 202 and SEQ ID NO: 203, SEQ ID NO: 204 and SEQ ID NO: 205, SEQ ID NO: 206 and SEQ ID NO: 207, SEQ ID NO: 208 and SEQ ID NO: 209, SEQ ID NO: 210 and SEQ ID NO: 211, SEQ ID NO: 212 and SEQ ID NO: 213, SEQ ID NO: 214 and SEQ ID NO: 215, SEQ ID NO: 216 and SEQ ID NO: 217, SEQ ID NO: 218 and SEQ ID NO: 219, SEQ ID NO: 220 and SEQ ID NO: 221, or SEQ ID NO: 222 and SEQ ID NO: 223, respectively.

58. The multimeric binding molecule of claim 50 or claim 51, wherein the target comprises a TNF receptor superfamily target, and wherein the antigen-binding domains can agonize the target.

59. The multimeric binding molecule of claim 58, wherein the target antigen comprises GITR, OX40, or a combination thereof, and wherein the antigen-binding domains can agonize the target.

60. The multimeric binding molecule of claim 59, wherein the target antigen comprises GITR, and wherein the antigen-binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL) comprising, respectively, the amino acid sequences SEQ ID NO: 35 and SEQ ID NO: 36, SEQ ID NO: 37 and SEQ ID NO: 38, SEQ ID NO: 39 and SEQ ID NO: 40, SEQ ID NO: 41 and SEQ ID NO: 42, or SEQ ID NO: 43 and SEQ ID NO: 44.

61. The multimeric binding molecule of claim 59, wherein the target antigen comprises OX40, and wherein the antigen-binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL) comprising, respectively, the amino acid sequences SEQ ID NO: 45 and SEQ ID NO: 46 or SEQ ID NO: 47 and SEQ ID NO: 48.

62. The multimeric binding molecule of any one of claims 1 to 49, wherein the target antigen comprises a tumor-associated antigen.

63. The multimeric binding molecule of claim 62, wherein the tumor associated antigen comprises B-cell maturation antigen (BCMA), CD19, CD20, EGFR, HER2 (ErbB2), ErbB3, ErbB4, CTLA4, PD-1, PD-L1, VEGF, VEGFR1, VEGFR2, CD52, CD30, prostate-specific membrane antigen (PSMA), CD38, GD2, SLAMF7, platelet-derived growth factor receptor A (PDGFRA), CD22, FLT3 (CD135), CD123, MUC-16, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1), mesothelin, tumor-associated calcium signal transducer 2 (Trop-2), glypican-3 (GPC-3), human blood group H type 1 trisaccharide (Globo-H), sialyl Tn antigen (STn antigen), CD33, or any combination thereof.

64. The multimeric binding molecule of claim 63, wherein the target antigen comprises CD20, and wherein the antigen-binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL) comprising, respectively, the amino acid sequences SEQ ID NO: 49 and SEQ ID NO: 50.

65. The multimeric binding molecule of any one of claims 1 to 64, wherein at least four, at least five, at least six, at least seven, at least eight, at least nine or ten of the antigen-binding domains of the binding molecule specifically bind to the same target antigen.

66. The multimeric binding molecule of any one of claims 1 to 47 or 49 to 65, wherein each binding unit comprises two IgA heavy chain constant regions or multimerizing

fragments or variants thereof, each comprising an IgA C α 1 domain, an IgA hinge, an IgA C α 2 domain, IgA C α 3 domain, and an IgA tailpiece domain.

67. The multimeric binding molecule of claim 66, wherein the IgA heavy chain constant regions comprise the amino acid sequence SEQ ID NO: 53, SEQ ID NO: 54, or any multimerizing variant or fragment thereof.

68. The multimeric binding molecule of any one of claims 1 to 46 or 48 to 65, wherein each binding unit comprises two IgM heavy chain constant regions or multimerizing fragments or variants thereof, each comprising an IgM C μ 4 domain and an IgM tailpiece domain.

69. The multimeric binding molecule of claim 68, wherein each IgM heavy chain constant region or multimerizing fragment or variant thereof further comprises an IgM C μ 3 domain, an IgM C μ 2 domain, an IgM C μ 1 domain, or any combination thereof, situated N-terminal to the IgM C μ 4 and IgM tailpiece domains.

70. The multimeric binding molecule of claim 68 or claim 69, wherein each IgM heavy chain constant region is a human IgM constant region or multimerizing variant or fragment thereof, comprising the amino acid sequence SEQ ID NO: 51, SEQ ID NO: 52, or a multimerizing variant or fragment thereof.

71. The multimeric binding molecule of claim 69 or 70, comprising a variant human IgM constant region, wherein the multimeric binding molecule has reduced CDC activity relative to a multimeric binding molecule comprising IgM heavy chain constant regions comprising the amino acid sequence SEQ ID NO: 51, SEQ ID NO: 52, or a multimerizing variant or fragment thereof.

72. The multimeric binding molecule of claim 71, wherein each IgM heavy chain constant region comprises a variant of the amino acid sequence SEQ ID NO: 51 or SEQ ID NO: 52, wherein the variant comprises an amino acid substitution at position P311 of SEQ ID NO: 51 or SEQ ID NO: 52, an amino acid substitution at position P313 of SEQ ID NO: 51 or SEQ ID NO: 52, or amino acid substitutions at positions P311 and P313 of SEQ ID NO: 51 or SEQ ID NO: 52.

73. The multimeric binding molecule of claim 69 or 70, wherein each IgM heavy chain constant region is a variant human IgM constant region with one or more single amino acid substitutions, deletions, or insertions relative to a reference IgM heavy chain constant region identical to the variant IgM heavy chain constant regions except for the one or more single amino acid substitutions, deletions, or insertions, and wherein the multimeric binding

molecule exhibits increased serum half-life upon administration to a subject animal relative to a multimeric binding molecule comprising the reference IgM heavy chain constant regions, and is administered in the same way to the same animal species.

74. The multimeric binding molecule of claim 73, wherein the variant IgM heavy chain constant regions comprise amino acid substitutions at one or more amino acid positions corresponding to amino acid, E345A, S401A, E402A, or E403A of the wild-type human IgM constant region SEQ ID NO: 51 or SEQ ID NO: 52.

75. An isolated polynucleotide comprising a nucleic acid encoding a subunit polypeptide of the multimeric binding molecule of any one of claims 1 to 74, wherein the subunit polypeptide comprises (a) an IgA or IgM heavy chain comprising an IgA or IgM heavy chain constant region or a multimerizing variant or fragment thereof associated with an antibody heavy chain variable region (VH), (b) an antibody light chain comprising an antibody light chain constant region associated with an antibody light chain variable region (VL), or (c) a modified J-chain comprising two or more of (i) a J-chain or functional fragment or variant thereof ("J"), (ii) an interleukin-15 (IL-15) protein or receptor-binding fragment or variant thereof ("I"), or (iii) an interleukin-15 receptor- α (IL-15R α) fragment comprising the sushi domain or a variant thereof capable of associating with I ("R"), wherein J and at least one of I and R are associated as a fusion protein, and wherein I and R can associate to function as an immune stimulatory complex, or (d) any combination thereof.

76. The polynucleotide of claim 75, wherein the subunit polypeptide comprises an IgM heavy chain comprising an IgM constant region or multimerizing fragment or variant thereof.

77. The polynucleotide of claim 76, wherein the IgM constant region or fragment or variant thereof comprises the amino acid sequence SEQ ID NO: 51 or SEQ ID NO: 52.

78. The polynucleotide of claim 75, wherein the subunit polypeptide comprises the antibody light chain.

79. The polynucleotide of claim 75, wherein the subunit polypeptide comprises the modified J-chain.

80. The polynucleotide of claim 79, wherein the subunit comprises the amino acid sequence SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID

NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, or SEQ ID NO: 32.

81. The polynucleotide of any one of claims 75 to 80, which comprises two, three, or more nucleic acid sequences encoding two, three or more of the subunit polypeptides.

82. An expression vector comprising the polynucleotide of any one of claims 75 to 81.

83. A host cell comprising the polynucleotide of any of claims 75 to 81 or the expression vector of claim 82.

84. A method for producing the multimeric binding molecule of any one of claims 1 to 74, comprising culturing the host cell of claim 83, and recovering the multimeric binding molecule.

85. A method for treating cancer, comprising administering to a subject in need of treatment the multimeric binding molecule of any one of claims 1 to 74.