

can determine how they are recognized by receptors such as asialo-glycoprotein (ASGP) receptor, which in turn determines how quickly they are cleared from systemic circulation. Each IgM heavy chain constant region has five sites of asparagine- (N-)linked glycosylation, and the J-chain has one N-linked glycosylation site. Thus, a pentameric, J-chain containing IgM contains up to 51 glycan moieties, which results in a complex glycosylation profile (Hennicke, J., *et al.*, *Anal. Biochem.* 539:162-166 (2017)). The complexity of glycans can make manufacture of homogenously glycosylated material difficult.

[0006] Despite the advances made in the design of multimeric antibodies, there remains a need to be able to manipulate the physical, pharmacokinetic and pharmacodynamic properties of these molecules.

SUMMARY

[0007] In one aspect, the present disclosure provides an isolated IgM-derived binding molecule comprising at least one variant IgM-derived heavy chain, wherein the at least one variant IgM-derived heavy chain comprises a variant IgM heavy chain constant region associated with a binding domain that specifically binds to a target, wherein at least one asparagine(N)-linked glycosylation motif of the variant IgM heavy chain constant region is mutated to prevent glycosylation at that motif, and wherein an N-linked glycosylation motif comprises the amino acid sequence N-X₁-S/T, wherein N is asparagine, X₁ is any amino acid except proline, and S/T is serine or threonine. This disclosure provides an isolated IgM-derived binding molecule, *e.g.*, an IgM antibody, IgM-like antibody, or other IgM-derived binding molecule, including at least one variant IgM-derived heavy chain, where the at least one variant IgM-derived heavy chain includes a variant IgM heavy chain constant region associated with a binding domain that specifically binds to a target, where at least one asparagine(N)-linked glycosylation motif of the variant IgM heavy chain constant region is mutated to prevent glycosylation at that motif, and where the N-linked glycosylation motif includes the amino acid sequence N-X₁-S/T, where N is asparagine, X₁ is any amino acid except proline, and S/T is serine or threonine. In certain **embodiment examples**, the variant IgM heavy chain constant region is derived from a human IgM heavy chain constant region that includes five N-linked glycosylation motifs N- X₁-S/T starting at amino acid positions corresponding to amino acid 46 (motif N1), amino acid 209 (motif N2), amino acid 272 (motif N3), amino acid 279 (motif N4), and amino acid 440 (motif

N5) of SEQ ID NO: 1 (alleleIGHM*03) or SEQ ID NO: 2 (alleleIGHM*04). In certain embodimentexamples, at least one, at least two, at least three, or at least four of the N- X₁-S/T motifs includes an amino acid insertion, deletion, or substitution that prevents glycosylation at that motif. In certain embodimentexamples, the IgM-derived binding molecule can include an amino acid insertion, deletion, or substitution at motif N1, motif N2, motif N3, motif N5, or any combination of two or more, three or more, or all four of motifs N1, N2, N3, or N5, where the amino acid insertion, deletion, or substitution prevents glycosylation at that motif.

[0008] In certain embodimentexamples, the IgM-derived binding molecule can include an amino acid substitution at an amino acid position corresponding to amino acid N46, N209, N272, or N440 of SEQ ID NO: 1 or SEQ ID NO: 2 where the substituted amino acid is any amino acid, an amino acid substitution at an amino acid position corresponding to amino acid S48, S211, S274, or S442 of SEQ ID NO: 1 or SEQ ID NO: 2 where the substituted amino acid is any amino acid except threonine, or any combination of two or more, three or more, or four or more of the amino acid substitutions. In certain embodimentexamples, the amino acid substitution can correspond to N46X₂, N46A, N46D, N46Q, N46K, S48X₃, S48A, N229X₂, N229A, N229D, N229Q, N229K, S231X₃, S231A, N272X₂, N272A, N272D, N272Q, N272K, S274X₃, S274A, N440X₂, N440A, N440D, N449Q, N449K, S242X₃, or S424A of SEQ ID NO: 1 or SEQ ID NO: 2, or any combination of two or more, three or more, or four or more of the amino acid substitutions, where X₂ is any amino acid and X₃ is any amino acid except threonine.

[0009] In certain embodimentexamples, the variant IgM heavy chain constant region is a variant human IgM constant region that includes the amino acid sequence SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, 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, or SEQ ID NO: 18.

[0010] In certain embodimentexamples, the variant IgM heavy chain constant region is mutated to introduce at least one new asparagine(N)-linked glycosylation motif into the variant IgM heavy chain constant region, where the at least one new asparagine(N)-linked glycosylation motif is introduced at a site in the variant IgM heavy chain constant region that is not naturally glycosylated in an IgM antibody. In certain embodimentexamples, the new asparagine(N)-linked glycosylation motif is at a position in the variant IgM heavy chain constant region that corresponds to the position of an asparagine(N)-linked glycosylation motif present in a different immunoglobulin isotype, for example, a human immunoglobulin isotype selected from the group consisting of human IgG1, human IgG2, human IgG3, human IgG4, human IgA1, human IgA2, human IgD, and human IgE.

[0011] In certain embodimentexamples, the target is a target epitope, a target antigen, a target cell, a target organ, or a target virus.

[0012] In certain embodimentexamples, the IgM-derived binding molecule is a pentameric or a hexameric IgM antibody that includes five or six bivalent IgM binding units, respectively, where each binding unit includes two IgM heavy chains each including a VH situated

amino terminal to the variant IgM constant region, and two immunoglobulin light chains each including a light chain variable domain (VL) situated amino terminal to an immunoglobulin light chain constant region, and where the VH and VL combine to form an antigen-binding domain that specifically binds to the target. In certain [embodimentexamples](#), the five or six IgM binding units are identical.

[0013] In certain [embodimentexamples](#) the IgM-derived binding molecule is pentameric, and further includes a J-chain, or functional fragment thereof, or a functional variant thereof. In certain [embodimentexamples](#), the J-chain is a mature human J-chain that includes the amino acid sequence SEQ ID NO: 20 or a functional fragment thereof, or a functional variant thereof. In certain [embodimentexamples](#), the J-chain is a functional variant J-chain including one or more single amino acid substitutions, deletions, or insertions relative to a reference J-chain identical to the variant J-chain except for the one or more single amino acid substitutions, deletions, or insertions, and the IgM-derived binding molecule that includes the variant J-chain exhibits an increased serum half-life upon administration to a subject animal relative to a reference IgM-derived binding molecule that is identical except for the one or more single amino acid substitutions, deletions, or insertions in the variant J-chain, and is administered in the same way to the same animal species. In certain [embodimentexamples](#), the variant J-chain or functional fragment thereof includes one, two, three, or four single amino acid substitutions, deletions, or insertions relative to the reference J-chain. In certain [embodimentexamples](#), the variant J-chain or functional fragment thereof includes an amino acid substitution at the amino acid position corresponding to amino acid Y102 of the wild-type mature human J-chain (SEQ ID NO: 20), for example, the amino acid corresponding to Y102 of SEQ ID NO: 20 can be substituted with alanine (A). In certain [embodimentexample](#) the J-chain is the variant human J-chain J*, which includes the amino acid sequence SEQ ID NO: 21.

[0014] In certain [embodimentexamples](#), the variant J-chain or functional fragment thereof includes an a mutation within the asparagine(N)-linked glycosylation motif N- X₁-S/T starting at the amino acid position corresponding to amino acid 49 (motif N6) of the mature human J-chain (SEQ ID NO: 20), where N is asparagine, X₁ is any amino acid except proline, and S/T is serine or threonine, and where the mutation prevents glycosylation at that motif. For example, the variant J-chain or functional fragment thereof can include an amino acid substitution at the amino acid position corresponding to amino acid N49 or amino acid S51 of SEQ ID NO: 20 where the amino acid corresponding to S51 is not substituted with

threonine (T), or where the variant J-chain includes amino acid substitutions at the amino acid positions corresponding to both amino acids N49 and S51 of SEQ ID NO: 20. In certain [embodimentexamples](#), the position corresponding to N49 of SEQ ID NO: 20 is substituted with alanine (A), glycine (G), threonine (T), serine (S) or aspartic acid (D). In certain [embodimentexamples](#) the position corresponding to N49 of SEQ ID NO: 20 is substituted with alanine (A). Where the J-chain is a variant human J-chain, the J-chain includes the amino acid sequence SEQ ID NO: 22. In certain [embodimentexamples](#), the position corresponding to N49 of SEQ ID NO: 20 is substituted with aspartic acid (D). Where the J-chain is a variant human J-chain, the J-chain includes the amino acid sequence SEQ ID NO: 23.

[0015] In certain [embodimentexamples](#), the J-chain or fragment or variant thereof is a modified J-chain further including a heterologous moiety, where the heterologous moiety is fused or conjugated to the J-chain or fragment or variant thereof. In certain [embodimentexamples](#) the heterologous moiety is a polypeptide fused to the J-chain or fragment or variant thereof. For example, the heterologous polypeptide can be fused to the J-chain or fragment or variant thereof via a peptide linker, including, *e.g.*, at least 5 amino acids, but no more than 25 amino acids, for example, the peptide linker can consist of GGGGSGGGGSGGGGS (SEQ ID NO: 29). In certain [embodimentexamples](#), 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 to both the N-terminus and C-terminus of the J-chain or fragment or variant thereof. In certain [embodimentexamples](#) the heterologous polypeptide includes a binding domain, for example, an antibody or antigen-binding fragment thereof. In certain [embodimentexamples](#) the antigen-binding fragment is a scFv fragment. In certain [embodimentexamples](#), the heterologous scFv fragment specifically binds to CD3ε. In certain [embodimentexamples](#), the modified J-chain includes the amino acid sequence SEQ ID NO: 24 (V15J), SEQ ID NO: 25 (V15J*), SEQ ID NO: 26 (V15J N49D), or SEQ ID NO: 55 (SJ*) or SEQ ID NOs: 20, 21, 22, or 23 fused via a peptide linker to an anti-CD3ε scFv including HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 amino acid sequences including SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54; SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 65, SEQ ID NO: 67, and SEQ ID NO: 69; SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 65, SEQ ID NO: 67, and SEQ ID NO: 70; SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 63, SEQ ID NO: 66, SEQ ID NO: 68, and SEQ ID NO: 71; SEQ ID NO: 58, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 66, SEQ ID NO: 68, and SEQ ID NO: 72; SEQ ID NO: 58, SEQ

ID NO: 61, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, and SEQ ID NO: 73, respectively.

[0016] In another aspect, the present disclosure provides a polynucleotide comprising a nucleic acid sequence that encodes the at least one variant IgM-derived heavy chain as described herein. In another aspect, the present disclosure provides a composition comprising the polynucleotide as described herein and (a) a nucleic acid sequence that encodes a light chain polypeptide subunit or (b) a nucleic acid sequence that encodes a light chain polypeptide subunit and a nucleic acid sequence that encodes a J-chain, or functional fragment thereof, or a functional variant thereof. In another aspect, the present disclosure provides a vector or set of vectors comprising the polynucleotide as described herein and (a) a nucleic acid sequence that encodes a light chain polypeptide subunit or (b) a nucleic acid sequence that encodes a light chain polypeptide subunit and a nucleic acid sequence that encodes a J-chain, or functional fragment thereof, or a functional variant thereof. The disclosure further provides a polynucleotide including a nucleic acid sequence that encodes the at least one variant IgM-derived heavy chain as provided herein, or a composition that includes such a polynucleotide. In certain embodimentexamples the composition can further include a nucleic acid sequence that encodes a light chain polypeptide subunit. In certain embodimentexamples the nucleic acid sequence encoding the at least one variant IgM-derived heavy chain and the nucleic acid sequence encoding the light chain polypeptide subunit are on separate vectors. In certain embodimentexamples they are on a single vector. In certain embodimentexamples the provided composition can further include a nucleic acid sequence that encodes a J-chain, or functional fragment thereof, or a functional variant thereof. In certain embodimentexamples the nucleic acid sequence encoding the at least one variant IgM-derived heavy chain, the nucleic acid sequence encoding the light chain polypeptide subunit, and the nucleic acid sequence encoding the J-chain are on a single vector or can be on two or more separate vectors. Such vectors are provided by the disclosure. In a further aspect, the present disclosure provides a host cell comprising the polynucleotide as described herein, the composition as described herein, or the vector or set of vectors as described herein, wherein the host cell can express the IgM-derived binding molecule as described herein. The disclosure also provides a host cell that includes any one or more of the provided polynucleotides, or vectors. In a further aspect, tThe disclosure also provides a method of producing the provided IgM-derived binding molecule, where the method includes culturing the provided host cell, and recovering the constant region or antibody.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0017] **FIGS. 1A-1B** show an alignment of the heavy chain constant regions of the various human immunoglobulin isotypes and subtypes, human IgG1 (IGHG1, SEQ ID NO: 34, amino acids 141-470 of GenBank AIC63046.1), human IgG2 (IGHG2, SEQ ID NO: 35, amino acids 1-326 of GenBank AXN93662.2), human IgG3 (IGHG3, SEQ ID NO: 36, amino acids 1 to 377 of GenBank AXN93659.2), human IgG4 (IGHG4, SEQ ID NO: 37, amino acids 1 to 327 of GenBank sp|P01861.1), human IgA1 (IGHA1, SEQ ID NO: 38, amino acids 144 to 496 of GenBank AIC59035.1), human IgA2 (IGHA2, SEQ ID NO: 39, amino acids 1 to 340 of GenBank P01877.4), human IgD (IGHD, SEQ ID NO: 40, amino acids 1 to 384 of GenBank P01880.3), human IgE (IGHE, SEQ ID NO: 41, amino acids 1-428 of GenBank P01854.1), and human IgM (IGHM, allele IGHM*04, SEQ ID NO: 2). Asparagine (N)-linked glycosylation motifs are shown by double-underline, with the asparagine residues in bold. Cysteine (C) amino acid residues that participate in intra-chain

WHAT IS CLAIMED IS:

1. An isolated IgM-derived binding molecule comprising at least one variant IgM-derived heavy chain, wherein the at least one variant IgM-derived heavy chain comprises a variant IgM heavy chain constant region associated with a binding domain that specifically binds to a target, wherein at least one asparagine(N)-linked glycosylation motif of the variant IgM heavy chain constant region is mutated to prevent glycosylation at that motif, and wherein an N-linked glycosylation motif comprises the amino acid sequence N-X₁-S/T, wherein N is asparagine, X₁ is any amino acid except proline, and S/T is serine or threonine.

2. The IgM-derived binding molecule of claim 1, wherein the variant IgM heavy chain constant region is derived from a human IgM heavy chain constant region comprising five N-linked glycosylation motifs N-X₁-S/T starting at amino acid positions corresponding to amino acid 46 (motif N1), amino acid 209 (motif N2), amino acid 272 (motif N3), amino acid 279 (motif N4), and amino acid 440 (motif N5) of SEQ ID NO: 1 (alleleIGHM*03) or SEQ ID NO: 2 (alleleIGHM*04).

3. The IgM-derived binding molecule of claim 2, wherein ~~at least one, at least two, at least three, or at least four of the N-X₁-S/T motifs comprises an amino acid insertion, deletion, or substitution that prevents glycosylation at that motif.~~the variant IgM heavy chain constant region comprises:

~~4.(a) The IgM-derived binding molecule of claim 3, comprising~~ an amino acid insertion, deletion, or substitution at motif N1, motif N2, motif N3, motif N5, or any combination of two or more, three or more, or all four of motifs N1, N2, N3, or N5, wherein the amino acid insertion, deletion, or substitution prevents glycosylation at that motif.

~~5.(b) The IgM-derived binding molecule of claim 4, comprising~~ an amino acid substitution at an amino acid position corresponding to amino acid N46, N209, N272, or N440 of SEQ ID NO: 1 or SEQ ID NO: 2 wherein the substituted amino acid is any amino acid, an amino acid substitution at an amino acid position corresponding to amino acid S48, S211, S274, or S442 of SEQ ID NO: 1 or SEQ ID NO: 2 wherein the substituted amino acid is any amino acid except threonine, or any combination of two or more, three or more, or four or more of the amino acid substitutions;

~~6.(c)~~ The IgM-derived binding molecule of claim ~~5~~, comprising an amino acid substitution corresponding to N46X₂, N46A, N46D, N46Q, N46K, S48X₃, S48A, N229X₂, N229A, N229D, N229Q, N229K, S231X₃, S231A, N272X₂, N272A, N272D, N272Q, N272K, S274X₃, S274A, N440X₂, N440A, N440D, N449Q, N449K, S242X₃, or S424A of SEQ ID NO: 1 or SEQ ID NO: 2, or any combination of two or more, three or more, or four or more of the amino acid substitutions, wherein X₂ is any amino acid and X₃ is any amino acid except threonine; or.

~~7.(d)~~ The IgM-derived binding molecule of any one of claims 1 to ~~6~~, wherein the variant IgM heavy chain constant region is a variant human IgM constant region comprising the amino acid sequence SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, 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, or SEQ ID NO: 18.

~~8.4.~~ The IgM-derived binding molecule of any one of claims 1 to ~~73~~, wherein the variant IgM heavy chain constant region is mutated to introduce at least one new asparagine(N)-linked glycosylation motif into the variant IgM heavy chain constant region, wherein the at least one new asparagine(N)-linked glycosylation motif is introduced at a site in the variant IgM heavy chain constant region that is not naturally glycosylated in an IgM antibody.

~~9.~~ The IgM-derived binding molecule of claim ~~48~~, wherein the new asparagine(N)-linked glycosylation motif is at a position in the variant IgM heavy chain constant region that corresponds to the position of an asparagine(N)-linked glycosylation motif present in a different immunoglobulin isotype.

~~10.5.~~ The IgM-derived binding molecule of claim ~~9~~, wherein the different immunoglobulin isotype is a human immunoglobulin isotype selected from the group consisting of human IgG1, human IgG2, human IgG3, human IgG4, human IgA1, human IgA2, human IgD, and human IgE.

~~11.6.~~ The IgM-derived binding molecule of any one of claims 1 to ~~105~~, wherein the target is a target epitope, a target antigen, a target cell, a target organ, or a target virus.

~~12.~~ The IgM-derived binding molecule of any one of claims 1 to ~~116~~, which is a pentameric or a hexameric IgM antibody comprising five or six bivalent IgM binding units,

respectively, wherein each binding unit comprises two IgM heavy chains each comprising a VH situated amino terminal to the variant IgM constant region, and two immunoglobulin light chains each comprising a light chain variable domain (VL) situated amino terminal to an immunoglobulin light chain constant region, and wherein the VH and VL combine to form an antigen-binding domain that specifically binds to the target.

~~13.7.~~ The IgM-derived binding molecule of claim 12, and wherein the five or six IgM binding units are identical.

~~14.8.~~ The IgM-derived binding molecule of claim 1 ~~or claim 13~~, which is pentameric, and further comprises a J-chain, or functional fragment thereof, or a functional variant thereof.

~~15.9.~~ The IgM-derived binding molecule of claim ~~148~~, wherein the J-chain is a mature human J-chain comprising the amino acid sequence SEQ ID NO: 20 or a functional fragment thereof, or a functional variant thereof.

~~16.—The IgM-derived binding molecule of claim 14 or claim 15, wherein the J-chain is a functional variant J-chain comprising one or more single amino acid substitutions, deletions, or insertions relative to a reference J-chain identical to the variant J-chain except for the one or more single amino acid substitutions, deletions, or insertions, and wherein the IgM-derived binding molecule exhibits an increased serum half-life upon administration to a subject animal relative to a reference IgM-derived binding molecule that is identical except for the one or more single amino acid substitutions, deletions, or insertions in the variant J-chain, and is administered in the same way to the same animal species.~~

~~17.—The IgM-derived binding molecule of claim 16, wherein the variant J-chain or functional fragment thereof comprises one, two, three, or four single amino acid substitutions, deletions, or insertions relative to the reference J-chain.~~

~~18.10.~~ The IgM-derived binding molecule of claim ~~116 or claim 17~~, wherein the variant J-chain or functional fragment thereof comprises an amino acid alanine (A) substitution at the amino acid position corresponding to amino acid Y102 of the wild-type mature human J-chain (SEQ ID NO: 20).

~~19.—The IgM-derived binding molecule of claim 18, wherein the amino acid corresponding to Y102 of SEQ ID NO: 20 is substituted with alanine (A).~~

~~20.—The IgM-derived binding molecule of claim 19, wherein the J-chain is the variant human J-chain J*, which comprises the amino acid sequence SEQ ID NO: 21.~~

~~21.11.~~ The IgM-derived binding molecule of any one of claims ~~16-8~~ to ~~1910~~, wherein the variant J-chain or functional fragment thereof comprises an a mutation within the

asparagine(N)-linked glycosylation motif N-X₁-S/T starting at the amino acid position corresponding to amino acid 49 (motif N6) of the mature human J-chain (SEQ ID NO: 20), wherein N is asparagine, X₁ is any amino acid except proline, and S/T is serine or threonine, and wherein the mutation prevents glycosylation at that motif.

~~12.~~ 12. The IgM-derived binding molecule of claim ~~24~~11, wherein:-

~~22.(a)~~ 22.(a) the variant J-chain or functional fragment thereof comprises an amino acid ~~substation~~substitution at the amino acid position corresponding to amino acid N49 or amino acid S51 SEQ ID NO: 20 wherein the amino acid corresponding to S51 is not substituted with threonine (T), or wherein the variant J-chain comprises amino acid substitutions at the amino acid positions corresponding to both amino acids N49 and S51 of SEQ ID NO: 20.

~~23.(b)~~ 23.(b) ~~The IgM-derived binding molecule of claim 22, wherein~~ the position corresponding to N49 of SEQ ID NO: 20 is substituted with alanine (A), glycine (G), threonine (T), serine (S) or aspartic acid (D)~~);~~);

~~24.(c)~~ 24.(c) ~~The IgM-derived binding molecule of claim 23, wherein~~ the position corresponding to N49 of SEQ ID NO: 20 is substituted with alanine (A)~~);~~ or (D); or

~~25.~~ 25. ~~The IgM-derived binding molecule of claim 24, wherein~~ the J-chain is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 22.

~~26.~~ 26. ~~The IgM-derived binding molecule of claim 23, wherein the position corresponding to N49 of SEQ ID NO: 20 is substituted with aspartic acid (D).~~

~~27.(d)~~ 27.(d) ~~The IgM-derived binding molecule of claim 26, wherein the J-chain is a variant human J-chain and comprises the amino acid sequence or~~ SEQ ID NO: 23.

~~28.13.~~ 28.13. The IgM-derived binding molecule of any one of claims ~~148 to 27~~ to 12, wherein the J-chain or fragment or variant thereof is a modified J-chain further comprising a heterologous moiety, wherein the heterologous moiety is fused or conjugated to the J-chain or fragment or variant thereof: via a peptide linker.

~~29.14.~~ 29.14. ~~The IgM-derived binding molecule of claim 28, wherein the heterologous moiety is a polypeptide fused to the J-chain or fragment or variant thereof;~~

~~30.~~ 30. ~~The IgM-derived binding molecule of claim 29, wherein the heterologous polypeptide is fused to the J-chain or fragment or variant thereof via a peptide linker.~~

~~31. The IgM-derived binding molecule of claim 30, wherein the peptide linker comprises at least 5 amino acids, but no more than 25 amino acids.~~

~~32. The IgM-derived binding molecule of claim 30 or claim 31, wherein the peptide linker consists of GGGGSGGGGSGGGGS (SEQ ID NO: 29).~~

~~33. The IgM-derived binding molecule of any one of claims 29 to 32, 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.~~

~~34. The IgM-derived binding molecule of any one of claims 29 to 33, wherein the heterologous polypeptide comprises a binding domain.~~

~~35. 14. The IgM-derived binding molecule of claim 34, wherein the binding domain of the heterologous polypeptide is an antibody or antigen-binding fragment thereof.~~

~~36.(a) The IgM-derived binding molecule of claim 35, wherein the antigen-binding fragment is a comprises an scFv fragment;~~

~~37.(b) The IgM-derived binding molecule of claim 36, wherein the heterologous comprises an scFv fragment that specifically binds to CD3ε; or~~

~~38.(c) The IgM-derived binding molecule of claim 37, comprises an scFv fragment that specifically binds to CD3ε, wherein the modified J-chain comprises the amino acid sequence SEQ ID NO: 24 (V15J), SEQ ID NO: 25 (V15J*), SEQ ID NO: 26 (V15J N49D), or SEQ ID NO: 55 (SJ*) or SEQ ID NOs: 20, 21, 22, or 23 fused via a peptide linker to an anti-CD3ε scFv comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 amino acid sequences comprising SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54; SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 65, SEQ ID NO: 67, and SEQ ID NO: 69; SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 65, SEQ ID NO: 67, and SEQ ID NO: 70; SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 63, SEQ ID NO: 66, SEQ ID NO: 68, and SEQ ID NO: 71; SEQ ID NO: 58, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 66, SEQ ID NO: 68, and SEQ ID NO: 72; SEQ ID NO: 58, SEQ ID NO: 61, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, and SEQ ID NO: 73, respectively.~~

~~39.15.~~ A polynucleotide comprising a nucleic acid sequence that encodes the at least one variant IgM-derived heavy chain of any one of claims 1 to ~~37~~14.

~~40.~~—A composition comprising the polynucleotide of claim ~~39~~15.

~~41.~~—~~The composition of claim 40, further comprising~~ and (a) a nucleic acid sequence that encodes a light chain polypeptide subunit.

~~42.16.~~ ~~The composition of claim 41, wherein the~~ or (b) a nucleic acid sequence encoding the at least one variant IgM-derived heavy chain and the nucleic acid sequence ~~encoding the~~that encodes a light chain polypeptide subunit ~~are on separate vectors~~and a nucleic acid sequence that encodes a J-chain, or functional fragment thereof, or a functional variant thereof.

~~43.~~—~~The composition of claim 41, wherein the~~A vector or set of vectors comprising the polynucleotide of claim 15 and ~~(a) a~~ nucleic acid sequence ~~encoding the at least one variant IgM-derived heavy chain and the~~that encodes a light chain polypeptide subunit or (b) a nucleic acid sequence ~~encoding the~~that encodes a light chain polypeptide subunit ~~are on a single vector.~~

~~44.17.~~ ~~The composition of any one of claims 41 to 43, further comprising~~and a nucleic acid sequence that encodes a J-chain, or functional fragment thereof, or a functional variant thereof.

~~45.~~—~~The composition of claim 44, wherein the nucleic acid sequence encoding the at least one variant IgM-derived heavy chain, the nucleic acid sequence encoding the light chain polypeptide subunit, and the nucleic acid sequence encoding the J-chain are on a single vector.~~

~~46.~~—~~The composition of claim 44, wherein the nucleic acid sequence encoding the at least one variant IgM-derived heavy chain, the nucleic acid sequence encoding the light chain polypeptide subunit, and the nucleic acid sequence encoding the J-chain are each on separate vectors.~~

~~47.~~—~~The vector or vectors of any one of claims 42, 43, 45, or 46.~~

~~48.18.~~ A host cell comprising the polynucleotide of claim ~~15~~39, the composition of ~~any one of claims~~claim ~~40~~16 to 46, or the vector or set of vectors of claim ~~17~~47, wherein the host cell can express the IgM-derived binding molecule of any one of claims 1 to ~~37~~14.

~~49.19.~~ A method of producing the IgM-derived binding molecule of any one of claims 1 to ~~37~~14, comprising culturing the host cell of claim ~~18~~48, and recovering the constant region or antibody.