

thereof. In one aspect, the present disclosure refers to an IgM antibody with enhanced serum half-life comprising five bivalent antibody binding units and a variant J-chain, wherein each binding unit comprises two IgM heavy chain constant regions, each associated with an antigen-binding domain or a heavy chain variable domain subunit (VH) thereof, wherein the variant J-chain comprises one, two, three, or four single amino acid substitutions relative to a reference J-chain identical to the variant J-chain except for the one, two, three, or four single amino acid substitutions; wherein the variant J-chain comprises an alanine (A), arginine (R), or serine (S) substitution at a position corresponding to amino acid Y102 of SEQ ID NO: 2, an alanine (A) substitution at a position corresponding to amino acid N49 of SEQ ID NO: 2, or an alanine (A), arginine (R), or serine (S) substitution at a position corresponding to amino acid Y102 of SEQ ID NO: 2 and an alanine (A) substitution at a position corresponding to amino acid N49 of SEQ ID NO: 2, and wherein the IgM antibody exhibits an increased serum half-life upon administration to a subject animal relative to a reference IgM antibody that is identical except for the one, two, three, or four single amino acid substitutions in the variant J-chain, and is to be administered in the same way to the same animal species.

[0008a] In another aspect, the present disclosure refers to an IgM antibody with enhanced serum half-life comprising five or six bivalent antibody binding units, wherein each binding unit comprises two variant IgM heavy chain constant regions, each associated with an antigen-binding domain or a heavy variable domain subunit (VH) thereof, wherein the variant IgM heavy chain constant regions each comprise one or two single amino acid substitutions relative to a reference IgM heavy chain constant region identical to the variant IgM heavy chain constant regions except for the one or two single amino acid substitutions, wherein the variant IgM heavy chain constant regions comprise an alanine (A) substitution at a position corresponding to amino acid R344 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid S345 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid S401 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid E402 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid E403 of SEQ ID NO: 12, or alanine (A) substitutions

at positions corresponding to amino acids S401 and E402 of SEQ ID NO: 12, and wherein the IgM antibody exhibits an increased serum half-life upon administration to a subject animal relative to a reference IgM antibody that is identical except for the one or two single amino acid substitutions in the IgM heavy chain constant regions, and is to be administered in the same way to the same animal species.

[0008b] In another aspect, the present disclosure refers to a composition comprising the IgM antibody as described herein, and a pharmaceutically acceptable carrier. In yet another aspect, the present disclosure refers to an isolated polynucleotide comprising a nucleic acid encoding the IgM antibody as described herein. In yet another aspect, the present disclosure refers to an expression vector comprising the polynucleotide as described herein. In yet another aspect, the present disclosure refers to a host cell comprising the polynucleotide as described herein or the expression vector as described herein.

5 **[0008c]** In certain examples the variant J-chain or functional fragment thereof includes 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. The provided variant J-chain can affect serum half-life of the provided IgM antibody or IgM-like antibody. For example, in certain examples the IgM antibody or IgM-like antibody exhibits an increased serum half-life upon administration to a subject animal relative to a reference IgM antibody or IgM-like antibody that is identical except for the one or more single amino acid substitutions,

WHAT IS CLAIMED IS:

1. An IgM antibody with enhanced serum half-life comprising five bivalent antibody binding units and a variant J-chain,

wherein each binding unit comprises two IgM heavy chain constant regions, each associated with an antigen-binding domain or a heavy chain variable domain subunit (VH) thereof,

wherein the variant J-chain comprises one, two, three, or four single amino acid substitutions relative to a reference J-chain identical to the variant J-chain except for the one, two, three, or four single amino acid substitutions;

wherein the variant J-chain comprises an alanine (A), arginine (R), or serine (S) substitution at a position corresponding to amino acid Y102 of SEQ ID NO: 2, an alanine (A) substitution at a position corresponding to amino acid N49 of SEQ ID NO: 2, or an alanine (A), arginine (R), or serine (S) substitution at a position corresponding to amino acid Y102 of SEQ ID NO: 2 and an alanine (A) substitution at a position corresponding to amino acid N49 of SEQ ID NO: 2, and wherein the IgM antibody exhibits an increased serum half-life upon administration to a subject animal relative to a reference IgM antibody that is identical except for the one, two, three, or four single amino acid substitutions in the variant J-chain, and is to be administered in the same way to the same animal species.

2. The IgM antibody of claim 1, wherein the reference J-chain comprises the amino acid sequence SEQ ID NO: 2, and wherein the variant J-chain comprises the amino acid sequence SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 10, or SEQ ID NO: 24.

3. The IgM antibody of claim 2, wherein the variant J-chain comprises the amino acid sequence SEQ ID NO: 3.

4. The IgM antibody of any one of claims 1 to 3, wherein the IgM heavy chain constant regions are variant IgM heavy chain constant regions comprising one or two single amino acid substitutions relative to a reference IgM heavy chain constant region identical to the variant IgM heavy chain constant regions except for the one or two single amino acid substitutions, wherein the variant IgM heavy chain constant regions comprise an alanine (A) substitution at a position corresponding to amino acid R344 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid S345 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid S401 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid E402 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid E403 of SEQ

ID NO: 12, or alanine (A) substitutions at positions corresponding to amino acids S401 and E402 of SEQ ID NO: 12, and wherein the IgM antibody exhibits a further increased serum half-life upon administration to a subject animal relative to a reference IgM antibody that is identical except for the one or two single amino acid substitutions in the IgM heavy chain constant regions, and is to be administered in the same way to the same animal species.

5. An IgM antibody with enhanced serum half-life comprising five or six bivalent antibody binding units,

wherein each binding unit comprises two variant IgM heavy chain constant regions, each associated with an antigen-binding domain or a heavy chain variable domain subunit (VH) thereof,

wherein the variant IgM heavy chain constant regions each comprise one or two single amino acid substitutions relative to a reference IgM heavy chain constant region identical to the variant IgM heavy chain constant regions except for the one or two single amino acid substitutions, wherein the variant IgM heavy chain constant regions comprise an alanine (A) substitution at a position corresponding to amino acid R344 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid S345 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid S401 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid E402 of SEQ ID NO: 12, an alanine (A) substitution at a position corresponding to amino acid E403 of SEQ ID NO: 12, or alanine (A) substitutions at positions corresponding to amino acids S401 and E402 of SEQ ID NO: 12, and

wherein the IgM antibody exhibits an increased serum half-life upon administration to a subject animal relative to a reference IgM antibody that is identical except for the one or two single amino acid substitutions in the IgM heavy chain constant regions, and is to be administered in the same way to the same animal species.

6. The IgM antibody of claim 5, wherein the reference IgM heavy chain constant region comprises the amino acid sequence SEQ ID NO: 12, and wherein the variant IgM heavy chain constant regions comprise the amino acid sequence SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID NO: 34.

7. The IgM antibody of claim 5 or claim 6, further comprising a J-chain or a variant J-chain.

8. The IgM antibody of claim 7, wherein the J-chain is a human J-chain comprising the amino acid sequence SEQ ID NO: 2.

9. The IgM antibody of claim 7, wherein the J-chain is a variant J-chain comprising the amino acid sequence SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 10, or SEQ ID NO: 24.

10. The IgM antibody of any one of claims 1 to 9, wherein the increased serum half-life comprises an increased alpha half-life ($t_{1/2\alpha}$), an increased beta half-life ($t_{1/2\beta}$), or an increased $t_{1/2\alpha}$ and an increased $t_{1/2\beta}$ and/or wherein the IgM antibody further exhibits an increased peak plasma concentration (C_{max}), an increased area under the curve (AUC), a modified clearance time, or any combination thereof relative to the reference antibody.

11. The IgM antibody of any one of claims 1 to 10, wherein the IgM heavy chain constant regions each comprise a C μ 4 domain and an IgM tailpiece (tp) domain.

12. The IgM antibody of claim 11, wherein the IgM heavy chain constant regions each further comprise a C μ 3 domain, a C μ 2 domain, a C μ 1 domain, or any combination thereof.

13. The IgM antibody of any one of claims 1 to 12, wherein each binding unit further comprises two light chain constant regions each associated with an antigen-binding domain or a light chain variable region (VL) thereof.

14. The IgM antibody of any one of claims 1 to 4 or 7 to 13, wherein the J-chain or variant J-chain further comprises one or more heterologous polypeptides directly or indirectly fused to the J-chain or variant J-chain.

15. The IgM antibody of claim 14, wherein the one or more heterologous polypeptides is/are fused to the J-chain or variant J-chain via a peptide linker comprising at least 5 amino acids, but no more than 25 amino acids.

16. The IgM antibody of claim 14 or claim 15, wherein the one or more heterologous polypeptides is/are fused to the N-terminus of the J-chain or variant J-chain, the C-terminus of the J-chain or variant J-chain, or wherein heterologous polypeptides are fused to both the N-terminus and C-terminus of the J-chain or variant J-chain, wherein the heterologous polypeptides can be the same or different.

17. The IgM antibody of claims 14 to 16, wherein at least one heterologous polypeptide comprises a binding domain comprising an antibody or an scFv.

18. The IgM antibody of claim 17, wherein at least one heterologous polypeptide can specifically bind to CD3ε.

19. A composition comprising the IgM antibody of any one of claims 1 to 18, and a pharmaceutically acceptable carrier.

20. An isolated polynucleotide comprising a nucleic acid encoding the IgM antibody of any one of claims 1 to 18.

21. An expression vector comprising the polynucleotide of claim 20.

22. A host cell comprising the polynucleotide of claim 20 or the expression vector of claim 21.