

2018/017888, WO 2018/017763, WO 2018/017889, WO 2018/017761, and WO 2019/169314, the contents of which are incorporated herein by reference in their entireties.

[0006] There remains a need to target CD123-expressing AML cells and induce T-cell mediated killing of those cells, while minimizing CRS. We have evaluated whether targeting CD123 with our CD3 bispecific IgM technology will not only effectively target CD123 expressing AML tumor cells for T cell mediated cytotoxicity, but will also produce responses with a favorable safety profile for the cytokine release syndrome that has sometimes been severe in patients treated with IgG based CD123 x CD3 bispecific antibodies. In addition, the high avidity binding of IgM antibodies may allow our CD123 x CD3 bispecific IgM to target tumor cells that express relatively lower levels of cell surface expression of CD123, as compared with IgG based bispecific antibodies.

SUMMARY

[0007] In one aspect, this disclosure provides a multimeric, bispecific or multispecific binding molecule including two or five bivalent binding units and a modified J-chain, where the modified J-chain includes a wild-type J-chain or a functional fragment or variant thereof and a J-chain-associated antigen-binding domain that specifically binds to an immune effector cell. Each binding unit includes two antibody heavy chains, each including an IgA, IgA-like, IgM, or IgM-like heavy chain constant region or multimerizing fragment thereof and at least a heavy chain variable region (VH) portion of a binding unit-associated antigen-binding domain, where at least three of the binding unit-associated antigen-binding domains specifically bind to CD123, and where the binding molecule can induce immune effector cell-dependent killing of cells expressing CD123.

[0008] In certain embodiment examples, the modified J-chain includes a variant J-chain or fragment thereof including 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 binding molecule, such that the binding molecule exhibits an increased serum half-life upon administration to an animal relative to a reference binding molecule that is identical except for the one or more single amino acid substitutions, deletions, or insertions in the J-chain, and is administered in the same way to the same animal species. In certain embodiment examples, the modified J-chain includes 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). In certain embodiment examples, the amino acid corresponding to Y102 of SEQ ID NO: 2 can be substituted with alanine

(A), serine (S), or arginine (R). In certain [embodimentexamples](#), the amino acid corresponding to Y102 of SEQ ID NO: 2 can be substituted with alanine (A). In certain [embodimentexamples](#), the J-chain is a variant human J-chain and includes the amino acid sequence SEQ ID NO: 3 (“J*”).

5 [0009] In certain [embodimentexamples](#), the J-chain-associated antigen-binding domain includes an antibody single chain Fv (scFv) fragment fused or chemically conjugated to the J-chain or fragment or variant thereof. For example, the scFv fragment can be fused to the J-chain via a peptide linker. In certain [embodimentexamples](#), the scFv fragment 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 scFv fragments can be fused to both the N-terminus and C-terminus of the J-chain or fragment or variant thereof.

[0010] In certain [embodimentexamples](#), the immune effector cell is a T cell or an NK cell. In those [embodimentexamples](#) where the immune effector cell is a T cell, the scFv fragment, in certain [embodimentexamples](#), can specifically bind to CD3ε. In certain [embodimentexamples](#), the T cell is a CD8⁺ cytotoxic T cell.

15 [0011] In certain [embodimentexamples](#), the scFv fragment comprises a heavy chain variable region (VH) and a light chain variable region (VL), where the VH comprises VH complementarity-determining regions VHCDR1, VHCDR2, and VHCDR3 and the VL comprises VL complementarity-determining regions VLCDR1, VLCDR2, and VLCDR3, where (a) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11 with zero, one, or two amino acid substitutions, respectively; (b) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 130, SEQ ID NO: 132, and SEQ ID NO: 135 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 138, SEQ ID NO: 140, and SEQ ID NO: 142 with zero, one, or two amino acid substitutions, respectively; (c) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 130, SEQ ID NO: 132, and SEQ ID NO: 135 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 138, SEQ ID NO: 140, and SEQ ID NO: 143 with zero, one, or two amino acid substitutions, respectively; (d) the VHCDR1,

VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 131, SEQ ID NO: 133, and SEQ ID NO: 136 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 139, SEQ ID NO: 141, and SEQ ID NO: 144 with zero, one, or two amino acid substitutions, respectively; (e) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 131, SEQ ID NO: 134, and SEQ ID NO: 136 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 139, SEQ ID NO: 141, and SEQ ID NO: 145 with zero, one, or two amino acid substitutions, respectively; or (f) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 131, SEQ ID NO: 134, and SEQ ID NO: 137 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 139, SEQ ID NO: 141, and SEQ ID NO: 146 with zero, one, or two amino acid substitutions, respectively.

[0012] In certain embodimentexamples, the scFv fragment includes a heavy chain variable region (VH) and a light chain variable region (VL), where the VH includes the VH complementarity-determining regions VHCDR1, VHCDR2, and VHCDR3 with the amino acid sequences SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, respectively, or SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7 with one, two, or three amino acid substitutions in one or more of the VHCDRs, and where the VL includes the VL complementarity-determining regions VLCDR1, VLCDR2, and VLCDR3 with the amino acid sequences SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11, respectively, or SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11 with one, two, or three amino acid substitutions in one or more of the VLCDRs. In certain embodimentexamples, the scFv fragment comprises the VH and VL amino acid sequences SEQ ID NO: 4 and SEQ ID NO: 8, SEQ ID NO: 119 and SEQ ID NO: 120, SEQ ID NO: 121 and SEQ ID NO: 122, SEQ ID NO: 123 and SEQ ID NO: 124, SEQ ID NO: 125 and SEQ ID NO: 126, or SEQ ID NO: 127 and SEQ ID NO: 128, respectively.

[0013] In certain embodimentexamples, the scFv fragment includes the VH amino acid sequence SEQ ID NO: 4 and the VL amino acid sequence SEQ ID NO: 8. In other embodimentexamples, the scFv fragment includes a heavy chain variable region (VH) and a light chain variable region (VL), where the VH and VL include the amino acid sequences SEQ ID NO: 13 and SEQ ID NO: 14, respectively. In certain embodimentexamples, the modified J chain includes

amino acids 20 to 420 of SEQ ID NO: 12, amino acids 20 to 412 of SEQ ID NO: 15, or amino acids 23 to 415 of SEQ ID NO: 16.

[0014] In certain embodimentexamples, the immune effector cell is an NK cell, and where the scFv fragment specifically binds to CD16.

[0015] In certain embodimentexamples, the modified J-chain can further include an immune stimulatory agent ("ISA") fused or chemically conjugated to the J-chain or fragment or variant thereof. In certain embodimentexamples, the ISA includes a cytokine or receptor-binding fragment or variant thereof. In certain embodimentexamples, the ISA includes (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 including the sushi domain or a variant thereof capable of associating with I ("R"), where the J-chain or fragment or variant thereof and at least one of I and R are associated as a fusion protein, and where I and R can associate to function as the ISA. In certain embodimentexamples, the ISA can be fused to the J-chain via a peptide linker.

[0016] In certain embodimentexample, each binding unit of the provided binding molecule further includes two light chains, each including a kappa or lambda light chain constant region and at least a light chain variable region (VL) portion of a binding unit-associated antigen binding domain.

[0017] In certain embodimentexamples, the provided binding molecule includes at least four, at least five, at least six, at least seven, at least eight, at least nine, or ten binding unit-associated antigen-binding domains that specifically bind to CD123. In certain embodimentexamples, the at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or least ten binding unit-associated antigen-binding domains bind to the same CD123 epitope. In certain embodimentexamples, all the binding unit-associated antigen binding domains of the provided binding molecule are identical.

[0018] In certain embodimentexample, the binding unit-associated antigen-binding domains include a heavy chain variable region (VH) and a light chain variable region (VL), where the VH and VL include six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, where the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 include the CDRs of an antibody having VH and VL amino acid sequences including or contained within SEQ ID NO: 32 and SEQ ID NO: 33, SEQ ID NO: 37 and SEQ ID NO: 38, SEQ ID NO: 42 and SEQ ID NO: 43, SEQ ID NO: 44 and SEQ ID NO: 45, SEQ ID NO: 46 and SEQ ID NO: 47, SEQ ID NO: 48 and

SEQ ID NO: 49, SEQ ID NO: 50 and SEQ ID NO: 51, SEQ ID NO: 52 and SEQ ID NO:
 53, SEQ ID NO: 54 and SEQ ID NO: 55, SEQ ID NO: 56 and SEQ ID NO: 57, SEQ ID
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 81, SEQ ID NO: 82 and SEQ ID NO: 83, SEQ ID NO: 84 and SEQ ID NO: 85, SEQ ID
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 and SEQ ID NO: 108, SEQ ID NO: 109 and SEQ ID NO: 110, SEQ ID NO: 111 and SEQ
 15 ID NO: 112, SEQ ID NO: 113 and SEQ ID NO: 114, SEQ ID NO: 115 and SEQ ID NO:
 116, or SEQ ID NO: 117 and SEQ ID NO: 118, respectively or the CDRs of an antibody
 including the VH and VL amino acid sequences including or contained within SEQ ID
 NO: 32 and SEQ ID NO: 33, SEQ ID NO: 37 and SEQ ID NO: 38, SEQ ID NO: 42 and
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 61, SEQ ID NO: 62 and SEQ ID NO: 63, SEQ ID NO: 64 and SEQ ID NO: 65, SEQ ID
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 89, SEQ ID NO: 90 and SEQ ID NO: 91, SEQ ID NO: 92 and SEQ ID NO: 93, SEQ ID
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 SEQ ID NO: 111 and SEQ ID NO: 112, SEQ ID NO: 113 and SEQ ID NO: 114, SEQ ID

NO: 115 and SEQ ID NO: 116, or SEQ ID NO: 117 and SEQ ID NO: 118, respectively, except for one or two amino acid substitutions in one or more of the CDRs.

[0019] In certain embodimentexamples, the binding unit-associated antigen-binding domains include an antibody VH and a VL, where the VH and VL include 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 including or contained within SEQ ID NO: 32 and SEQ ID NO: 33, SEQ ID NO: 37 and SEQ ID NO: 38, SEQ ID NO: 42 and SEQ ID NO: 43, SEQ ID NO: 44 and SEQ ID NO: 45, SEQ ID NO: 46 and SEQ ID NO: 47, SEQ ID NO: 48 and SEQ ID NO: 49, SEQ ID NO: 50 and SEQ ID NO: 51, SEQ ID NO: 52 and SEQ ID NO: 53, SEQ ID NO: 54 and SEQ ID NO: 55, SEQ ID NO: 56 and SEQ ID NO: 57, SEQ ID NO: 58 and SEQ ID NO: 59, SEQ ID NO: 60 and SEQ ID NO: 61, SEQ ID NO: 62 and SEQ ID NO: 63, SEQ ID NO: 64 and SEQ ID NO: 65, SEQ ID NO: 66 and SEQ ID NO: 67, SEQ ID NO: 68 and SEQ ID NO: 69, SEQ ID NO: 70 and SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73, SEQ ID NO: 74 and SEQ ID NO: 75, SEQ ID NO: 76 and SEQ ID NO: 77, SEQ ID NO: 78 and SEQ ID NO: 79, SEQ ID NO: 80 and SEQ ID NO: 81, SEQ ID NO: 82 and SEQ ID NO: 83, SEQ ID NO: 84 and SEQ ID NO: 85, SEQ ID NO: 86 and SEQ ID NO: 87, SEQ ID NO: 88 and SEQ ID NO: 89, SEQ ID NO: 90 and SEQ ID NO: 91, SEQ ID NO: 92 and SEQ ID NO: 93, SEQ ID NO: 94 and SEQ ID NO: 95, 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: 107 and SEQ ID NO: 108, SEQ ID NO: 109 and SEQ ID NO: 110, SEQ ID NO: 111 and SEQ ID NO: 112, SEQ ID NO: 113 and SEQ ID NO: 114, SEQ ID NO: 115 and SEQ ID NO: 116, or SEQ ID NO: 117 and SEQ ID NO: 118, respectively.

[0020] In certain embodimentexamples, the provided binding molecule is a dimeric binding molecule that includes two bivalent binding units, where each binding unit includes two antibody heavy chains, each including an IgA or IgA-like heavy chain constant region or multimerizing fragment thereof. In certain embodimentexamples the provided dimeric binding molecule further includes a secretory component, or fragment or variant thereof. In certain embodimentexamples, the IgA or IgA-like heavy chain constant regions or multimerizing fragments thereof each include a Cα3 and a tailpiece (tp) domain, and can further include a Cα1 domain, a Cα2 domain, an IgA hinge region, or any combination thereof. In certain embodimentexamples, the IgA or IgA-like heavy chain constant regions are human IgA or IgA-like constant regions and can include the amino acid sequence SEQ ID NO: 24, SEQ ID

NO: 25, or any multimerizing variant or fragment thereof. In certain embodimentexamples each binding unit includes two IgA or IgA-like heavy chains each including a VH situated amino terminal to the IgA constant region or fragment thereof, and two immunoglobulin light chains each including a VL situated amino terminal to an immunoglobulin light chain constant region.

[0021] In certain embodimentexamples, the provided binding molecule is a pentameric binding molecule including five bivalent binding units, where each binding unit includes two IgM or IgM-like heavy chain constant regions or multimerizing fragments thereof. In certain embodimentexamples, the IgM or IgM-like heavy chain constant regions or multimerizing fragments thereof each include a C μ 4 domain and a tailpiece (tp) domain or fragment or variant thereof and can further include a C μ 1 domain, a C μ 2 domain, a C μ 3 domain, or any combination thereof. In certain embodimentexamples the IgM or IgM-like heavy chain constant regions are human IgM constant regions and can include the amino acid sequence SEQ ID NO: 22, SEQ ID NO: 23, or a multimerizing variant or fragment thereof. In certain embodimentexamples each binding unit includes two IgM heavy chains each including a VH situated amino terminal to the IgM constant region or fragment thereof, and two immunoglobulin light chains each including a VL situated amino terminal to an immunoglobulin light chain constant region.

[0022] In certain embodimentexamples, the binding units include variant human IgM constant regions, where the multimeric binding molecule has reduced CDC activity relative to a multimeric binding molecule including IgM heavy chain constant regions including the amino acid sequence SEQ ID NO: 22, SEQ ID NO: 23, or a multimerizing variant or fragment thereof. In certain embodimentexamples, each IgM heavy chain constant region includes a variant of the amino acid sequence SEQ ID NO: 22 or SEQ ID NO: 23, where the variant includes an amino acid substitution at position P311 of SEQ ID NO: 22 or SEQ ID NO: 23, an amino acid substitution at position P313 of SEQ ID NO: 22 or SEQ ID NO: 23, or amino acid substitutions at positions P311 and P313 of SEQ ID NO: 22 or SEQ ID NO: 23.

[0023] In certain embodimentexamples, the binding units include variant human IgM constant regions 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; where the binding molecule exhibits increased serum half-life upon

administration to a subject animal relative to a multimeric binding molecule including the reference IgM heavy chain constant regions, and is administered in the same way to the same animal species. In certain embodiment examples, the variant IgM heavy chain constant regions include 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: 22 or SEQ ID NO: 23.

[0024] This disclosure further provides composition, *e.g.*, a pharmaceutical composition, that includes the provided binding molecule.

[0025] In another aspect, This disclosure also provides a polynucleotide that includes a nucleic acid sequence that encodes a polypeptide subunit of the provided binding molecule.

[0026] In certain embodiment examples, the polypeptide subunit includes an IgM or IgM-like heavy chain constant region and at least an antibody VH portion of the binding unit-associated antigen-binding domain of the binding molecule. In certain embodiment examples, the polypeptide subunit includes a human IgM constant region or fragment thereof fused to the C-terminal end of a VH that includes: (a) HCDR1, HCDR2, and HCDR3 regions including the CDRs contained in the VH amino acid sequence including or contained within SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, or SEQ ID NO: 117; or the CDRs contained in the VH amino acid sequence including or contained within SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, or SEQ ID NO: 117 except for one or two single amino acid substitutions in one or more of the HCDRs; or (b) an

amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to the mature VH amino acid sequence including or contained within SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, or SEQ ID NO: 117.

[0027] In certain embodiment examples, the polypeptide subunit includes a light chain constant region and an antibody VL portion of the antigen-binding domain of the multimeric binding molecule. In certain embodiment examples, the polypeptide subunit includes a human kappa or lambda light chain constant region or fragment thereof fused to the C-terminal end of a VL including: (a) LCDR1, LCDR2, and LCDR3 regions including the CDRs contained in the VL amino acid sequence including or contained within SEQ ID NO: 33, SEQ ID NO: 38, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, or SEQ ID NO: 118; or the CDRs contained in the VL amino acid sequence SEQ ID NO: 33, SEQ ID NO: 38, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, or SEQ ID NO: 118 except for one or two single amino acid substitutions in one or more of the LCDRs; or (b) an amino acid sequence at least

80%, at least 85%, at least 90%, at least 95% or 100% identical to the mature VL amino acid sequence including or contained within SEQ ID NO: 33, SEQ ID NO: 38, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, or SEQ ID NO: 118.

[0028] In certain embodimentexamples, the polypeptide subunit includes a modified J-chain, where the modified J-chain includes a wild-type J-chain or a functional fragment or variant thereof and a J-chain-associated antigen-binding domain that specifically binds to an immune effector cell. In certain embodimentexamples, the modified J-chain includes an amino acid sequence at least 80%, 85%, 90%, 95%, or 100% identical to amino acids 20 to 420 of SEQ ID NO: 12, amino acids 20 to 412 of SEQ ID NO: 15, or amino acids 23 to 415 of SEQ ID NO: 16.

[0029] This disclosure further provides a composition that includes two or more of the aforementioned polynucleotides. The polynucleotides can be situated are on two or more separate vectors, or on a single vector. Such a vector or vectors are also provided.

[0030] In another aspect, tThis disclosure also provides a host cell that includes one or more provided polynucleotide(s) or the provided vector or vectors, where the host cell can express the provided binding molecule or a subunit thereof. In another aspect, tThis disclosure further provides a method of producing the provided binding molecule, where the method includes culturing the host cell and then recovering the binding molecule.

[0031] In a further aspect, this disclosure provides a use of a binding molecule as described herein in the manufacture of a medicament for treating cancer or other malignancy, wherein the binding molecule can induce immune effector cell-mediated killing of cancer cells. This disclosure also provides a method of treating cancer or other malignancy, where the method includes administering to a subject in need of cancer treatment an effective amount of the provided binding molecule, where the binding molecule can induce immune effector cell-mediated killing of cancer cells. In certain embodimentexample the cancer or malignancy is a hematologic cancer or malignancy, for example, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML),

B-cell acute lymphoblastic leukemia (B-cell ALL), classical Hodgkin's lymphoma, hairy cell leukemia, chronic lymphocytic leukemia (CLL), systemic mastocytosis, or plasmacytoid

WHAT IS CLAIMED IS:

1. A multimeric, bispecific or multispecific binding molecule comprising two or five bivalent binding units and a modified J-chain,

wherein the modified J-chain comprises a wild-type J-chain or a functional fragment or variant thereof and a J-chain-associated antigen-binding domain that specifically binds to an immune effector cell,

wherein each binding unit comprises two antibody heavy chains, each comprising an IgA, IgA-like, IgM, or IgM-like heavy chain constant region or multimerizing fragment thereof and at least a heavy chain variable region (VH) portion of a binding unit-associated antigen-binding domain, wherein at least three of the binding unit-associated antigen-binding domains specifically bind to CD123, and

wherein the binding molecule can induce immune effector cell-dependent killing of cells expressing CD123.

2. The binding molecule of claim 1, wherein the modified J-chain comprises 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 binding molecule; and wherein the binding molecule exhibits an increased serum half-life upon administration to an animal relative to a reference binding molecule that is identical except for the one or more single amino acid substitutions, deletions, or insertions in the J-chain, and is administered in the same way to the same animal species.

3. The binding molecule of claim 2, wherein the modified J-chain 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).

4. The binding molecule of claim 3, wherein the amino acid corresponding to Y102 of SEQ ID NO: 2 is substituted with alanine (A), serine (S), or arginine (R).

5. The binding molecule of claim 4, wherein the amino acid corresponding to Y102 of SEQ ID NO: 2 is substituted with alanine (A).

6. The binding molecule of claim 5, wherein the J-chain is a variant human J-chain and comprises the amino acid sequence SEQ ID NO: 3 (“J*”).

7. The binding molecule of ~~any one of claims 1 to 6~~claim 1, wherein the J-chain-associated antigen-binding domain comprises an antibody single chain Fv (scFv) fragment fused or chemically conjugated to the J-chain or fragment or variant thereof.

8. The binding molecule of claim 7, wherein the scFv fragment is fused to the J-chain via a peptide linker.

9. The binding molecule of ~~claim 7 or~~ claim 8, wherein the scFv fragment 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 binding molecule of any one of claims 7 to 9, wherein the immune effector cell is a T cell or an NK cell.~~

~~11. The binding molecule of claim 10, wherein the immune effector cell is a T cell, and wherein the scFv fragment specifically binds to CD3.~~

~~12.10.~~ The binding molecule of claim ~~10 or claim 11~~7, wherein the ~~T cell~~immune effector cell is a CD8⁺ cytotoxic T cell, and wherein the scFv fragment specifically binds to CD3.

~~13.11.~~ The binding molecule of claim ~~11 or claim 12~~10, wherein the scFv fragment comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises VH complementarity-determining regions VHCDR1, VHCDR2, and VHCDR3 and the VL comprises VL complementarity-determining regions VLCDR1, VLCDR2, and VLCDR3, wherein

(a) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11 with zero, one, or two amino acid substitutions, respectively;

(b) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 130, SEQ ID NO: 132, and SEQ ID NO: 135 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 138, SEQ ID NO: 140, and SEQ ID NO: 142 with zero, one, or two amino acid substitutions, respectively;

(c) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 130, SEQ ID NO: 132, and SEQ ID NO: 135 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino

acid sequences SEQ ID NO: 138, SEQ ID NO: 140, and SEQ ID NO: 143 with zero, one, or two amino acid substitutions, respectively;

(d) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 131, SEQ ID NO: 133, and SEQ ID NO: 136 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 139, SEQ ID NO: 141, and SEQ ID NO: 144 with zero, one, or two amino acid substitutions, respectively;

(e) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 131, SEQ ID NO: 134, and SEQ ID NO: 136 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 139, SEQ ID NO: 141, and SEQ ID NO: 145 with zero, one, or two amino acid substitutions, respectively; or

(f) the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences SEQ ID NO: 131, SEQ ID NO: 134, and SEQ ID NO: 137 with zero, one, or two amino acid substitutions, respectively, and the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences SEQ ID NO: 139, SEQ ID NO: 141, and SEQ ID NO: 146 with zero, one, or two amino acid substitutions, respectively.

~~14.12.~~ The binding molecule of claim ~~1311~~, wherein the scFv fragment comprises the VH and VL amino acid sequences SEQ ID NO: 4 and SEQ ID NO: 8, SEQ ID NO: 119 and SEQ ID NO: 120, SEQ ID NO: 121 and SEQ ID NO: 122, SEQ ID NO: 123 and SEQ ID NO: 124, SEQ ID NO: 125 and SEQ ID NO: 126, or SEQ ID NO: 127 and SEQ ID NO: 128, respectively.

~~15.13.~~ The binding molecule of claim ~~11 or claim 1210~~, wherein the scFv fragment comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the amino acid sequences SEQ ID NO: 13 and SEQ ID NO: 14, respectively.

~~16.14.~~ The binding molecule of claim ~~1311~~ wherein the modified J chain comprises an amino acid sequence comprising amino acids 20 to 420 of SEQ ID NO: 12, amino acids 20 to 412 of SEQ ID NO: 15, or amino acids 23 to 415 of SEQ ID NO: 16.

~~17.15.~~ The binding molecule of claim ~~107~~, wherein the immune effector cell is an NK cell, and wherein the scFv fragment specifically binds to CD16.

~~18.—The binding molecule of any one of claims 1 to 17, wherein the modified J-chain further comprises an immune stimulatory agent (“ISA”) fused or chemically conjugated to the J-chain or fragment or variant thereof.~~

~~19.—The binding molecule of claim 18, wherein the ISA comprises a cytokine or receptor-binding fragment or variant thereof.~~

~~20.—The binding molecule of claim 19, 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 the J-chain or fragment or variant thereof 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.~~

~~21.—The binding molecule of any one of claims 18 to 20, wherein the ISA is fused to the J-chain via a peptide linker.~~

~~22.—The binding molecule of any one of claims 1 to 21, wherein each binding unit further comprises two light chains, each comprising a kappa or lambda light chain constant region and at least a light chain variable region (VL) portion of a binding unit-associated antigen-binding domain.~~

~~23.—The binding molecule of any one of claims 1 to 22, which comprises at least four, at least five, at least six, at least seven, at least eight, at least nine, or ten binding unit-associated antigen-binding domains that specifically bind to CD123.~~

~~24.—The binding molecule of claim 23, wherein the at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or least ten binding unit-associated antigen-binding domains bind to the same CD123 epitope.~~

~~25.16.~~ The binding molecule of claim ~~24~~1, wherein all the binding unit-associated antigen binding domains are identical.

~~26.17.~~ The binding molecule of ~~any one of claims 23 to 25~~claim 16, wherein the binding unit-associated antigen-binding domains comprise 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 amino acid sequences comprising or contained within SEQ ID NO: 32 and SEQ ID NO: 33, SEQ ID NO: 37 and SEQ ID NO: 38, SEQ ID NO: 42 and SEQ ID NO: 43, SEQ ID NO: 44 and SEQ ID NO: 45, SEQ ID NO: 46 and SEQ ID NO: 47, SEQ ID NO: 48 and SEQ ID NO: 49, SEQ ID NO: 50 and SEQ ID NO: 51, SEQ ID NO: 52 and SEQ ID NO: 53, SEQ ID NO: 54 and SEQ ID NO: 55, SEQ ID NO: 56 and SEQ ID NO: 57, SEQ ID NO: 58 and SEQ ID NO: 59, SEQ ID NO: 60 and SEQ ID NO: 61, SEQ ID NO: 62 and SEQ ID NO: 63, SEQ ID NO: 64 and SEQ ID

NO: 65, SEQ ID NO: 66 and SEQ ID NO: 67, SEQ ID NO: 68 and SEQ ID NO: 69, SEQ ID NO: 70 and SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73, SEQ ID NO: 74 and SEQ ID NO: 75, SEQ ID NO: 76 and SEQ ID NO: 77, SEQ ID NO: 78 and SEQ ID NO: 79, SEQ ID NO: 80 and SEQ ID NO: 81, SEQ ID NO: 82 and SEQ ID NO: 83, SEQ ID NO: 84 and SEQ ID NO: 85, SEQ ID NO: 86 and SEQ ID NO: 87, SEQ ID NO: 88 and SEQ ID NO: 89, SEQ ID NO: 90 and SEQ ID NO: 91, SEQ ID NO: 92 and SEQ ID NO: 93, SEQ ID NO: 94 and SEQ ID NO: 95, 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: 107 and SEQ ID NO: 108, SEQ ID NO: 109 and SEQ ID NO: 110, SEQ ID NO: 111 and SEQ ID NO: 112, SEQ ID NO: 113 and SEQ ID NO: 114, SEQ ID NO: 115 and SEQ ID NO: 116, or SEQ ID NO: 117 and SEQ ID NO: 118, respectively or the CDRs of an antibody comprising the VH and VL amino acid sequences comprising or contained within SEQ ID NO: 32 and SEQ ID NO: 33, SEQ ID NO: 37 and SEQ ID NO: 38, SEQ ID NO: 42 and SEQ ID NO: 43, SEQ ID NO: 44 and SEQ ID NO: 45, SEQ ID NO: 46 and SEQ ID NO: 47, SEQ ID NO: 48 and SEQ ID NO: 49, SEQ ID NO: 50 and SEQ ID NO: 51, SEQ ID NO: 52 and SEQ ID NO: 53, SEQ ID NO: 54 and SEQ ID NO: 55, SEQ ID NO: 56 and SEQ ID NO: 57, SEQ ID NO: 58 and SEQ ID NO: 59, SEQ ID NO: 60 and SEQ ID NO: 61, SEQ ID NO: 62 and SEQ ID NO: 63, SEQ ID NO: 64 and SEQ ID NO: 65, SEQ ID NO: 66 and SEQ ID NO: 67, SEQ ID NO: 68 and SEQ ID NO: 69, SEQ ID NO: 70 and SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73, SEQ ID NO: 74 and SEQ ID NO: 75, SEQ ID NO: 76 and SEQ ID NO: 77, SEQ ID NO: 78 and SEQ ID NO: 79, SEQ ID NO: 80 and SEQ ID NO: 81, SEQ ID NO: 82 and SEQ ID NO: 83, SEQ ID NO: 84 and SEQ ID NO: 85, SEQ ID NO: 86 and SEQ ID NO: 87, SEQ ID NO: 88 and SEQ ID NO: 89, SEQ ID NO: 90 and SEQ ID NO: 91, SEQ ID NO: 92 and SEQ ID NO: 93, SEQ ID NO: 94 and SEQ ID NO: 95, 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: 107 and SEQ ID NO: 108, SEQ ID NO: 109 and SEQ ID NO: 110, SEQ ID NO: 111 and SEQ ID NO: 112, SEQ ID NO: 113 and SEQ ID NO: 114, SEQ ID NO: 115 and SEQ ID NO: 116, or SEQ ID NO: 117 and SEQ ID NO: 118, respectively, except for one or two amino acid substitutions in one or more of the CDRs.

~~27. —The binding molecule of claim 25, wherein the binding unit-associated antigen-binding domains comprise an antibody VH and a 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 or contained within~~

~~SEQ ID NO: 32 and SEQ ID NO: 33, SEQ ID NO: 37 and SEQ ID NO: 38, SEQ ID NO: 42 and SEQ ID NO: 43, SEQ ID NO: 44 and SEQ ID NO: 45, SEQ ID NO: 46 and SEQ ID NO: 47, SEQ ID NO: 48 and SEQ ID NO: 49, SEQ ID NO: 50 and SEQ ID NO: 51, SEQ ID NO: 52 and SEQ ID NO: 53, SEQ ID NO: 54 and SEQ ID NO: 55, SEQ ID NO: 56 and SEQ ID NO: 57, SEQ ID NO: 58 and SEQ ID NO: 59, SEQ ID NO: 60 and SEQ ID NO: 61, SEQ ID NO: 62 and SEQ ID NO: 63, SEQ ID NO: 64 and SEQ ID NO: 65, SEQ ID NO: 66 and SEQ ID NO: 67, SEQ ID NO: 68 and SEQ ID NO: 69, SEQ ID NO: 70 and SEQ ID NO: 71, SEQ ID NO: 72 and SEQ ID NO: 73, SEQ ID NO: 74 and SEQ ID NO: 75, SEQ ID NO: 76 and SEQ ID NO: 77, SEQ ID NO: 78 and SEQ ID NO: 79, SEQ ID NO: 80 and SEQ ID NO: 81, SEQ ID NO: 82 and SEQ ID NO: 83, SEQ ID NO: 84 and SEQ ID NO: 85, SEQ ID NO: 86 and SEQ ID NO: 87, SEQ ID NO: 88 and SEQ ID NO: 89, SEQ ID NO: 90 and SEQ ID NO: 91, SEQ ID NO: 92 and SEQ ID NO: 93, SEQ ID NO: 94 and SEQ ID NO: 95, 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: 107 and SEQ ID NO: 108, SEQ ID NO: 109 and SEQ ID NO: 110, SEQ ID NO: 111 and SEQ ID NO: 112, SEQ ID NO: 113 and SEQ ID NO: 114, SEQ ID NO: 115 and SEQ ID NO: 116, or SEQ ID NO: 117 and SEQ ID NO: 118, respectively.~~

28.18. The binding molecule of ~~any one of claims 1 to 27~~claim 16, which is a dimeric binding molecule comprising two bivalent binding units, wherein each binding unit comprises two antibody heavy chains, each comprising an IgA or IgA-like heavy chain constant region or multimerizing fragment thereof.

~~29.—The binding molecule of claim 28, further comprising a secretory component, or fragment or variant thereof.~~

~~30.—The binding molecule of claim 28 or claim 29, wherein the IgA or IgA-like heavy chain constant regions or multimerizing fragments thereof each comprise a C α 3 and a tailpiece (tp) domain.~~

~~31.—The binding molecule of claim 30, wherein the IgA or IgA-like heavy chain constant regions further comprise a C α 1 domain, a C α 2 domain, an IgA hinge region, or any combination thereof.~~

~~32.—The binding molecule of any one of claims 28 to 31, wherein the IgA or IgA-like heavy chain constant regions are human IgA or IgA-like constant regions.~~

~~33.—The binding molecule of claim 32, wherein the IgA heavy chain constant regions comprise the amino acid sequence SEQ ID NO: 24, SEQ ID NO: 25, or any multimerizing variant or fragment thereof.~~

~~34.—The binding molecule of any one of claims 28 to 33, wherein each binding unit comprises two IgA or IgA-like heavy chains each comprising a VH situated amino terminal to the IgA constant region or fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.~~

35.19. The binding molecule of ~~any one of claims 1 to 27~~claim 17, which is a pentameric binding molecule comprising five bivalent binding units, wherein each binding unit comprises two IgM or IgM-like heavy chain constant regions or multimerizing fragments thereof.

~~36.—The binding molecule of claim 35, wherein the IgM or IgM-like heavy chain constant regions or multimerizing fragments thereof each comprise a C μ 4 domain and a tailpiece (tp) domain or fragment or variant thereof.~~

~~37.—The binding molecule of claim 35 or claim 36, wherein the IgM or IgM-like heavy chain constant regions or multimerizing fragments thereof further comprise a C μ 1 domain, a C μ 2 domain, a C μ 3 domain, or any combination thereof.~~

38.20. The binding molecule of ~~any one of claims 35 to 37~~claim 19, wherein the IgM or IgM-like heavy chain constant regions are human IgM constant regions, and 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: 22, SEQ ID NO: 23, or a multimerizing variant or fragment thereof.

~~39.—The binding molecule of claim 38, 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: 22, SEQ ID NO: 23, or a multimerizing variant or fragment thereof.~~

~~40.—The binding molecule of claim 38 or claim 39, 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: 22, SEQ ID NO: 23, or a multimerizing variant or fragment thereof.~~

41.21. The binding molecule of claim ~~40~~20, wherein each IgM heavy chain constant region comprises a variant of the amino acid sequence SEQ ID NO: 22 or SEQ ID NO: 23, wherein the variant comprises an amino acid substitution at position P311 of SEQ ID NO: 22 or SEQ ID NO: 23, an amino acid substitution at position P313 of SEQ ID NO: 22 or SEQ ID

NO: 23, or amino acid substitutions at positions P311 and P313 of SEQ ID NO: 22 or SEQ ID NO: 23.

~~42. The binding molecule of claim 38 or claim 39, 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; wherein the binding molecule exhibits increased serum half life upon administration to a subject animal relative to a binding molecule comprising the reference IgM heavy chain constant regions, which is administered in the same way to the same animal species.~~

~~43. The multimeric binding molecule of claim 42, 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: 22 or SEQ ID NO: 23.~~

~~44. The binding molecule of any one of claims 35 to 43, wherein each binding unit comprises two IgM heavy chains each comprising a VH situated amino terminal to the IgM constant region or fragment thereof, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.~~

~~45. A composition comprising the binding molecule of any one of claims 1 to 44.~~

~~46.~~22. A polynucleotide comprising a nucleic acid sequence that encodes a polypeptide subunit of the binding molecule of ~~any one of claims 1 to 44~~claim 1.

~~47. The polynucleotide of claim 46, wherein the polypeptide subunit comprises an IgM or IgM-like heavy chain constant region and at least an antibody VH portion of the binding unit-associated antigen-binding domain of the binding molecule.~~

~~48. The polynucleotide of claim 47, wherein the polypeptide subunit comprises a human IgM constant region or fragment thereof fused to the C-terminal end of a VH comprising:~~

~~(a) HCDR1, HCDR2, and HCDR3 regions comprising the CDRs contained in the VH amino acid sequence comprising or contained within SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID~~

~~NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, or SEQ ID NO: 117; or the CDRs contained in the VH amino acid sequence comprising or contained within SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, or SEQ ID NO: 117 except for one or two single amino acid substitutions in one or more of the HCDRs; or~~

~~(b) an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to the mature VH amino acid sequence comprising or contained within SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 107, SEQ ID NO: 109, SEQ ID NO: 111, SEQ ID NO: 113, SEQ ID NO: 115, or SEQ ID NO: 117.~~

~~49.—The polynucleotide of any one of claims 46 to 48, wherein the polypeptide subunit comprises a light chain constant region and an antibody VL portion of the antigen-binding domain of the multimeric binding molecule.~~

~~50.—The polynucleotide of claim 49, wherein the polypeptide subunit comprises a human kappa or lambda light chain constant region or fragment thereof fused to the C-terminal end of a VL comprising:~~

~~(a) LCDR1, LCDR2, and LCDR3 regions comprising the CDRs contained in the VL amino acid sequence comprising or contained within SEQ ID NO: 33, SEQ ID NO: 38, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ~~

~~ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, or SEQ ID NO: 118; or the CDRs contained in the VL amino acid sequence SEQ ID NO: 33, SEQ ID NO: 38, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, or SEQ ID NO: 118 except for one or two single amino acid substitutions in one or more of the LCDRs; or~~

~~(b) an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to the mature VL amino acid sequence comprising or contained within SEQ ID NO: 33, SEQ ID NO: 38, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 99, SEQ ID NO: 101, SEQ ID NO: 103, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, or SEQ ID NO: 118.~~

~~51. —The polynucleotide of any one of claims 46 to 50, wherein the polypeptide subunit comprises a modified J chain, wherein the modified J chain comprises a wild-type J chain or a functional fragment or variant thereof and a J chain-associated antigen-binding domain that specifically binds to an immune effector cell.~~

~~52. —The polynucleotide of claim 51, wherein the modified J chain comprises an amino acid sequence at least 80%, 85%, 90%, 95%, or 100% identical to amino acids 20 to 420 of SEQ ID NO: 12, amino acids 20 to 412 of SEQ ID NO: 15, or amino acids 23 to 415 of SEQ ID NO: 16.~~

~~53. —A composition comprising the polynucleotide of any one of claims 46 to 48, the polynucleotide of any one of claims 46, 49, or 50, and the polynucleotide of claim 51 or claim 52.~~

~~54.—The composition of claim 53, wherein the polynucleotides are on two or more separate vectors.~~

~~55.—The composition of claim 53, wherein the polynucleotides are on a single vector.~~

~~56.—The composition of any one of claims 53 to 55, further comprising a polynucleotide comprising a nucleic acid sequence encoding a J chain, or fragment thereof, or variant thereof.~~

~~57.—The vector of claim 55.~~

~~58.—The vectors of claim 54.~~

~~59.23.~~ A host cell comprising the polynucleotide of ~~any one of claims 46 to 52~~claim 22, ~~the composition of any one of claims 53 to 56, or the vector or vectors of any one of claims 57 or 58,~~ wherein the host cell can express the binding molecule ~~of any one of claims 1 to 44,~~ or a subunit thereof.

~~60.24.~~ A method of producing ~~the a~~ binding molecule ~~of any one of claims 1 to 44,~~ comprising culturing the host cell of claim ~~59~~23, and recovering the binding molecule.

~~61.25.~~ A ~~method of treating cancer or other malignancy, comprising administering to a subject in need of treatment an effective amount of~~ Use of athe binding molecule of any one of claims 1 to ~~44~~21 in the manufacture of a medicament for treating cancer or other malignancy, wherein the binding molecule can induce immune effector cell-mediated killing of cancer cells.

~~62.—The method of claim 61, wherein the cancer or malignancy is a hematologic cancer or malignancy.~~

~~63.—The method of claim 62, wherein the cancer is acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), B-cell acute lymphoblastic leukemia (B-cell ALL), classical Hodgkin's lymphoma, hairy cell leukemia, chronic lymphocytic leukemia (CLL), systemic mastocytosis, or plasmacytoid dendritic cell leukemia.~~

~~64.—The method of any one of claims 61 to 63, wherein the J chain-associated antigen-binding domain binds to CD3 ϵ , and wherein the binding molecule induces T-cell mediated killing of malignant cells.~~

~~65.—The method of claim 64, wherein the treatment results in reduced cytokine release relative to IgG-based anti-CD123-anti-CD3 bispecific antibodies.~~

~~66.—The method of any one of claims 61 to 65, wherein the subject is human.~~