where each binding unit includes two IgA or IgM heavy chain constant regions or fragments thereof, each associated with an antigen-binding domain, where at least three of the antigen-binding domains of the binding molecule specifically and agonistically bind to a tumor necrosis factor (TNF) superfamily receptor protein that can induce apoptosis of a cell expressing the TNF superfamily receptor protein, and where the binding molecule can cross-link at least three identical TNF superfamily receptor proteins expressed on the surface of a cell, thereby inducing apoptosis of the cell.

[0010a] In one aspect, the present disclosure refers to a multimeric binding molecule comprising two, five, or six bivalent binding units,

wherein each binding unit comprises:

(a) two IgA heavy chain constant regions each comprising a Cα1 domain, a Cα2 domain, and a Cα3-tp domain; or

(b) two IgM heavy chain constant regions each comprise a Cμl domain, a Cμ2 domain, a Cμ3 domain, and a Cμ4-tp domain,

wherein each heavy chain constant region is associated with an antigen-binding domain,

wherein at least three of the antigen-binding domains of the binding molecule specifically and agonistically bind to a tumor necrosis factor (TNF) superfamily receptor protein, and

wherein the binding molecule can cross-link at least three identical TNF superfamily receptor proteins expressed on the surface of a cell, thereby activating signal transduction in the cell; and

wherein the antibody can activate TNF superfamily receptor-mediated signal transduction in a TNF receptor superfamily-expressing cell at a higher potency than an equivalent amount of a bivalent IgG antibody comprising two of the same antigen binding domains, which also specifically binds to and agonizes the same TNF superfamily receptor protein,

and wherein:

(1) the signal transduction can trigger apoptosis, and wherein the TNF superfamily receptor protein is TNFR1 (DR1), TNFR2, TNFR1/2, CD40 (p50), Fas (CD95, Apo1, DR2), CD30, 4-1BB (CD137, ILA), TRAILR1 (DR4, Apo2), TRAILR3 (DcR1), TRAILR4 (DcR2), OPG (OCIF), TWEAKR (FN14), LIGHTR (HVEM), DcR3, DR3, EDAR, XEDAR, or a combination thereof;

(2) the signal transduction can trigger proliferation, and wherein the TNF superfamily receptor protein is TNFR1/2, GITR (AITR), TACI, BCMA, TWEAKR (FN14), RANK

(TRANCER), CD27, CD40 (p50), OX40 (CD134), LT-βR, TNFR1 (DR1), TNFR2, or a combination thereof; or

(3) the signal transduction can trigger morphogenesis, and wherein the TNF superfamily receptor protein is Fas (CD95, Apo1, DR2), TRAILR1 (DR4, Apo2), TRAILR3 (DcR1), TRAILR4 (DcR2), OPG (OCIF), CD40 (p50), EDAR, XEDAR, TNFR1/2, or a combination thereof.

[0010b] In another aspect, the present disclosure refers to a composition comprising the multimeric binding molecule as described herein.

[0010c] In another aspect, the present disclosure refers to a composition comprising a polynucleotide comprising a nucleic acid sequence that encodes an IgM heavy chain constant region and at least an antibody VH portion of the antigen-binding domain of the multimeric binding molecule as described herein, and a polynucleotide comprising a nucleic acid sequence that encodes a light chain constant region and an antibody VL portion of the antigen-binding domain of the multimeric binding molecule as described herein.

[0010d] In another aspect, the present disclosure refers to the vector as described herein.

[0010e] In another aspect, the present disclosure refers to the vectors as described herein.

[0010f] In another aspect, the present disclosure refers to a host cell comprising the composition as described herein, or the vector or vectors as described herein, wherein the host cell can express the binding molecule as described herein.

[0010g] In another aspect, the present disclosure refers to a method of producing the binding molecule as described herein, comprising culturing the host cell as described herein, and recovering the binding molecule.

[0010h] In yet another aspect, the present disclosure refers to a method of inducing TNF superfamily receptor-mediated apoptosis or lipid raft formation in a TNF superfamily receptor-expressing cell *in vitro*, which comprises contacting the TNF superfamily receptor-expressing cell with the multimeric binding molecule as described here.

[0010i] In yet another aspect, the present disclosure refers to a use of the multimeric binding molecule as described herein, in the manufacture of a medicament for treating cancer in a subject, wherein the cancer cells in the subject express the TNF superfamily receptor.

[0010j] In yet another aspect, the present disclosure refers to the multimeric binding molecule as described herein for use in therapy.

[0011] In certain aspects a dimeric, pentameric, or hexameric binding molecule as provided herein can induce TNF superfamily receptor-mediated apoptosis in a TNF receptor

superfamily-expressing cell at a higher potency than an equivalent amount of a bivalent IgG antibody or fragment thereof, which also specifically binds to and agonizes the same TNF superfamily receptor protein. In certain aspects, the three or more antigen-binding domains that specifically bind to and agonize the TNF superfamily receptor protein do not cross-react with other TNF superfamily receptor proteins. In certain aspects, the three or more antigen-binding domains that specifically bind to and agonize the TNF superfamily receptor protein can cross-react with other TNF superfamily receptor proteins.

[0012] In certain aspects, a dimeric, pentameric, or hexameric binding molecule as provided herein can include at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve antigen-binding domains that specifically and agonistically bind to a TNF superfamily receptor protein expressed on the surface of the cell, thereby inducing apoptosis of the cell. In certain aspects, the at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve antigen-binding domains bind to the same extracellular epitope of a single type of TNF superfamily receptor molecule expressed on the surface of the cell. In certain aspects, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve antigen-binding domains each specifically bind one of a group of two or more different extracellular epitopes of a single type of TNF superfamily receptor molecule expressed on the surface of the cell.

[0013] The binding units of a dimeric, pentameric, or hexameric binding molecule provided herein can be human, humanized, or chimeric immunoglobulin binding units.

[0014] In certain aspects, a dimeric, pentameric, or hexameric binding molecule as provided herein can bind to, without limitation, TNFR1 (DR1), TNFR2, TNFR1/2, CD40 (p50), Fas (CD95, Apo1, DR2), CD30, 4-1BB (CD137, ILA), TRAILR1 (DR4, Apo2), TRAILR2

WHAT IS CLAIMED IS:

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

wherein each binding unit comprises:

(a) two IgA heavy chain constant regions each comprising a Cα1 domain, a Cα2 domain, and a Cα3-tp domain; or

(b) two IgM heavy chain constant regions each comprise a Cμl domain, a Cμ2 domain, a Cμ3 domain, and a Cμ4-tp domain~~or fragments thereof~~,

wherein each heavy chain constant region is associated with an antigen-binding domain,

wherein at least three of the antigen-binding domains of the binding molecule specifically and agonistically bind to a tumor necrosis factor (TNF) superfamily receptor protein ~~that can induce apoptosis of a cell expressing the TNF superfamily receptor protein~~, and

wherein the binding molecule can cross-link at least three identical TNF superfamily receptor proteins expressed on the surface of a cell, thereby activating signal transduction in the cell; and

wherein the antibody can activate TNF superfamily receptor-mediated signal transduction in a TNF receptor superfamily-expressing cell at a higher potency than an equivalent amount of a bivalent IgG antibody comprising two of the same antigen binding domains, which also specifically binds to and agonizes the same TNF superfamily receptor protein,

and wherein:

(1) the signal transduction can trigger apoptosis, and wherein the TNF superfamily receptor protein is TNFR1 (DR1), TNFR2, TNFR1/2, CD40 (p50), Fas (CD95, Apo1, DR2), CD30, 4-1BB (CD137, ILA), TRAILR1 (DR4, Apo2), TRAILR3 (DcR1), TRAILR4 (DcR2), OPG (OCIF), TWEAKR (FN14), LIGHTR (HVEM), DcR3, DR3, EDAR, XEDAR, or a combination thereof;

(2) the signal transduction can trigger proliferation, and wherein the TNF superfamily receptor protein is TNFR1/2, GITR (AITR), TACI, BCMA, TWEAKR (FN14), RANK (TRANCER), CD27, CD40 (p50), OX40 (CD134), LT-βR, TNFR1 (DR1), TNFR2, or a combination thereof; or

(3) the signal transduction can trigger morphogenesis, and wherein the TNF superfamily receptor protein is Fas (CD95, Apo1, DR2), TRAILR1 (DR4, Apo2), TRAILR3 (DcR1), TRAILR4

(DcR2), OPG (OCIF), CD40 (p50), EDAR, XEDAR, TNFR1/2, or a combination thereof. ~~inducing apoptosis of the cell~~.

~~2. The multimeric binding molecule of claim 1, which induces TNF superfamily receptor-mediated apoptosis in a TNF receptor superfamily-expressing cell at a higher potency than an equivalent amount of a bivalent IgG antibody or fragment thereof, which also specifically binds to and agonizes the same TNF superfamily receptor protein.~~

2. The multimeric binding molecule of claim 1, wherein the TNF superfamily receptor protein is CD40 (p50), 4-1BB (CD137, ILA), GITR (AITR), or OX40 (CD134).

~~3. The multimeric binding molecule of claim 1 or claim 2, wherein the at least three antigen-binding domains that specifically bind to and agonize the TNF superfamily receptor protein do not cross-react with other TNF superfamily receptor proteins.~~

~~4. The multimeric binding molecule of claim 1 or claim 2, wherein the at least three antigen-binding domains that specifically bind to and agonize the TNF superfamily receptor protein can cross-react with other TNF superfamily receptor proteins.~~

~~5.~~3. The multimeric binding molecule of claim 1~~3~~ or claim 2, which comprises ~~at least three,~~ at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve antigen-binding domains that specifically and agonistically bind to a TNF superfamily receptor protein expressed on the surface of the cell, thereby activating signal transduction in the cell~~inducing apoptosis of the cell~~.

~~6.~~4. The multimeric binding molecule of claim 3, wherein the ~~at least three,~~ at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve antigen-binding domains bind to the same extracellular epitope of a single type of TNF superfamily receptor molecule expressed on the surface of the cell.

~~7.~~5. The multimeric binding molecule of claim 3, wherein ~~at least three,~~ the at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve antigen-binding domains each specifically bind one of a group of two or more different

extracellular epitopes of a single type of TNF superfamily receptor molecule expressed on the surface of the cell.

~~8.~~6. The multimeric binding molecule of any one of claims 1 to 5, wherein the two, five, or six binding units are human, humanized, or chimeric immunoglobulin binding units.

~~9. The multimeric binding molecule of any one of claims 1 to 8, wherein the TNF superfamily receptor protein is TNFR1 (DR1), TNFR2, TNFR1/2, CD40 (p50), Fas (CD95, Apo1, DR2), CD30, 4-1BB (CD137, ILA), TRAILR1 (DR4, Apo2), TRAILR2 (DR5), TRAILR3 (DcR1), TRAILR4 (DcR2), OPG (OCIF), TWEAKR (FN14), LIGHTR (HVEM), DcR3, DR3, EDAR, XEDAR, or a combination thereof.~~

~~10. The multimeric binding molecule of any one of claims 1 to 9, wherein the at least three antigen-binding domains specifically and agonistically bind to DR5.~~

~~11. The multimeric binding molecule of claim 10, wherein the at least three antigen-binding domains do not specifically bind to DR4, DcR1, or DcR2.~~

~~12. The multimeric binding molecule of claim 10, wherein the at least three antigen-binding domains can also specifically bind to DR4.~~

~~13.~~7. The multimeric binding molecule of any one of claims 1 to 6~~11~~, wherein the cell is a cancer cell.

~~14. The multimeric binding molecule of any one of claims 1 to 13, wherein at the least three antigen-binding domains of the binding molecule are DR5 binding domains, and wherein at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve 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 SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID~~

~~NO: 7 and SEQ ID NO: 8; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; 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; or SEQ ID NO: 88 and SEQ ID NO: 89; respectively, or the ScFv sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73 or the six CDRs with one or two amino acid substitutions in one or more of the CDRs.~~

~~15. The multimeric binding molecule of any one of claims 1 to 14, wherein at the least three antigen-binding domains of the binding molecule are anti-DR5 binding domains, and wherein at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or twelve 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 SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID NO: 5 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ~~

~~ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; 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; or SEQ ID NO: 88 and SEQ ID NO: 89; respectively, or wherein the VH and VL are contained in an ScFv with an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73.~~

~~16. The multimeric binding molecule of claim 15, wherein at least four, at least ten, or twelve antigen-binding domains comprise antibody VH and VL regions comprising the amino acid sequences SEQ ID NO: 1 and SEQ ID NO: 2, SEQ ID NO; 5 and SEQ ID NO: 6, SEQ ID NO; 84 and SEQ ID NO: 85, or SEQ ID NO; 88 and SEQ ID NO: 89, respectively.~~

~~17.~~8. The multimeric binding molecule of any one of claims 1 to 1, which is a dimeric binding molecule comprising two bivalent IgA binding units ~~or fragments thereof~~ and a J chain or fragment or variant thereof, wherein each binding unit comprises two IgA heavy chain constant regions ~~or fragments thereof~~ each associated with an antigen-binding domain.

~~18.~~9. The multimeric binding molecule of claim 8, further comprising a secretory component~~, or fragment or variant thereof~~.

~~19. The multimeric binding molecule of claim 17 or claim 18, wherein the IgA heavy chain constant regions or fragments thereof each comprise a Cα2 domain or a Cα3-tp domain.~~

~~20. The multimeric binding molecule of claim 19, wherein one or more IgA heavy chain constant regions or fragments thereof further comprise a Cα1 domain.~~

~~21.~~10. The multimeric binding molecule of ~~any one of~~ claim~~s~~ 8 ~~to~~or claim 9~~20~~, wherein the IgA heavy chain constant region ~~is as~~s are human IgA constant region~~s~~.

~~22.~~11. The multimeric binding molecule of any one of claims 8 to 10, wherein each binding unit comprises two IgA 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.

~~23.~~12. The multimeric binding molecule of any one of claims 1 to 7~~16~~, which is a pentameric or a hexameric binding molecule comprising five or six bivalent IgM binding units, respectively, wherein each binding unit comprises two IgM heavy chain constant regions ~~or fragments thereof~~ each associated with an antigen-binding domain.

~~24. The multimeric binding molecule of claim 23, wherein the IgM heavy chain constant regions or fragments thereof each comprise a Cμ3 domain and a Cμ4-tp domain.~~

~~25. The multimeric binding molecule of claim 23 or claim 24, wherein one or more IgM heavy chain constant regions or fragments thereof further comprise a Cμ2 domain, a Cμ1 domain, or any combination thereof.~~

~~26.~~13. The multimeric binding molecule of ~~any one of claims~~claim 12 ~~to 25~~, wherein the binding molecule is pentameric, and further comprises a J chain, or fragment thereof, or variant thereof.

~~27.~~14. The multimeric binding molecule of ~~any one of claims~~claim 12 ~~to~~ or claim 13, wherein the IgM heavy chain constant region~~s~~ ~~is a~~are human IgM constant region~~s~~.

~~28.~~15. The multimeric binding molecule of any one of claims 12 to 14, 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.

~~29. The multimeric binding molecule of any one of claims 1 to 28, wherein each binding unit comprises two heavy chains and two light chains, wherein the heavy chains and light chains comprise VH and VL amino acid sequences at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 1 and SEQ ID NO: 2; SEQ ID NO: 3 and SEQ ID NO: 4; SEQ ID~~

~~NO: 5 and SEQ ID NO: 6; SEQ ID NO: 7 and SEQ ID NO: 8; SEQ ID NO: 9 and SEQ ID NO: 10; SEQ ID NO: 11 and SEQ ID NO: 12; SEQ ID NO: 13 and SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16; SEQ ID NO: 17 and SEQ ID NO: 18; SEQ ID NO: 19 and SEQ ID NO: 20; SEQ ID NO: 21 and SEQ ID NO: 22; SEQ ID NO: 23 and SEQ ID NO: 24; SEQ ID NO: 25 and SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 28; SEQ ID NO: 29 and SEQ ID NO: 30; SEQ ID NO: 31 and SEQ ID NO: 32; SEQ ID NO: 33 and SEQ ID NO: 34; SEQ ID NO: 35 and SEQ ID NO: 36; SEQ ID NO: 37 and SEQ ID NO: 38; SEQ ID NO: 39 and SEQ ID NO: 40; SEQ ID NO: 41 and SEQ ID NO: 42; SEQ ID NO: 43 and SEQ ID NO: 44; SEQ ID NO: 45 and SEQ ID NO: 46; SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; SEQ ID NO: 51 and SEQ ID NO: 52; SEQ ID NO: 53 and SEQ ID NO: 54; SEQ ID NO: 55 and SEQ ID NO: 56; 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; or SEQ ID NO: 88 and SEQ ID NO: 89; respectively, or wherein the heavy chains and light chains comprise VH and VL amino acid sequences contained in an ScFv with an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73.~~

~~30. The multimeric binding molecule of claim 29, wherein the heavy chains and light chains comprise the VH and VL amino acid sequences SEQ ID NO: 1 and SEQ ID NO: 2, SEQ ID NO; 5 and SEQ ID NO: 6, SEQ ID NO; 84 and SEQ ID NO: 85, or SEQ ID NO; 88 and SEQ ID NO: 89, respectively.~~

~~31. The multimeric binding molecule of any one of claims 1 to 16 or 23 to 30, wherein the binding molecule is a pentameric IgM molecule, further comprising a J chain.~~

~~32.~~16. A composition comprising the multimeric binding molecule of any one of claims 1 to 15~~31~~.

~~33. A polynucleotide comprising a nucleic acid sequence that encodes a polypeptide subunit of the binding molecule of any one of claims 1 to 31.~~

34. The polynucleotide of claim 33, wherein the polypeptide subunit comprises an IgM heavy chain constant region and at least an antibody VH portion of the antigen-binding domain of the multimeric binding molecule.

35. The polynucleotide of claim 34, 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 SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, 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: 82, SEQ ID NO: 84, SEQ ID NO: 86, or SEQ ID NO: 88, or in the ScFv amino acid sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73; or the CDRs contained in the VH amino acid sequence SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, 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: 82, SEQ ID NO: 84, SEQ ID NO: 86, or SEQ ID NO: 88, or in the ScFv amino acid sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73 with 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 SEQ ID NO: SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ

~~ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, 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: 82, SEQ ID NO: 84, SEQ ID NO: 86, or SEQ ID NO: 88, or the VH portion of an ScFv with the amino acid sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73.~~

~~36. The polynucleotide of any one of claims 33 to 35, 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.~~

~~37. The polynucleotide of claim 36, 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 SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, 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: 83, SEQ ID NO: 85, SEQ ID NO: 87, or SEQ ID NO: 89, or in the ScFv amino acid sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73; or the CDRs contained in the VL amino acid sequence SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO:~~

~~40, 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: 83, SEQ ID NO: 85, SEQ ID NO: 87, or SEQ ID NO: 89, or in the ScFv amino acid sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73, with 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 SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, 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: 83, SEQ ID NO: 85, SEQ ID NO: 87, or SEQ ID NO: 89, or the VL portion of an ScFv with the amino acid sequence SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, or SEQ ID NO: 73.~~

~~38.~~17. A composition comprising ~~the~~ a polynucleotide comprising a nucleic acid sequence that encodes an IgM heavy chain constant region and at least an antibody VH portion of the antigen-binding domain of the multimeric binding molecule of any one of claims 1~~33~~ to 7~~35~~ or 12 to 15, and ~~the~~ a polynucleotide comprising a nucleic acid sequence that encodes a light chain constant region and an antibody VL portion of the antigen-binding domain of the multimeric binding molecule of any one of claims 1 to 7 or 12 to 15~~of any one of claims 33, 36, or 37~~.

18. The composition of claim 17, further comprising a polynucleotide comprising a nucleic acid sequence encoding a J chain, or fragment thereof, or variant thereof.

~~39.~~19. The composition of claim 17 or claim 18, wherein the polynucleotides are on separate vectors.

~~40.~~20. The composition of claim 17 or claim 18, wherein the polynucleotides are on a single vector.

~~41. The composition of any one of claims 38 to 40, further comprising a polynucleotide comprising a nucleic acid sequence encoding a J chain, or fragment thereof, or variant thereof.~~

~~42.~~21. The vector of claim 20.

~~43.~~22. The vectors of claim 18.

~~44.~~23. A host cell comprising ~~the polynucleotide of any one of claims 33 to 37,~~ the composition of any one of claims 17 to 1, or the vector or vectors of ~~any one of claims~~claim 21 or claim 22, wherein the host cell can express the binding molecule of any one of claims 1 to 7 or 12 to 15~~1 to 31, or a subunit thereof~~.

~~45.~~24. A method of producing the binding molecule of any one of claims 1 to 7 or 12 to 15~~1 to 31~~, comprising culturing the host cell of claim 23, and recovering the binding molecule.

~~46.~~25. A method of inducing TNF superfamily receptor-mediated apoptosis or lipid raft formation in a TNF superfamily receptor-expressing cell *in vitro*, which comprises contacting the TNF superfamily receptor~~-~~-expressing cell with the multimeric binding molecule of any one of claims 1 to 15~~31~~.

~~47. A method of inducing TNF superfamily receptor lipid raft formation in a TNF superfamily receptor-expressing cell, which comprises contacting the TNF superfamily receptor-expressing cell with the multimeric binding molecule of any one of claims 1 to 31.~~

~~48.~~26. Use of ~~A method of treating cancer comprising administering to a subject in need of treatment an effective amount of~~ the multimeric binding molecule of any one of claims 1 to 15~~31~~, in the manufacture of a medicament for treating cancer in a subject, wherein the cancer cells in the subject express ~~a~~ the TNF superfamily receptor ~~with apoptotic activity, and wherein the multimeric binding molecule can induce apoptosis of the cancer cells~~.

~~49. The method of claim 48, wherein the multimeric binding molecule can induce greater apoptosis of cancer cells than non-cancer cells.~~

~~50. The method of claim 49, wherein the non-cancer cells are normal hepatocytes.~~

~~51. The method of any one of claims 48 to 50, wherein the TNF superfamily receptor is DR5.~~

~~52.~~27. The ~~method~~ use of ~~any one of claims~~claim 26 ~~to 51~~, wherein the subject is human.

~~53.~~28. The multimeric binding molecule of any one of claims 1 to 15 for use in therapy.