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,

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.

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, which comprises 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.

4. The multimeric binding molecule of claim 3, wherein 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 bind to the same extracellular epitope of a single type of TNF superfamily receptor molecule expressed on the surface of the cell.

5. The multimeric binding molecule of claim 3, wherein 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.

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.

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

8. The multimeric binding molecule of any one of claims 1 to **Error! Reference source not found.**, which is a dimeric binding molecule comprising two bivalent IgA binding units and a J chain or fragment or variant thereof, wherein each binding unit comprises two IgA heavy chain constant regions each associated with an antigen-binding domain.

9. The multimeric binding molecule of claim 8, further comprising a secretory component.

10. The multimeric binding molecule of claim 8 or claim 9, wherein the IgA heavy chain constant regions are human IgA constant regions.

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, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.

12. The multimeric binding molecule of any one of claims 1 to 7, 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 each associated with an antigen-binding domain.

13. The multimeric binding molecule of claim 12, wherein the binding molecule is pentameric, and further comprises a J chain, or fragment thereof, or variant thereof.

14. The multimeric binding molecule of claim 12 or claim 13, wherein the IgM heavy chain constant regions are human IgM constant regions.

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, and two immunoglobulin light chains each comprising a VL situated amino terminal to an immunoglobulin light chain constant region.

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

17. 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 of any one of claims 1 to 7 or 12 to 15, 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 of any one of claims 1 to 7 or 12 to 15.

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.

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

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

21. The vector of claim 20.

22. The vectors of claim 189.

23. A host cell comprising the composition of any one of claims 17 to **Error! Reference source not found.**, or the vector or vectors of 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.

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

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.

26. Use of the multimeric binding molecule of any one of claims 1 to 15, in the manufacture of a medicament for treating cancer in a subject, wherein the cancer cells in the subject express the TNF superfamily receptor.

27. The use of claim 26, wherein the subject is human.

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