[0020] In another aspect, disclosed herein is a pharmaceutical composition comprising an effective amount of a multi-specific antibody construct described herein and a pharmaceutically acceptable carrier.

[0021] In another aspect, disclosed herein is a method of treating a proliferative disease in a human subject, comprising administering to the human subject a pharmaceutical composition comprising an effective amount of an antibody construct described herein. In some embodiments, the proliferative disease is cancer. In some embodiments, the cancer is neuroblastoma, glioblastoma, small cell lung cancer, or sarcoma.

[0022] In some embodiments, administering the pharmaceutical composition results in decreased pain compared to treatment with an anti-GD2 monoclonal antibody. In some embodiments, the anti-GD2 monoclonal antibody is dinutuximab or hu14.18.

[0023] In another aspect, disclosed herein is a method of selectively targeting a tumor cell in a subject, comprising administering to the subject a pharmaceutical composition comprising an effective amount of an antibody construct described herein.

[0023a] In another aspect, disclosed herein is a use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating a proliferative disease in a human subject, wherein the medicament is to be administered to the human subject.

[0023b] In another aspect, disclosed herein is a use of a pharmaceutical composition as described herein in the manufacture of a medicament for selectively targeting a tumor cell in a subject.

[0023c] In another aspect, disclosed herein is a pharmaceutical composition as described herein for use in therapy.

5. BRIEF DESCRIPTION OF THE DRAWINGS

[0024] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0025] **FIG. 1** is a slide outlining the need for the antibody constructs disclosed herein and the approach to solving that need that is met by the antibody constructs disclosed herein.

[0026] FIG. 2 identifies the goal of creating the antibody constructs disclosed herein.

[0027] FIG. 3A, FIG. 3B, FIG. 3C, and FIG. 3D are schematics comparing anti-GD2 antibody which binds to GD2 antigen (**FIG. 3A**) on neuroblastoma and peripheral nerve cells (**FIG. 3B**) with anti-GD2 x B7H3 SNIPER^{TM} antibody (INV721) that binds B7H3 antigen (**FIG. 3C**) on neuroblastoma cells but not nerve cells (**FIG. 3D**).

[0028] FIG. 4 outlines the project workflow for generating the antibody constructs disclosed herein.

WHAT IS CLAIMED IS:

1. A multi-specific antibody construct, comprising:

a first antigen binding site (ABS) specific for a first tumor cell surface antigen, wherein the first tumor cell antigen is B7 Homolog 3 (B7H3); and

a second antigen binding site (ABS) specific for a second tumor cell surface antigen, wherein the second tumor cell antigen is disialoganglioside (GD2).

2. The multi-specific antibody construct of claim 1, wherein the first ABS binds human B7H3 with a K_D that is greater than 10 nM, the second ABS binds human GD2 with a K_D that is greater than 10 nM, and wherein the antibody construct binds to a tumor cell expressing B7H3 and GD2 with a K_D that is less than 100 nM.

3. The multi-specific antibody construct of claim 2, wherein the antibody construct exhibits lower binding to cells that express GD2 but not B7H3 compared to cells that express both GD2 and B7H3.

4. The multi-specific antibody construct of claim 3, wherein the antibody construct has greater antibody-dependent cellular cytotoxicity (ADCC) activity against a cell that expresses B7H3 and GD2 as compared to ADCC activity against a cell that expresses GD2 but does not express B7H3.

5. The multi-specific antibody construct of any of the preceding claims, wherein the antibody constructs bind less to nerve cells as compared to dinutuximab at comparable concentrations.

6. The multi-specific antibody construct of any of the preceding claims, wherein the first ABS comprises:

a) a first heavy chain variable region (VH) CDR1,

b) a first VH CDR2,

c) a first VH CDR3,

d) a first light chain variable region (VL) CDR1,

e) a first VL CDR2, and

f) a first VL CDR3.

7. The multi-specific antibody construct of claim 6, wherein the first ABS comprises:

a) a first VH CDR1 with the amino acid sequence of SEQ ID NO:22

b) a first VH CDR2 with the amino acid sequence of SEQ ID NO:27,

c) a first VH CDR3 with the amino acid sequence of SEQ ID NO:32,

d) a first VL CDR1 with the amino acid sequence of SEQ ID NO:7,

e) a first VL CDR2 with the amino acid sequence of SEQ ID NO:12, and

f) a first VL CDR3 with the amino acid sequence of SEQ ID NO:17.

8. The multi-specific antibody construct of any of the preceding claims, wherein the first ABS comprises:

a first heavy chain variable region (VH) with the amino acid sequence of SEQ ID NO: 2 and a first light chain variable region (VL) with the amino acid sequence of SEQ ID NO: 1.

9. The multi-specific antibody construct of any of the preceding claims, wherein the second ABS comprises:

a) a second heavy chain variable region (VH) CDR1,

b) a second VH CDR2,

c) a second VH CDR3,

d) a second light chain variable region (VL) CDR1,

e) a second VL CDR2, and

f) a second VL CDR3.

10. The multi-specific antibody construct of claim 9, wherein the second ABS comprises:

a) a second VH CDR1 with the amino acid sequence of SEQ ID NO:57,

b) a second VH CDR2 with the amino acid sequence of SEQ ID NO:62,

c) a second VH CDR3 with the amino acid sequence of SEQ ID NO:67,

d) a second VL CDR1 with the amino acid sequence of SEQ ID NO:42,

e) a second VL CDR2 with the amino acid sequence of SEQ ID NO:47, and

f) a second VL CDR3 with the amino acid sequence of SEQ ID NO:52.

11. The multi-specific antibody construct of any of the preceding claims, wherein the second ABS comprises:

a second heavy chain variable region (VH) with the amino acid sequence of SEQ ID NO: 4 and a second light chain variable region (VL) with the amino acid sequence of SEQ ID NO: 3.

12. The antibody construct of any of the preceding claims, wherein the antibody construct comprises a first, second, third, and fourth polypeptide chain, wherein:

a) the first polypeptide chain comprises a domain A, a domain B, a domain D, and a domain E, wherein the domains are arranged, from N-terminus to C-terminus, in a A-B-D-E orientation, wherein domain A comprises a variable region domain amino acid sequence, and wherein domain B, domain D, and domain E each comprise a constant region domain amino acid sequence;

b) the second polypeptide chain comprises a domain F and a domain G, wherein the domains are arranged, from N-terminus to C-terminus, in a F-G orientation, and wherein domain F has a variable region domain amino acid sequence and domain G comprises a constant region domain amino acid sequence;

c) the third polypeptide chain comprises a domain H, a domain I, a domain J, and a domain K, wherein the domains are arranged, from N-terminus to C-terminus, in a H-I-J-K orientation, wherein domain H has a variable region domain amino acid sequence, and wherein domain I, domain J, and domain K each have a constant region amino acid sequence;

d) the fourth polypeptide chain comprises a domain L and a domain M, wherein the domains are arranged, from N-terminus to C-terminus, in a L-M orientation, and wherein domain L has a variable region domain amino acid sequence and domain M comprises a constant region amino acid sequence, or portion thereof;

e) the first and second polypeptides are associated through an interaction between the A and F domains and an interaction between the B and G domains;

f) the third and fourth polypeptides are associated through an interaction between

the H and L domains and an interaction between the I and M domains; and

g) the first and third polypeptides are associated through an interaction between the D and J domains and an interaction between the E and K domains.

13. The antibody construct of claim 12, wherein:

domain A is a V_L domain;

domain B comprises a CH3 domain;

domain D is a CH2 domain;

domain E is a CH3 domain;

domain F is a V_H domain;

domain G comprises a CH3 domain;

domain H is a V_L domain;

domain I is a C_L domain;

domain J is a CH2 domain;

domain K is a CH3 domain;

domain L is a V_H domain; and

domain M is a CH1 domain.

14. The antibody construct of claim 13, wherein:

domains D and J have the amino acid sequence of human IgG1 CH2 domain;
domain I has the amino acid sequence of human C kappa light chain; and
domain M has the amino acid sequence of human IgG1 CH1 region.

15. The antibody construct of claim 14, wherein:

domain B has a CH3 amino acid sequence with a T366K mutation and a C-terminal extension incorporating a KSC tripeptide sequence followed by the DKTHT motif of an IgG1 hinge region;

domain E has a CH3 amino acid sequence with a S354C and a T366W mutation;

domain G has a CH3 amino acid sequence with a L351D mutation and a C-terminal extension incorporating a GEC amino acid disulfide motif; and

domain K has a CH3 amino acid sequence with a Y349C, a T366S, a L368A, a Y407V mutation, and optionally a D356E and a L358M mutation.

16. The antibody construct of claim 14, wherein:

domain B has a CH3 amino acid sequence and a C-terminal extension incorporating a KSC tripeptide sequence followed by the DKTHT motif of an IgG1 hinge region;

domain E has a CH3 amino acid sequence with a S354C and a T366W mutation;

domain G has a CH3 amino acid sequence and a C-terminal extension incorporating a GEC amino acid disulfide motif; and

domain K has a CH3 amino acid sequence with a Y349C, a T366S, a L368A, a Y407V mutation, and optionally a D356E and a L358M mutation.

17. The antibody construct of claim 14, wherein:

domain B has a CH3 amino acid sequence with a Y349C mutation and a C-terminal extension incorporating a PGK tripeptide sequence that is followed by the DKTHT motif of an IgG1 hinge region;

domain E has a CH3 amino acid sequence with a S354C and a T366W mutation;

domain G has a CH3 amino acid sequence with a S354C mutation and a C-terminal extension incorporating a PGK tripeptide sequence; and

domain K has a CH3 amino acid sequence with a Y349C, a T366S, a L368A, a Y407V mutation, and optionally a D356E and a L358M mutation.

18. The antibody construct of claim 14, wherein:

domain B has a CH3 amino acid sequence with a P343V mutation, a Y349C mutation, and a C-terminal extension incorporating a PGK tripeptide sequence that is followed by the DKTHT motif of an IgG1 hinge region;

domain E has a CH3 amino acid sequence with a S354C and a T366W mutation;

domain G has a CH3 amino acid sequence with a S354C mutation and a C-terminal extension incorporating a PGK tripeptide sequence; and

domain K has a CH3 amino acid sequence with a Y349C, a T366S, a L368A, a Y407V mutation, and optionally a D356E and a L358M mutation.

19. The antibody construct of any one of claims 15-18, wherein the first ABS is formed by domains A and F and the second ABS is formed by domains H and L.

20. The antibody construct of any of the preceding claims, wherein the antibody construct is conjugated to a therapeutic agent.

21. A pharmaceutical composition comprising an effective amount of the multi-specific antibody construct of any one of the preceding claims and a pharmaceutically acceptable carrier.

22. Use of a pharmaceutical composition of claim 21 in the manufacture of a medicament for treating a proliferative disease in a human subject, wherein the medicament is to be administered to the human subject.

23. The use of claim 22, wherein the proliferative disease is cancer.

24. The use of claim 23, wherein the cancer is neuroblastoma, glioblastoma, small cell lung cancer, or sarcoma.

25. The use of any one of claims 22-24, wherein the administration results in decreased pain compared to treatment with an anti-GD2 monoclonal antibody.

26. The use of claim 25, wherein the anti-GD2 monoclonal antibody is dinutuximab or hu14.18.

27. Use of a pharmaceutical composition of claim 21 in the manufacture of a medicament for selectively targeting a tumor cell in a subject.

28. A pharmaceutical composition of claim 21 for use in therapy.