expressed mainly during fetal development and is highly restricted to just a few regenerative tissues post development. A de-N-acetylated form of polySia (dPSA) on the surface of cancer but not post-development human cells, and can serve as a tumor antigen for cancer identification and therapy.

[0005] Thus, new agents capable of targeting cells expressing dPSA and delivering cargo, such as cytoxic moieties, are needed.

BRIEF SUMMARY OF THE INVENTION

[0006] Provided herein is a dPSA-binding agent conjugate comprising immunoglobulin heavy and light chain polypeptides and a payload conjugated to the binding agent. Also provided herein is a method of using the dPSA-binding agents to deliver a payload to a cell expressing dPSA, and for use to kill cancer cells or otherwise treat cancer.

[0007] Related compositions and methods also are provided, as will be apparent from the following detailed description.

[0007a] In one aspect, provided herein is a dPSA binding agent conjugate comprising a dPSA binding agent and a cytotoxic payload conjugated thereto, wherein the cytotoxic payload is is monomethyl auristatin E / Dolastatin-10 (MMAE), Monomethylauristatin F (MMAF), Mertansine (DM1), N2'-deaetyl-N2'-(4-mercapto-4-methyl-1-oxopentyl) maytansine (DM4), 12-Ethyl-9-hydroxycamptothecin (7-ethyl-10-hydroxycamptothecin (SN-38), Exatecan mesylate (DX-8951f), PNU-1596821, Pyrrolobenzodiazepine (PBD or SGD-1882), an Exatecan derivative, or a Captothecin derivative.

[0007b] In another aspect, provided herein is a dPSA binding agent comprising an immunoglobulin heavy chain comprising SEQ ID NO: 57 and an an immunoglobulin light chain comprising SEQ ID NO: 58 or SEQ ID NO: 59.

[0007c] In another aspect, provided herein is a dPSA binding agent comprising an immunoglobulin heavy chain comprising SEQ ID NO: 60 and an an immunoglobulin light chain comprising SEQ ID NO: 58 or SEQ ID NO: 59.

[0007d] In another aspect, provided herein is a dPSA binding agent conjugate comprising the dPSA binding agent as disclosed herein and a cytotoxic payload.

[0007e] In another aspect, provided herein is a nucleic acid encoding the immunoglobulin heavy chain and/or light chain variable region of the dPSA-binding agent as disclosed herein, optionally in a vector.

[0007f] In another aspect, provided herein is a cell comprising the nucleic acid as disclosed herein.

[0007g] In another aspect, provided herein is a cell line that expresses the dPSA binding agent as disclosed herein.

[0007h] In another aspect, provided herein is an *in vitro* method of preparing a dPSA-binding agent as disclosed herein, the method comprising expressing a nucleotide sequence encoding the immunoglobulin heavy chain polypeptide and a nucleic acid sequence encoding the immunoglobulin light chain polypeptide in a cell.

[0007i] In another aspect, provided herein is a composition comprising (a) the dPSA-binding agent conjugate as disclosed herein, or dPSA binding agent as disclosed herein or nucleic acid encoding same, and (b) a pharmaceutically acceptable carrier.

[0007j] In another aspect, provided herein is a *in vitro* method of killing a cancer cell that expresses dPSA, the method comprising contacting the cancer cell with a dPSA binding agent conjugate as disclosed herein, dPSA binding agent as disclosed herein, or composition as disclosed herein.

[0007k] In another aspect, provided herein is a use of a dPSA binding agent conjugate of any as disclosed herein, dPSA binding agent as disclosed herein, or composition as disclosed herein in the manufacture of a medicament for killing a cancer cell that expresses dPSA, wherein the use comprises that the cancer cell is to be contacted with a dPSA binding agent conjugate as disclosed herein, dPSA binding agent as disclosed herein, or composition as disclosed herein.

[0007l] In another aspect, provided herein is a use of a dPSA binding agent conjugate of any as disclosed herein, dPSA binding agent as disclosed herein, or composition as disclosed herein in the manufacture of a medicament for treating cancer characterized by dPSA expression.

[0007m] In another aspect, provided herein is an *in vitro* method of delivering a cytotoxic payload to a cell that expresses dPSA, the method comprising contacting the cell with a dPSA binding agent conjugate as disclosed herein.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

[0008] Figure 1 is a graph depicting mean fluorescence intensity (MFI) of SAC-1 antibody vs. concentration of SEAM 3 reference antibody demonstrating that the test antibody does not bind the same epitope as the reference antibody.

[0009] Figure 2 is a graph depicting mean fluorescence intensity (MFI) of SAC-2 antibody vs. concentration of SEAM 3 reference antibody demonstrating that the test antibody does not bind the same epitope as the reference antibody.

[0010] Figures 3A and 3B show proteins co-immunoprecipitated by SAC-1, SAC-2, and a control IgG1 antibody on SDS-PAGE.

[0011] Figures 4A, 4B, and 4C show SAC-3 staining of normal human breast tissue (Fig. 4A) and a breast tumor (Fig. 4C) compared with staining of the tumor by a control IgG2a antibody (Fig. 4B).

[0012] Figures 5A, 5B, and 5C show graphs depiciting the amount of SAC-1 (Fig. 5A) or SAC-2 antibody (Fig. 5B) vs. relative luminescence units (RLU) demonstrating ADCC for each antibody against various cell lines, as well as quantitative values (Fig. 5C).

CLAIMS:

1. A dPSA binding agent conjugate comprising a dPSA binding agent and a cytotoxic payload conjugated thereto, wherein the cytotoxic payload is is monomethyl auristatin E / Dolastatin-10 (MMAE), Monomethylauristatin F (MMAF), Mertansine (DM1), N2'-deaetyl-N2'-(4-mercapto-4-methyl-1-oxopentyl) maytansine (DM4), 12-Ethyl-9-hydroxycamptothecin (7-ethyl-10-hydroxycamptothecin (SN-38), Exatecan mesylate (DX-8951f), PNU-1596821, Pyrrolobenzodiazepine (PBD or SGD-1882), an Exatecan derivative, or a Captothecin derivative.

2. The dPSA binding agent conjugate of claim 1, wherein the cytotoxic payload is MMAE, Exatecan, or an Exatecan dervivative.

3. The dPSA-binding agent conjugate of claim 1 or 2, wherein the dPSA binding agent comprises:

(a) an immunoglobulin heavy chain variable region comprising SEQ ID NO: 51 or at least the complementarity determining regions (CDRs) thereof; and an immunoglobulin light chain variable region comprising SEQ ID NO: 52 or 53 or at least the CDRs thereof;

(b) an immunoglobulin heavy chain variable region comprising any of SEQ ID NOs: 17-20 or at least the complementarity determining regions (CDRs) thereof; and an immunoglobulin light chain variable region comprising SEQ ID NO: 21 or at least the CDRs thereof;

(c) an immunoglobulin heavy chain variable region comprising any of SEQ ID NOs: 1-4 or at least the complementarity determining regions (CDRs) thereof; and an immunoglobulin light chain variable region comprising SEQ ID NO: 5 or at least the CDRs thereof;

or (d) an immunoglobulin heavy chain variable region comprising SEQ ID NO: 35 or at least the complementarity determining regions (CDRs) thereof; and an immunoglobulin light chain variable region comprising SEQ ID NO: 36 or at least the CDRs thereof.

4. The dPSA binding agent conjugate of claim 1 or 2, wherein the dPSA binding agent comprises:

(a) an immunoglobulin heavy chain variable region comprising:

CDRH1 comprising any one of SEQ ID NOs: 6-9;

CDRH2 comprirsing SEQ ID NO: 10;

CDRH3 comrpising SEQ ID NO: 11;

and an immunoglobulin light chain variable region comprising

CDRL1 comprising SEQ ID NO: 12;

CDRL2 comprising SEQ ID NO: 13; and

CDRL3 comprising SEQ ID NO: 14;

(b) an immunoglobulin heavy chain variable region comprising:

CDRH1 comprising any one of SEQ ID NOs: 24-27;

CDRH2 comprirsing SEQ ID NO: 28;

CDRH3 comrpising SEQ ID NO: 29;

and an immunoglobulin light chain variable region comprising

CDRL1 comprising SEQ ID NO: 30;

CDRL2 comprising SEQ ID NO: 31; and

CDRL3 comprising SEQ ID NO: 32;

(c) an immunoglobulin heavy chain variable region comprising:

CDRH1 comprising SEQ ID NO: 39;

CDRH2 comprising SEQ ID NO: 40; and

CDRH3 comrpising SEQ ID NO: 41 or 47;

and an immunoglobulin light chain variable region comprising

CDRL1 comprising SEQ ID NO: 42;

CDRL2 comprising SEQ ID NO: 43 or 56; and

CDRL3 comprising SEQ ID NO: 44;

or (d) an immunoglobulin heavy chain variable region comprising:

CDRH1 comprising SEQ ID NO: 45;

CDRH2 comprising SEQ ID NO: 46; and

CDRH3 comrpising SEQ ID NO: 41 or 47;

and an immunoglobulin light chain variable region comprising

CDRL1 comprising SEQ ID NO: 48;

CDRL2 comprising SEQ ID NO: 49 or 56; and

CDRL3 comprising SEQ ID NO: 50.

5. The dPSA binding agent conjugate of claim 1 or 2, wherein the dPSA binding agent comprises a heavy chain immunoglobulin polypeptide comprising SEQ ID NO: 57 or SEQ ID NO: 60, and a light chain immunoglobulin polypeptide comprising SEQ ID NO: 58 or SEQ ID NO: 59.

6. The dPSA-binding agent conjugate of any of claims 1-4, wherein the dPSA-binding agent is an antibody or an antigen-binding antibody fragment.

7. The dPSA binding agent conjugate of any of claims 1-4, wherein the dPSA-binding agent is an IgG1 or IgG4 antibody.

8. The dPSA-binding agent conjugate of any of claims 1-4, wherein the dPSA-binding agent is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, or a dAb fragment.

9. The dPSA binding agent conjugate of any of claims 1-8, wherein the dPSA-binding agent comprises an Fc region, and the Fc region comprises a modification that reduces FcγR binding and/or reduces complement dependent cytotoxicity (CDC) or antibody-dependent cytotoxicity (ADCC).

10. The dPSA binding agent conjugate of any of claims 1-9, wherein the cytotoxic payload is conjugated to the dPSA binding agent by a linker.

11. A dPSA binding agent comprising an immunoglobulin heavy chain comprising SEQ ID NO: 57 and an an immunoglobulin light chain comprising SEQ ID NO: 58 or SEQ ID NO: 59.

12. A dPSA binding agent comprising an immunoglobulin heavy chain comprising SEQ ID NO: 60 and an an immunoglobulin light chain comprising SEQ ID NO: 58 or SEQ ID NO: 59.

13. The dPSA binding agent of claim 11 or 12, wherein the dPSA binding agent is afucosylated.

14. The dPSA binding agent of claim 11, wherein the dPSA binding agent comprises an immunoglobulin heavy chain comprising SEQ ID NO: 57 with a modification that reduces FcγR binding and/or reduces complement dependent cytotoxicity (CDC) or antibody-dependent cytotoxicity (ADCC).

15. A dPSA binding agent conjugate comprising the dPSA binding agent of any of claims 11-14 and a cytotoxic payload.

16. The dPSA binding agent conjugate of claim 15, wherein the cytotoxic payload is is monomethyl auristatin E / Dolastatin-10 (MMAE), Monomethylauristatin F (MMAF), Mertansine (DM1), N2'-deaetyl-N2'-(4-mercapto-4-methyl-1-oxopentyl) maytansine (DM4), 12-Ethyl-9-hydroxycamptothecin (7-ethyl-10-hydroxycamptothecin (SN-38), Exatecan mesylate (DX-8951f), PNU-1596821, Pyrrolobenzodiazepine (PBD or SGD-1882), an Exatecan derivative or a Captothecin derivative.

17. The dPSA binding agent conjugate of claim 15 or 16, wherein the cytotoxic payload is MMAE, Exatecan mesylate, or an Exatecan derviative.

18. A nucleic acid encoding the immunoglobulin heavy chain and/or light chain variable region of the dPSA-binding agent of any one of claims 11-14, optionally in a vector.

19. The nucleic acid of claim 18, further encoding a leader sequence for the immunoglobulin heavy chain and/or light chain variable region.

20. A cell comprising the nucleic acid of claim 18 or 19.

21. A cell line that expresses the dPSA binding agent of any one of claims 11-14.

22. An *in vitro* method of preparing a dPSA-binding agent of any one of claims 11-14, the method comprising expressing a nucleotide sequence encoding the immunoglobulin heavy chain polypeptide and a nucleic acid sequence encoding the immunoglobulin light chain polypeptide in a cell.

23. A composition comprising (a) the dPSA-binding agent conjugate of any one of claims 1-10 or 15-17, or dPSA binding agent of any one of claims 11-14 or nucleic acid encoding same, and (b) a pharmaceutically acceptable carrier.

24. An *in vitro* method of killing a cancer cell that expresses dPSA, the method comprising contacting the cancer cell with a dPSA binding agent conjugate of any of claims 1-10 or 15-17, dPSA binding agent of any one of claims 11-14, or composition of claim 23.

25. Use of a dPSA binding agent conjugate of any of claims 1-10 or 15-17, dPSA binding agent of any one of claims 11-14, or composition of claim 23 in the manufacture of a medicament for killing a cancer cell that expresses dPSA, wherein the use comprises that the cancer cell is to be contacted with a dPSA binding agent conjugate of any of claims 1-10 or 15-17, dPSA binding agent of any one of claims 11-14, or composition of claim 23.

26. Use of a dPSA binding agent conjugate of any of claims 1-10 or 15-17, dPSA binding agent of any one of claims 11-14, or composition of claim 23 in the manufacture of a medicament for treating cancer characterized by dPSA expression.

27. An *in vitro* method of delivering a cytotoxic payload to a cell that expresses dPSA, the method comprising contacting the cell with a dPSA binding agent conjugate of any of claims 1-10 or 15-17.

28. The method of claim 27, wherein the cell is a cancer cell.