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[0011] Notwithstanding all such prior success, a need remains for additional therapeutic agents which target and kill tumor cells expressing B7-H3. The present invention is directed to this and other goals.

SUMMARY

[0012] The present disclosure is directed to novel B7-H3-binding molecules capable of binding to human and non-human B7-H3, and in particular to such molecules that are cross-reactive with B7-H3 of a non-human primate (*e.g.*, a cynomolgus monkey). The disclosure additionally pertains to B7-H3-binding molecules that comprise Variable Light Chain and/or Variable Heavy Chain (VH) Domains that have been humanized and/or deimmunized so as to exhibit a reduced immunogenicity upon administration to recipient

subjects. The disclosure particularly pertains to bispecific, trispecific or multispecific B7-H3-binding molecules, including bispecific diabodies, BiTEs, bispecific antibodies, trivalent binding molecules, *etc*. that comprise: (i) such B7-H3-binding Variable Domains and (ii) a domain capable of binding to an epitope of a molecule present on the surface of an effector cell. The disclosure is also directed to pharmaceutical compositions that contain any of such B7-H3-binding molecules, and to methods involving the use of any of such B7-H3-binding molecules in the treatment of cancer and other diseases and conditions. The disclosure also particularly pertains to a molecule that comprises the human B7-H3 binding domain of a humanized anti-human B7-H3 antibody conjugated to at least one drug moiety (a "**B7-H3-ADC**"). The disclosure is also directed to pharmaceutical compositions that contain such **B7-H3-ADC**s, and to methods involving the use of any of such **B7-H3-ADC**s in the treatment of cancer and other diseases and conditions.

[0012a] In one aspect, the disclosure provides a conjugate (**B7-H3-ADC**) comprising a B7-H3 binding molecule and a cytotoxic drug moiety, the conjugate comprising the formula:

$$\mathbf{Ab\text{-}(LM)_m\text{-}(D)_n,}$$

wherein:

Ab is an isolated B7-H3 binding molecule comprising an antibody, a diabody, or an epitope-binding fragment thereof, which is capable of binding to B7-H3, wherein said B7-H3 binding molecule comprises

(i) a humanized Variable Light Chain (VL) domain comprising the amino acid sequence of **SEQ ID NO:20**; and

(ii) a humanized Variable Heavy Chain (VH) domain comprising the amino acid sequence of **SEQ ID NO:21**.

D is a cytotoxic drug moiety, wherein said cytotoxic drug moiety comprises a cytotoxin, a radioisotope, an immunomodulator, a cytokine, a lymphokine, a chemokine, a growth factor, a tumor necrosis factor, a hormone, a hormone antagonist, an enzyme, an oligonucleotide, a DNA, an RNA, an siRNA, an RNAi, a microRNA, a photoactive therapeutic agent, an anti-angiogenic agent, a pro-apoptotic agent, a peptide, a lipid, a carbohydrate, a chelating agent, or combinations thereof;

LM comprises at least one bond or a Linker Molecule that covalently links Ab and D;

m is an integer between 0 and n and denotes the number of **LM** of the **B7-H3-ADC**;

and

n is an integer between 1 and 10 and denotes the number of cytotoxic drug moieties covalently linked to the **B7-H3-ADC** molecule.

[0012b] In one aspect, the disclosure provides a conjugate (**B7-H3-ADC**) comprising a B7-H3 binding molecule and a cytotoxic drug moiety, the conjugate comprising the formula:

$$\mathbf{Ab\text{-}(LM)_m\text{-}(D)_n,}$$

wherein:

said **Ab** comprises an isolated B7-H3 binding molecule comprising an antibody, a diabody, or an epitope-binding fragment thereof, which is capable of binding to B7-H3, wherein said B7-H3 binding molecule comprises

(i) a light chain comprising the Variable Light Chain (VL) domain comprising the amino acid sequence of **SEQ ID NO:20** and a CL Kappa Domain of **SEQ ID NO:1**; and

(ii) a heavy chain comprising the Variable Heavy Chain (VH) domain comprising the amino acid sequence of **SEQ ID NO:21**, a CH1 Domain of **SEQ ID NO:3**, a Hinge Domain of **SEQ ID NO:7** and a Fc Domain comprising a CH2-CH3 Domain of **SEQ ID NO:12**;

said **D** comprises *seco*-duocarmycin; and

said **LM** comprises a Linker Molecule comprising a maleimide linker moiety, a valine-citrulline dipeptide linker, and a para-aminobenzyloxycarbonyl moiety.

[0012c] In one aspect, the disclosure provides a pharmaceutical composition that comprises an effective amount of the **B7-H3-ADC** as disclosed herein and a pharmaceutically acceptable carrier, excipient or diluent.

[0012d] In one aspect, the disclosure provides use of the **B7-H3-ADC** as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a disease or condition associated with or characterized by the expression of B7-H3.

[0013] In detail, one example of the present disclosure provides a B7-H3-binding molecule that comprises a Variable Light Chain (VL) Domain and a Variable Heavy Chain (VH) Domain, wherein said Variable Heavy Chain Domain comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, and said Variable Light Chain Domain comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, wherein at least three of said domains, at least four of said domains, at least five of said domains or all of said domains are selected from the group consisting of:

(1) a CDR_H1 Domain comprising the amino acid sequence of **SEQ ID NO:27**;
(2) a CDR_H2 Domain comprising the amino acid sequence of **SEQ ID NO:28**;
(3) a CDR_H3 Domain comprising the amino acid sequence of **SEQ ID NO:29**;
(4) a CDR_L1 Domain comprising the amino acid sequence of **SEQ ID NO:23**;
(5) a CDR_L2 Domain comprising the amino acid sequence of **SEQ ID NO:24**; and
(6) a CDR_L3 Domain comprising the amino acid sequence of **SEQ ID NO:25**.

[0014] The disclosure additionally concerns the example of such B7-H3-binding molecule that comprises said Variable Light Chain (VL) Domain that comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and said Variable Heavy Chain (VH) Domain that comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(1) said CDR_H1 Domain comprises the amino acid sequence of **SEQ ID NO:27**;
(2) said CDR_H2 Domain comprises the amino acid sequence of **SEQ ID NO:28**;

(3) said CDR_H3 Domain comprises the amino acid sequence of **SEQ ID NO:29**.

[0015] The disclosure additionally concerns the example of such B7-H3-binding molecule that comprises said Variable Light Chain (VL) Domain that comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and said Variable Heavy Chain (VH) Domain that comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(1) said CDR_L1 Domain comprises the amino acid sequence of **SEQ ID NO:23**;

(2) said CDR_L2 Domain comprises the amino acid sequence of **SEQ ID NO:24**; and

(3) said CDR_L3 Domain comprises the amino acid sequence of **SEQ ID NO:25**.

[0016] The disclosure additionally concerns the example of such B7-H3-binding molecules wherein said Variable Heavy Chain (VH) Domain comprises the amino acid sequence of **SEQ ID NO:26** or **SEQ ID NO:31**.

[0017] The disclosure additionally concerns the example of such B7-H3-binding molecules wherein said Variable Light Chain (VL) Domain comprises the amino acid sequence of **SEQ ID NO:22** or **SEQ ID NO:30**.

[0018] The disclosure additionally concerns B7-H3-binding molecules that comprise a VL Domain and a VH Domain, wherein said VL Domain comprises the amino acid sequence of **SEQ ID NO:20**.

[0019] The disclosure additionally concerns B7-H3-binding molecules that comprise a VL Domain and a VH Domain, wherein said VH Domain comprises the amino acid sequence of **SEQ ID NO:21**.

[0020] The disclosure additionally concerns B7-H3-binding molecules that comprise a VL Domain and a VH Domain, wherein said VL Domain comprises the amino acid of **SEQ ID NO:20** and said VH Domain comprises the amino acid sequence of **SEQ ID NO:21**.

[0021] The disclosure further concerns the example of such B7-H3-binding molecules, wherein the molecule is an antibody or an epitope-binding fragment thereof. The disclosure also concerns the examples of such a B7-H3-binding molecule, wherein the molecule is a bispecific antibody or a diabody, especially a diabody, or diabody complex,

that comprises two, three, four or five polypeptide chains each having an N-terminus and a C-terminus in which such polypeptide chains are associated together via one or more covalent, and especially one or more covalent disulfide, bonds. The disclosure additionally concerns the example of such B7-H3-binding molecules wherein the molecule is a trivalent binding molecule, and especially wherein the trivalent binding molecule is a covalently bonded complex that comprises three, four, five, or more polypeptide chains. The disclosure further concerns the example of such a B7-H3-binding molecule, wherein the molecule comprises an Fc Domain. The disclosure additionally concerns the example of such B7-H3-binding molecules wherein the molecule is a diabody and comprises an Albumin-Binding Domain, and especially a deimmunized Albumin-Binding Domain.

[0022] The disclosure further concerns the examples of all such B7-H3-binding molecules that additionally comprise an Fc Domain, and especially wherein the Fc Domain is a variant Fc Domain that comprises one or more amino acid modifications that reduces the affinity of the variant Fc Domain for an FcγR and/or enhances the serum half-life of the B7-H3-binding molecule, and more particularly, wherein the modifications comprise at least one substitution selected from the group consisting of:

(a) L234A;

(b) L235A;

(c) L234A and L235A;

(d) M252Y; M252Y and S254T;

(e) M252Y and T256E;

(f) M252Y, S254T and T256E; and

(g) K288D and H435K;

wherein the numbering is that of the EU index as in Kabat.

[0023] The disclosure further concerns the example of such B7-H3-binding molecules, wherein the molecule is bispecific, and particularly concerns the example wherein the molecule comprises two epitope-binding sites capable of immunospecific binding to an epitope of B7-H3 and two epitope-binding sites capable of immunospecific binding to an epitope of a molecule present on the surface of an effector cell, or the example wherein the molecule comprises one epitope-binding site capable of immunospecific binding to an epitope of B7-H3 and one epitope-binding site capable of

immunospecific binding to an epitope of a molecule present on the surface of an effector cell.

[0024] The disclosure additionally concerns the example of such B7-H3 binding molecules wherein the molecule is a trivalent binding molecule, and particularly concerns the examples wherein the molecule comprises, one epitope-binding site capable of immunospecific binding to an epitope of B7-H3, one epitope-binding site capable of immunospecific binding to an epitope of a first molecule present on the surface of an effector cell; and one epitope-binding site capable of immunospecific binding to an epitope of a second molecule present on the surface of an effector cell, wherein such first and second molecules are not B7-H3.

[0025] The disclosure further concerns the example of such a B7-H3-binding molecule, wherein the molecule is capable of simultaneously binding to B7-H3 and to a second epitope, and particularly concerns the example wherein the second epitope is an epitope of a second molecule present on the surface of an effector cell (especially wherein the second epitope is an epitope of CD2, CD3, CD8, CD16, TCR, or NKG2D, and most particularly wherein the second epitope is an epitope of CD3). The disclosure additionally concerns the example of such B7-H3-binding molecules, wherein the effector cells is a cytotoxic T-cell or a Natural Killer (NK) cell. The disclosure additionally concerns the example of such B7-H3-binding molecules, wherein the molecule is also capable of binding a third epitope, and particularly concerns the example wherein the third epitope is an epitope of CD8. The disclosure further concerns the examples of such molecules wherein molecule mediates coordinated binding of a cell expressing B7-H3 and a cytotoxic T cell.

[0026] The disclosure further provides pharmaceutical compositions comprising an effective amount of any of the above-described B7-H3-binding molecules and a pharmaceutically acceptable carrier, excipient or diluent.

[0027] The disclosure is additionally directed to the use of any of the above-described B7-H3-binding molecules in the treatment of a disease or condition associated with or characterized by the expression of B7-H3, or in a method of treating a disease or condition characterized by the expression of B7-H3, particularly wherein the disease or condition associated with or characterized by the expression of B7-H3 is cancer, and more

particularly, wherein the cancer is selected from the group consisting of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, an adrenal cancer, a bladder cancer, a bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a B-cell cancer, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, a gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, a hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

[0028] A second example of the present disclosure is directed to a molecule that comprises the human B7-H3 binding domain of a humanized anti-human B7-H3 antibody conjugated to at least one drug moiety (a "**B7-H3-ADC**"). The disclosure is also directed to pharmaceutical compositions that contain such **B7-H3-ADCs**, and to methods involving the use of any of such **B7-H3-ADCs** in the treatment of cancer and other diseases and conditions.

[0029] In detail, the disclosure provides an anti-B7-H3 antibody drug conjugate (**B7-H3-ADC**) comprising the formula:

$$\mathbf{Ab\text{-}(LM)_m\text{-}(D)_n,}$$

wherein:

Ab is an antibody that binds to B7-H3 that comprises a humanized Variable Heavy Chain (VH) Domain and a humanized Variable Light Chain (VL) Domain, or is a B7-H3-binding fragment thereof, and;

D is a cytotoxic drug moiety;

LM is a Linker Molecule that covalently links **Ab** and **D**;

m is an integer between 0 and n and denotes the number of Linker Molecules of the **B7-H3-ADC**;

and

n is an integer between 1 and 10 and denotes the number of cytotoxic drug moieties covalently linked to the ADC.

[0030] The disclosure further provides such **B7-H3-ADCs**, wherein the Linker Molecule **LM** is absent (*i.e.*, **m** = 0), and **B7-H3-ADCs** that possess more than one Linker Molecule **LM** (*i.e.*, **m** is an integer from 2 through **n**), each of which Linker Molecule **LM** covalently links a cytotoxic drug moiety **D** to the **Ab** of such **B7-H3-ADCs**. The disclosure further provides such **B7-H3-ADCs** whose **Ab** are covalently linked to more than one Linker Molecule **LM**, wherein all such Linker Molecules are identical. The cytotoxic drug moieties **D** that are covalently linked to the **Ab** of such **B7-H3-ADCs** may all be identical or may include 2, 3, 4, or more non-identical cytotoxic drug moieties **D**. The disclosure further provides such **B7-H3-ADCs** whose **Ab** are covalently linked to more than one Linker Molecule **LM**, wherein all such Linker Molecules are not identical. The cytotoxic drug moieties **D** that are covalently linked to the **Ab** of such **B7-H3-ADCs** may all be identical or may include 2, 3, 4, or more non-identical cytotoxic drug moieties **D**.

[0031] The disclosure further provides such **B7-H3-ADCs**, wherein:

(A) (i) the humanized VL Domain comprises the amino acid sequence of **SEQ ID NO:99**, and

(ii) the humanized VH Domain comprises the amino acid sequence of **SEQ ID NO:104**;

or

(B) (i) the humanized VL Domain comprises the amino acid sequence of **SEQ ID NO:20**, and

(ii) the humanized VH Domain comprises the amino acid sequence of **SEQ ID NO:21**;

or

(C) (i) the humanized VL Domain comprises the amino acid sequence of **SEQ ID NO:30**, and

(ii) the humanized VH Domain comprises the amino acid sequence of **SEQ ID NO:31**.

[0032] The disclosure further provides such **B7-H3-ADCs**, wherein the humanized VL Domain comprises the amino acid sequence of **SEQ ID NO:99** and the humanized VH Domain comprises the amino acid sequence of **SEQ ID NO:104**.

[0033] The disclosure further provides such **B7-H3-ADCs**, wherein the humanized VL Domain comprises the amino acid sequence of **SEQ ID NO:20** and the humanized VH Domain comprises the amino acid sequence of **SEQ ID NO:21**.

[0034] The disclosure further provides such **B7-H3-ADCs**, wherein the humanized the humanized VL Domain comprises the amino acid sequence of **SEQ ID NO:30** and the humanized VH Domain comprises the amino acid sequence of **SEQ ID NO:31**.

[0035] The disclosure further provides such **B7-H3-ADCs**, wherein the **Ab** is an antibody or an antigen binding fragment of an antibody.

[0036] The disclosure further provides such **B7-H3-ADCs**, wherein the **B7-H3-ADC** comprises an Fc Domain of a human IgG (especially a human IgG1, IgG2, IgG3, or IgG4).

[0037] The disclosure further provides such **B7-H3-ADCs**, wherein the **B7-H3-ADC** comprises a variant Fc Domain that comprises:

(a) one or more amino acid modifications that reduces the affinity of the variant Fc Domain for an FcγR; and/or

(b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Domain.

[0038] The disclosure further provides such **B7-H3-ADCs** that comprise a variant Fc Domain, wherein the modifications that reduces the affinity of the variant Fc Domain for an FcγR comprise the substitution of L234A; L235A; or L234A and L235A, wherein the numbering is that of the EU index as in Kabat.

[0039] The disclosure further provides such **B7-H3-ADCs** that comprise a variant Fc Domain, wherein the modifications that that enhances the serum half-life of the variant Fc Domain comprise the substitution of M252Y; M252Y and S254T; M252Y and T256E;

M252Y, S254T and T256E; or K288D and H435K, wherein the numbering is that of the EU index as in Kabat.

[0040] The disclosure further provides such **B7-H3-ADCs** wherein at least one of the **LM** is a Linker Molecule, and particularly wherein the **LM** Linker Molecule is a peptidic linker and/or a cleavable linker.

[0041] The disclosure further provides such **B7-H3-ADCs** wherein the molecule comprises the formula:

$$\mathbf{Ab - [V\text{-}(W)_k\text{-}(X)_1\text{-}A] - D}$$

wherein:

V is the cleavable **LM** Linker Molecule,

$\mathbf{(W)_k\text{-}(X)_1\text{-}A}$ is an elongated, self-eliminating spacer system, that self-eliminates via a l,(4+2n)-elimination,

W and **X** are each a l,(4+2n) electronic cascade spacer, being the same or different,

A is either a spacer group of formula $(\mathbf{Y})_m$, wherein **Y** is a l,(4+2n) electronic cascade spacer, or a group of formula **U**, being a cyclisation elimination spacer,

k, 1 and m are independently an integer of 0 (included) to 5 (included),

n is an integer of 0 (included) to 10 (included),

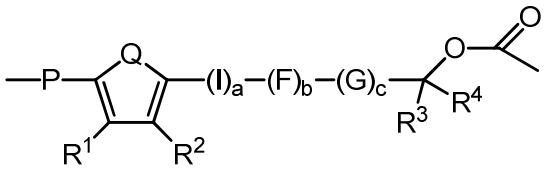
with the provisos that:

when **A** is $(\mathbf{Y})_m$: then $k+l+m \geq 1$, and

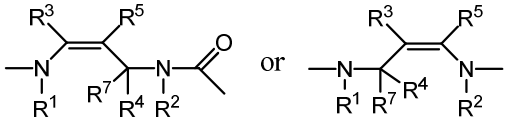
if $k+l+m=l$, then $n>l$;

when **A** is **U**: then $k+1 \geq 1$.

W, **X**, and **Y** are independently selected from compounds having the formula:



or the formula:



wherein:

a, b and c are independently selected to be an integer of 0 or 1; provided that a + b + c = 2 or 3;

R^1 and/or R^2 independently represent H, C1-6 alkyl, the alkyl being optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_x), amino (NH_2), mono-substituted amino (NR_xH), disubstituted amino ($NR_x^1R_x^2$), nitro (NO_2), halogen, CF_3, CN, $CONH_2$, SO_2Me, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_X), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_X$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate (S(=O)ORx), sulphinyl (S(=O)Rx), phosphonooxy ($OP(=O)(OH)_2$), and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group; and

R^3, R^4, R^5, R^6, R^7 and R^8 independently represent H, C_{1-6} alkyl, C_{3-20} heterocyclyl, C_{5-20} aryl, C_{1-6} alkoxy, hydroxy (OH), amino (NH_2), mono-substituted amino (NR_xH), disubstituted amino ($NR_x^1R_x^2$), nitro (NO_2), halogen, CF_3, CN, $CONH_2$, SO_2Me, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_x$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$), and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, and two or more of the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, or R^8 are optionally connected to one another to form one or more aliphatic or aromatic cyclic structures.

[0042] The disclosure further provides such **B7-H3-ADCs** wherein the **LM** Linker Molecule comprises:

(24) p-aminophenylpentadienyloxycarbonyl-p-aminocinnamyl;

(25) p-aminophenylpentadienyloxycarbonyl-p-aminobenzyl;

or

(26) p-aminophenylpentadienyloxycarbonyl-p-aminophenylpentadienyl.

[0043] The disclosure further provides such **B7-H3-ADCs** wherein the **LM** Linker Molecule is conjugated to the side chain of an amino acid of a polypeptide chain of **Ab** and binds the **Ab** to a molecule of the cytotoxic drug moiety **D**, and in particular, wherein the cytotoxic drug moiety **D** comprises a cytotoxin, a radioisotope, an immunomodulator, a cytokine, a lymphokine, a chemokine, a growth factor, a tumor necrosis factor, a hormone, a hormone antagonist, an enzyme, an oligonucleotide, a DNA, an RNA, an siRNA, an RNAi, a microRNA, a photoactive therapeutic agent, an anti-angiogenic agent, a pro-apoptotic agent, a peptide, a lipid, a carbohydrate, a chelating agent, or a combinations thereof.

[0044] The disclosure further provides such **B7-H3-ADCs** wherein the **LM** Linker Molecule is conjugated to the side chain of an amino acid of a polypeptide chain of **Ab** and binds the **Ab** to a molecule of the cytotoxic drug moiety **D**, and in particular, wherein the cytotoxic drug moiety **D** comprises a cytotoxin selected from the group consisting of a tubulysin (especially a tubulysin cytotoxin selected from the group consisting of tubulysin A, tubulysin B, tubulysin C, and tubulysin D), an auristatin (especially an auristatin cytotoxin selected from the group consisting of MMAE (N-methylvaline-valine-dolaisoleuine-dolaproine-norephedrine) and MMAF (N-methylvaline-valine-dolaisoleuine-dolaproine-phenylalanine), a maytansinoid (especially a maytansinoid cytotoxin selected from the group consisting of Mytansine, DM1 and DM4), a calicheamicin (especially a calicheamicin cytotoxin selected from the group consisting of calicheamicin γ1, calicheamicin β1Br, calicheamicin γ1Br, calicheamicin α2I, calicheamicin α3I, calicheamicin β1I, calicheamicin γ1I, and calicheamicin Δ1I), a pyrrolobenzodiazepine (especially a pyrrolobenzodiazepine cytotoxin selected from the group consisting of vadastuximab talirine, SJG-136, SG2000, SG2285 and SG2274), and a duocarmycin (especially a duocarmycin cytotoxin and is selected from the group consisting of duocarmycin A, duocarmycin B1, doucarmycin B2, duocarmycin C1, duocarmycin C2, duocarmycin D, duocarmycin SA, CC-1065, adozelesin, bizelesin, carzelesin (U-80244) and spiro-duocarmycin (DUBA)).

[0045] The disclosure further provides pharmaceutical compositions comprising an effective amount of any of the above-described **B7-H3-ADCs** and a pharmaceutically acceptable carrier, excipient or diluent.

[0046] The disclosure is additionally directed to the use of any of the above-described **B7-H3-ADCs** in the treatment of a disease or condition associated with or characterized by the expression of B7-H3, or in a method of treating a disease or condition characterized by the expression of B7-H3, particularly wherein the disease or condition associated with or characterized by the expression of B7-H3 is cancer, and more particularly, wherein the cancer is selected from the group consisting of: an acute myeloid leukemia, an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, a glioblastoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a malignant mesothelioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, a non-small cell lung cancer, an ovarian cancer, a pancreatic cancer, a pharyngeal cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a renal cell carcinoma, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0047] **Figure 1** provides a schematic of a representative covalently bonded diabody having two epitope-binding sites composed of two polypeptide chains, each having an E-coil or K-coil Heterodimer-Promoting Domain (alternative Heterodimer-Promoting