

ADCC-activity (as described in US Patent 8,835,606 B2 all amino acid and nucleic acid sequences, herein, incorporated by reference). The ADCC-enhanced hu14.18-IgG1(K322A) may induce less complement-fixation/CDC-mediated pain, while killing tumor cells via an ADCC mechanism of action. ADCC-enhanced hu14.18-IgG1(K322A) is in clinical development (phase 2) , but has not been approved. A chimeric anti-GD2 antibody with wild-type IgG1 isotype (dinutuximab) was approved for a defined set of pediatric neuroblastoma patients, and neuropathic pain associated with this treatment is known to occur and can require co-administration with pain relief agents.

[0010a] In one aspect, the present disclosure describes an antibody drug conjugate (“ADC”) comprising a growth inhibitory agent and/or an anti-proliferative agent linked to an antibody by way of a linker, wherein the antibody comprises the anti-GD2 antibody light chain variable region of SEQ ID NO: 1, the anti-GD2 antibody heavy chain variable region of SEQ ID NO:2, and an Fc region with one mutation decreasing complement fixation relative to antibody-dependent, cell-mediated cytotoxicity, wherein the one mutation causes an absolute decrease in complement fixation.

[0010b] In another aspect, the present disclosure describes a pharmaceutical composition comprising the ADC of the disclosure and a pharmaceutically acceptable excipient.

[0010c] In another aspect, the present disclosure describes a use of the pharmaceutical composition of the disclosure in the manufacture of a medicament for treating cancer.

[0010d] In another aspect, the present disclosure describes an antibody drug conjugate (“ADC”) comprising a growth inhibitory agent and/or an anti-proliferative agent linked to an anti-GD2 antibody by way of a linker, wherein said anti-GD2 antibody comprises the amino acid sequence of SEQ ID NO:4 and the amino acid sequence of SEQ ID NO:1, said linker is β -glucuronide, and said growth inhibitory agent is Exatecan.

[0010e] In another aspect, the present disclosure describes a pharmaceutical composition comprising the ADC of the disclosure and a pharmaceutically acceptable excipient.

[0010f] In another aspect, the present disclosure describes a use of the pharmaceutical composition of the disclosure in the manufacture of a medicament for treating cancer, wherein a therapeutically effective amount of the medicament is to be administered to a subject.

[0011] In some examples, the present disclosure describes anti-GD2 hu14.18 antibody as an ADC with both ADCC and CDC antibody effector functions reduced or absent, thereby, providing the benefit of a larger therapeutic window to treat

unmet medical needs. Designing hu14.18 antibodies without significant ADCC or CDC effector functions may reduce the risk of neuropathic pain induced by administration of anti-GD2 hu14.18 antibodies, while the conjugation of a drug to the antibody provides a different mechanism of action for such an anti-GD2-ADC to eliminate tumor cells. The combination of anti-GD2 hu14.18 lacking significant ADCC and CDC effector functions that delivers a potent conjugated drug as an ADC improves existing treatments and is likely to fill the (as of yet) unmet medical needs of patients. In selected examples, the selected cytotoxic drug should be free of neurotoxic properties.

[0012] Binding of an antibody to a specific antigen target is a property of the antigen-binding fragment (Fab) domain, including the specific light chain and heavy chain variable region complementarity-determining regions (CDR) amino acid sequences. Antibody effector functions and binding to Fc gamma receptors (FcγR) and neonatal Fc receptor (FcRn) are properties of the immunoglobulin (Ig) constant domains. There are different immunoglobulin constant domain genes, and these constant domain genes fused together with the Fab domain sequence determine the isotype of the antibody (IgM, IgG1, IgG2, etc.). In naturally occurring or recombinant antibodies the same antigen-binding domain amino acid sequences may be expressed fused to different constant domain isotypes, to produce antibodies with the same antigen target-binding specificity, but with different effector function properties. The abilities of an antibody to mediate activation of components of the immune system are termed the “effector functions” of the antibody, and important effector functions are mediated through binding to FcγR on immune cells and to complement proteins such as complement component 1q (C1q) in blood and extracellular fluids. Depending on the isotype an antibody links the specific antigen target on a cell to the immune system and can induce directed attack on the target cell by immune functions, such as Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC). Binding of the Ig constant domains to FcRn plays an important role in the in vivo half-life of an antibody,

through increased recycling back to the circulation after an antibody has been internalized into cells. There have been a large number of investigations to test the role of specific amino acid residues in antibody constant domains for antibody effector functions and binding of antibodies to FcγR and complement proteins. Some changes in the amino acid sequence of human Ig constant domains may be used to produce recombinant antibodies with altered properties for antibody effector functions and binding of antibodies to FcγR and complement proteins. In selected examples, the present disclosure is to provides ADC proteins that bind the target GD2 to deliver ADC molecules to cells and without significant antibody effector functions.

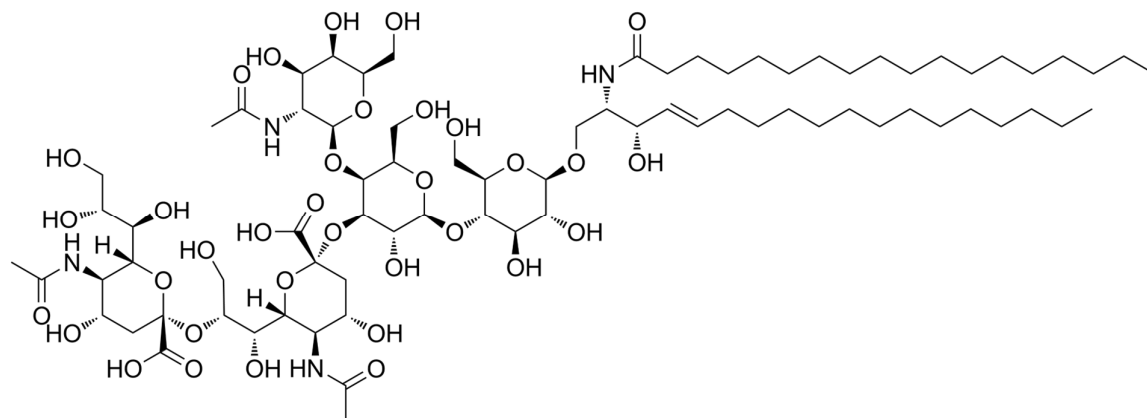
[0013] In some examples of the present disclosure , the production and use of an anti-GD2 hu14.18-IgG1.4(K322A)-delK antibody conjugated to a small molecule toxic payload from the class of Exatecan topoisoemrase-I inhibitors for the treatment of different tumor indications, e.g. sarcomas, neuroblastoma and SCLC is described. This novel ADC offers a preferred therapeutic window as compared to other GD2 antibody therapies already in clinical use.

[0014] In preferred examples of the present disclosure , the Fc-part effector functionality was engineered out of the ADC and, instead, the non-neurotoxic payload Exatecan was used to kill tumor cells with a resulting absence of PNS injury and obvious clinical pain signals in rats and monkeys after repeated infusions of Molecule 1.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0015] “GD2” is a disialoganglioside expressed on tumors of neuroectodermal origin, including human neuroblastoma and melanoma, with highly restricted expression on normal tissues, principally to the central and peripheral nervous system in humans. GD2 is defined by the following chemical structure:



Which corresponds to the following IUPAC name:

CLAIMS

1. An antibody drug conjugate (“ADC”) comprising a growth inhibitory agent and/or an anti-proliferative agent linked to an antibody by way of a linker, wherein the antibody comprises the anti-GD2 antibody light chain variable region of SEQ ID NO: 1, the anti-GD2 antibody heavy chain variable region of SEQ ID NO:2, and an Fc region with one mutation decreasing complement fixation relative to antibody-dependent, cell-mediated cytotoxicity, wherein the one mutation causes an absolute decrease in complement fixation.
2. The antibody of claim 1, wherein the one mutation eliminates complement fixation.
3. The antibody of claim 1, wherein the Fc region is derived from IgG.
4. The antibody of claim 3, wherein the IgG is IgG1.
5. The antibody of claim 1, further comprising a CH1 domain.
6. The antibody of claim 5, wherein the Fc region is derived from IgG.
7. The antibody of claim 5, wherein the IgG is IgG1.
8. The antibody of claim 1, further comprising a CL domain.
9. The antibody of claim 8, further comprising a CH1 domain.
10. The linker of claim 1, wherein said linker is cleavable by glucuronidase.
11. The linker of claim 1, wherein said linker is cleavable by legumain.
12. The growth inhibitory agent of claim 1, wherein said growth inhibitory agent is Exatecan.
13. The ADC of claim 1 which has an average drug-to-antibody ratio in the range of 1-10.
14. The ADC of claim 1 which has an average drug-to-antibody ratio in the range of 2-4.
15. The ADC of claim 1, wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% homologous to the heavy chain variable region amino acid sequence set forth in SEQ ID

NO:2 and a light chain variable region comprising an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% homologous to the light chain variable region amino acid sequence set forth in SEQ ID NO:1.

16. A pharmaceutical composition comprising the ADC of claim 1 and a pharmaceutically acceptable excipient.

17. Use of the pharmaceutical composition of claim 16 in the manufacture of a medicament for treating cancer.

18. An antibody drug conjugate ("ADC") comprising a growth inhibitory agent and/or an anti-proliferative agent linked to an anti-GD2 antibody by way of a linker, wherein said anti-GD2 antibody comprises the amino acid sequence of SEQ ID NO:4 and the amino acid sequence of SEQ ID NO:1, said linker is β -glucuronide, and said growth inhibitory agent is Exatecan.

19. The ADC of claim 18, wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% homologous to the heavy chain variable region amino acid sequence set forth in SEQ ID NO:4 and a light chain variable region comprising an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% homologous to the light chain variable region amino acid sequence set forth in SEQ ID NO:1.

20. A pharmaceutical composition comprising the ADC of claim 18 and a pharmaceutically acceptable excipient.

21. Use of the pharmaceutical composition of claim 20 in the manufacture of a medicament for treating cancer, wherein a therapeutically effective amount of the medicament is to be administered to a subject.

22. The use of claim 21, wherein the administration of said medicament is associated with a decrease in peripheral neuropathy associated with the administration of other ADCs approved for human use.