Claims

1. An isolated anti-GCC antibody molecule that binds to the same epitope on GCC as, or competes for binding to GCC with, an antibody molecule comprising a light chain variable region and a heavy chain variable region, wherein the light chain variable region comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), and the heavy chain variable region comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3),

wherein the light chain variable region comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO:112, an LCDR2 comprising the amino acid sequence of SEQ ID NO:114 and an LCDR3 comprising the amino acid sequence of SEQ ID NO:116; and

wherein the heavy chain variable region comprises: an HCDR1 comprising the amino acid sequence of SEQ ID NO:106, an HCDR2 comprising the amino acid sequence of SEQ ID NO:108 and an HCDR3 comprising the amino acid sequence of SEQ ID NO:110.

2. The antibody molecule of claim 1, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:20, and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:18.

3. The antibody molecule of claim 1 or claim 2 that binds to, or competes for binding to, an epitope on GCC, wherein the epitope resides within, or comprises:

(a) amino acid residues 1 to 50 of SEQ ID NO:228;

(b) amino acid residues 25 to 50 of SEQ ID NO:228;

(c) amino acid residues 33 to 50 of SEQ ID NO:228;

(d) amino acid residues 24 to 420 of SEQ ID NO:228; and/or

(e) amino acid residues 24 to 75 of SEQ ID NO:228.

4. The antibody molecule of claim 3, wherein the epitope comprises one or more amino acid residues from amino acid residues 50 to 1073 of SEQ ID NO:228.

5. The antibody molecule of claim 3 or claim 4, wherein the epitope is a conformational epitope.

6. The antibody molecule of claim 1 or claim 2, wherein the antibody molecule binds a fragment of GCC comprising:

(a) amino acid residues 1 to 50 of SEQ ID NO:228;

(b) amino acid residues 25 to 50 of SEQ ID NO:228;

(c) amino acid residues 33 to 50 of SEQ ID NO:228;

(d) amino acid residues 24 to 420 of SEQ ID NO:228; and/or

(e) amino acid residues 24 to 75 of SEQ ID NO:228.

7. An isolated anti-GCC antibody molecule comprising a light chain variable region and a heavy chain variable region and an Fc region, wherein the light chain variable region comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), and the heavy chain variable region comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3),

wherein the light chain variable region comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO:112, an LCDR2 comprising the amino acid sequence of SEQ ID NO:114 and an LCDR3 comprising the amino acid sequence of SEQ ID NO:116;

wherein the heavy chain variable region comprises: an HCDR1 comprising the amino acid sequence of SEQ ID NO:106, an HCDR2 comprising the amino acid sequence of SEQ ID NO:108 and an HCDR3 comprising the amino acid sequence of SEQ ID NO:110; and

wherein the Fc region is mutated to modify effector function.

8. The antibody molecule of claim 7, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:20, and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:18.

9. A bispecific antibody molecule having binding specificity to GCC and a second antigen, wherein the bispecific antibody molecule comprises a light chain variable region and a heavy chain variable region forming a binding site for GCC, wherein the light chain variable region comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), and the heavy chain variable region comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3),

wherein the light chain variable region comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO:112, an LCDR2 comprising the amino acid sequence of SEQ ID NO:114 and an LCDR3 comprising the amino acid sequence of SEQ ID NO:116; and

wherein the heavy chain variable region comprises: an HCDR1 comprising the amino acid sequence of SEQ ID NO:106, an HCDR2 comprising the amino acid sequence of SEQ ID NO:108 and an HCDR3 comprising the amino acid sequence of SEQ ID NO:110.

10. The bispecific antibody molecule of claim 9, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:20, and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:18.

11. The bispecific antibody molecule of claim 9 or claim 10, comprising:

(a) two antibody molecules conjugated together, one with binding specificity to GCC and another with binding specificity to a second antigen;

(b) a single antibody molecule that comprises one chain with binding specificity to GCC and a second chain with binding specificity to a second antigen; or

(c) a single chain antibody molecule that has binding specificity to GCC and a second antigen.

12. An anti-GCC antibody molecule conjugated to a radiolabel, wherein the antibody molecule comprises a light chain variable region and a heavy chain variable

region, wherein the light chain variable region comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), and the heavy chain variable region comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3),

wherein the light chain variable region comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO:112, an LCDR2 comprising the amino acid sequence of SEQ ID NO:114 and an LCDR3 comprising the amino acid sequence of SEQ ID NO:116; and

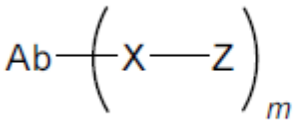
wherein the heavy chain variable region comprises: an HCDR1 comprising the amino acid sequence of SEQ ID NO:106, an HCDR2 comprising the amino acid sequence of SEQ ID NO:108 and an HCDR3 comprising the amino acid sequence of SEQ ID NO:110.

13. The antibody molecule of claim 12, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:20, and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:18.

14. The antibody molecule of claim 12 or claim 13, wherein the radiolabel comprises an α-emitter, a β-emitter, or a positron-emitting radionuclide.

15. The antibody molecule of claim 14, wherein the α-emitter is ^{213}Bi or ^{225}Ac and the β-emitter is ^{90}Y or ^{177}Lu.

16. An immunoconjugate of formula (***I***):



(***I***)

or a pharmaceutically acceptable salt thereof, wherein:

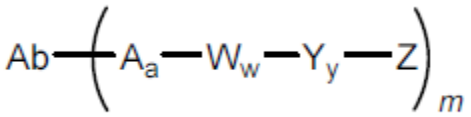
Ab is the antibody molecule of any one of claims 1 to 15;

X is a linker moiety which connects Ab and Z;

Z is a therapeutic agent or a label; and

m is the number of –X-Z moieties per antibody molecule in the immunoconjugate of formula (***I***), and *m* is an integer from about 1 to about 15.

17. The immunoconjugate of claim 16, wherein the linker –X- has the formula -Aa-Ww-Yy-, and the immunoconjugate is characterized by formula (***II***):



(***II***)

or a pharmaceutically acceptable salt thereof, wherein:

-A- is a Stretcher unit;

a is 0 or 1;

each –W- independently is an Amino Acid unit;

w is an integer ranging from 0 to 12;

-Y- is a self-immolative Spacer unit;

y is 0, 1, or 2;

Z is a therapeutic agent or label; and

m is an integer from about 1 to about 15.

18. The immunoconjugate of claim 16 or claim 17, wherein Z is a detectable label or a radiolabel.

19. The immunoconjugate of claim 18, wherein the radiolabel comprises an α-emitter, a β-emitter, or a positron-emitting radionuclide.

20. The immunoconjugate of claim 19, wherein the α-emitter is ^{213}Bi or ^{225}Ac and the β-emitter is ^{90}Y or ^{177}Lu.

21. The immunoconjugate of claim 16 or claim 17, wherein Z is a cytostatic or cytotoxic agent.

22. The immunoconjugate of claim 21, wherein the cytostatic or cytotoxic agent is selected from an antimetabolite; an alkylating agent; an anthracycline; an antibiotic; an antimitotic agent; a topoisomerase inhibitor; and a proteasome inhibitor.

23. The immunoconjugate of claim 22, wherein the antimetabolite is selected from azathioprine, 6-mercaptopurine, 6-thioguanine, fludarabine, pentostatin, cladribine, 5-fluorouracil (5-FU), floxuridine (FUDR), cytosine arabinoside (cytarabine), methotrexate, trimethoprim, pyrimethamine, and pemetrexed; the alkylating agent is selected from cyclophosphamide, mechlorethamine, uramustine, melphalan, chlorambucil, thiotepa/chlorambucil, ifosfamide, carmustine, lomustine, streptozocin, busulfan, dibromomannitol, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, and temozolomide; the anthracycline is selected from daunorubicin, doxorubicin, epirubicin, idarubicin, and valrubicin; the antibiotic is selected from dactinomycin, bleomycin, mithramycin, anthramycin, streptozotocin, gramicidin D, mitomycins, duocarmycins, and calicheamicins; the antimitotic agent is selected from maytansinoids, auristatins, dolastatins, cryptophycins, vinca alkaloids, taxanes, and colchicines; the topoisomerase inhibitor is selected from irinotecan, topotecan, amsacrine, etoposide, teniposide, and mitoxantrone; and the proteasome inhibitor is a peptidyl boronic acid.

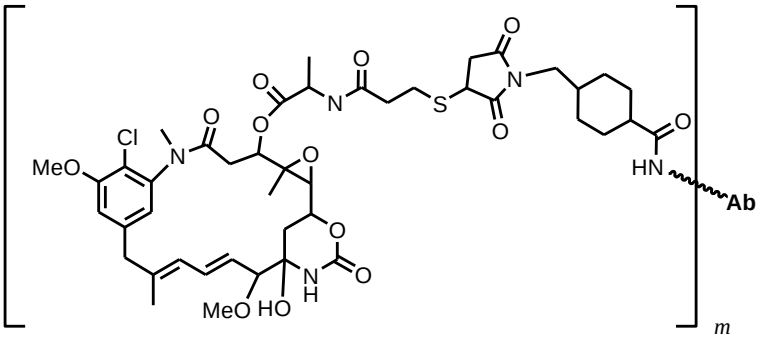
24. The immunoconjugate of claim 23, wherein the mitomycin is mitomycin C; the duocarmycin is CC-1065; the vinca alkaloid is selected from vincristine, vinblastine, vindesine, and vinorelbine; and the taxane is paclitaxel or docetaxel.

25. The immunoconjugate of claim 16 or claim 17, wherein Z is a maytansinoid or maytansine, a dolastatin, or an auristatin.

26. The immunoconjugate of claim 25, wherein the maytansinoid or maytansine is $N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-1-oxopentyl)maytansine (DM3), $N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl)-maytansine (DM1), or $N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)maytansine (DM4); and the auristatin is AEB, AEVB, AFP, MMAE, or MMAF.

27. The immunoconjugate of any one of claims 16, 25, or 26, wherein

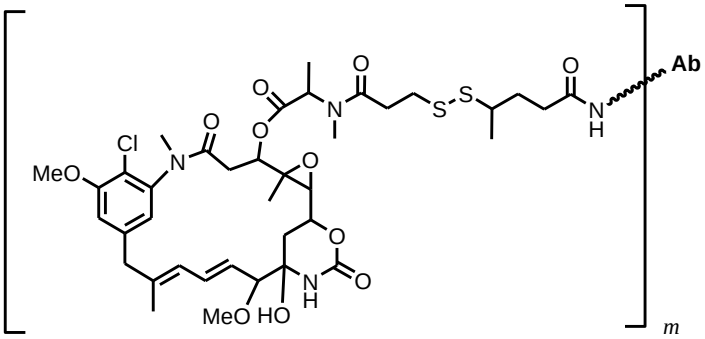
(a) the immunoconjugate has formula (***I-1***):



(***I-1***)

or a pharmaceutically acceptable salt thereof, wherein *m* is an integer from about 1 to about 15; or

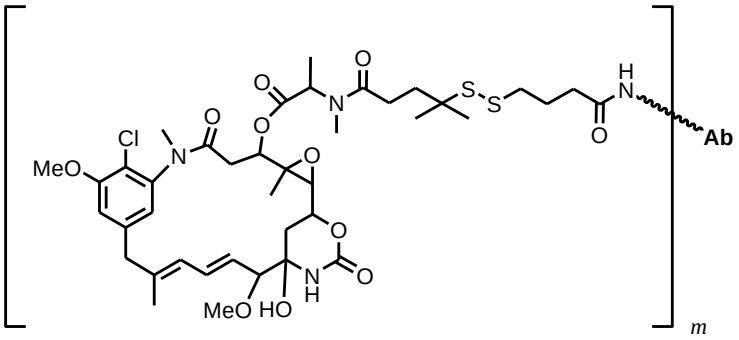
(b) the immunoconjugate has formula (***I-2***):



(***I-2***)

or a pharmaceutically acceptable salt thereof, wherein *m* is an integer from about 1 to about 15; or

(c) the immunoconjugate has formula (***I-3***):



(***I-3***)

or a pharmaceutically acceptable salt thereof, wherein *m* is an integer from about 1 to about 15.

28. The immunoconjugate of any one of claims 16 to 27, wherein *m* is an integer from about 1 to about 10, about 3 to about 7, or about 3 to about 5.

29. The immunoconjugate of any one of claims 16 to 28, wherein *m* is about 4.

30. An antibody molecule of any one of claims 1 to 15, or an immunoconjugate of any one of claims 16 to 29, for use in a method of treating a cancer in a subject.

31. Use of the antibody molecule of any one of claims 1 to 15, or an immunoconjugate of any one of claims 16 to 29, in the manufacture of a medicament for treating a cancer in a subject.

32. The antibody molecule, immunoconjugate, or use of claim 30 or claim 31, wherein the cancer is a cancer of the gastrointestinal system or a metastatic lesion thereof, a primary or metastatic colorectal cancer, a gastric cancer, an esophageal cancer, a pancreatic cancer, or a lung cancer.

33. The antibody molecule, immunoconjugate, or use of any one of claims 30 to 32, wherein the antibody or immunoconjugate is used in combination with one or more additional therapeutic agents.

34. The antibody molecule, immunoconjugate, or use of claim 33, wherein the one or more additional therapeutic agents comprise 5-fluorouracil (5-FU), capecitibine, leucovorin, irinotecan, oxaliplatin, bevacizumab cetuximab, panitumum, or any combination thereof.

35. The antibody molecule, immunoconjugate, or use of claim 34, wherein the combination is selected from oxaliplatin/capecitibine (XELOX), 5-FU/leucovorin/oxaliplatin (FOLFOX), 5-FU/leucovorin/irinotecan (FOLFIRI), FOLFOX plus bevacizumab, and FOLOFIRI plus bevacizumab.

36. The antibody molecule, immunoconjugate, or use of claim 33, wherein the one or more additional therapeutic agents comprise a chemotherapeutic agent.

37. The antibody molecule, immunoconjugate, or use of claim 36, wherein the chemotherapeutic agent is a DNA damaging agent.

38. The antibody molecule, immunoconjugate, or use of claim 37, wherein the DNA damaging agent is selected from a topoisomerase I inhibitor; a topoisomerase II inhibitor; an alkylating agent; a DNA intercalator; a free radical generator; a nucleoside mimetic; and an agent that disrupts cell replication.

39. The antibody molecule, immunoconjugate, or use of claim 38, wherein the topoisomerase I inhibitor is selected from irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin; the topoisomerase II inhibitor is selected from etoposide, teniposide, and daunorubicin; the alkylating agent is selected from melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide; the DNA intercalator is selected from cisplatin, oxaliplatin, and carboplatin; the free radical generator is bleomycin; the nucleoside mimetic is selected from 5-fluorouracil, capecitibine, gemcitabine, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea; and the agent that disrupts cell replication is selected from paclitaxel, docetaxel, related analogs of paclitaxel or docetaxel, vincristine, vinblastine, related analogs of vincristine or vinblastine, thalidomide, lenalidomide, related analogs of

thalidomide or lenalidomide, protein tyrosine kinase inhibitors, proteasome inhibitors, NF-κB and IκB kinase inhibitors, antibodies which bind to proteins overexpressed in cancers and thereby downregulate cell replication, and other inhibitors of proteins or enzymes known to be upregulated, over-expressed, or activated in cancers, the inhibition of which downregulates cell replication.

40. The antibody molecule, immunoconjugate, or use of claim 39, wherein the related analog of thalidomide or lenalidomide is CC-5013 or CC-4047; the protein tyrosine kinase inhibitor is imatinib mesylate, or gefitinib; the proteasome inhibitor is bortezomib; and the antibody which binds to proteins overexpressed in cancers and thereby downregulates cell replication is selected from trastuzumab, rituximab, cetuximab, and bevacizumab.

41. The antibody molecule, immunoconjugate, or use of any one of claims 30 to 40, wherein the cancer has been determined to express a GCC molecule.

42. A pharmaceutical composition comprising the antibody molecule of any one of claims 1 to 15, or the immunoconjugate of any one of claims 16 to 29, and a pharmaceutically acceptable carrier.

43. A container comprising the pharmaceutical composition of claim 42.

44. A kit comprising the antibody molecule of any one of claims 1 to 15, or the immunoconjugate of any one of claims 16 to 29.

45. A method of producing an immunoconjugate, comprising providing the antibody molecule of any one of claims 1 to 11; and contacting the antibody molecule with a non-antibody moiety comprising a therapeutic agent or label under conditions that allow the production of an immunoconjugate, thereby producing the immunoconjugate.

46. An expression vector comprising isolated nucleic acid sequences encoding the antibody molecule of any one of claims 1 to 11.

47. A cell comprising the expression vector of claim 46.

48. A method of producing an antibody molecule of any one of claims 1 to 11, comprising culturing the cell of claim 47 under conditions that allow the production of an antibody molecule, thereby producing the antibody molecule of any one of claims 1 to 11.

49. A method of detecting a GCC molecule, comprising contacting the GCC molecule with an antibody molecule of any one of claims 1 to 15 and determining if the antibody molecule binds to the GCC molecule.