

MONOCLONAL ANTIBODY THAT SPECIFICALLY BINDS TO GD2

Field of the invention

The present invention relates to the field of biotechnology and medicine, in particular to a monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 (ganglioside GD2). The invention further relates to nucleic acids encoding said antibody, expression vectors, host cells and methods for producing same, methods for producing the antibodies according to the invention, pharmaceutical compositions comprising the antibody according to the invention, pharmaceutical compositions comprising the antibody according to the invention and other therapeutically active compounds, methods for treating diseases or disorders mediated by GD2, uses of the antibodies or pharmaceutical compositions thereof for treating diseases or disorders mediated by GD2, and uses of the antibodies and other therapeutically active compounds for treating diseases or disorders mediated by GD2.

Background of the invention

GD2 is the first ganglioside proven to be an effective target antigen for cancer immunotherapy.

Gangliosides are composed of glycosphingolipids and sialic acids (N-acetylneuraminic acid, Neu5Ac or NANA), which are nine-carbon monosaccharides. Ganglioside nomenclature is based on the number and position of the NANA residues. Monosaccharides are first added to ceramide to form lactosylceramide, and then NANA residues are added to form gangliosides. Each sugar is bound by specific glycosyltransferases. GD2 has two NANA (α -2,8 sialic acid and α -2,3 sialic acid), and is derived from precursor GD3 by adding Gal-NAc through the enzyme GM2/GD2 synthase (β 1,4-N-acetylgalactosaminyltransferase). The end-terminal penta-oligosaccharide constitutes the specific epitope of GD2 to which the most specific antibodies are directed. This critical enzyme GM2/GD2 synthase responsible for making GD2 has been successfully exploited as a molecular marker of minimal residual neuroblastoma in the bone marrow, with major prognostic impact on patient survival. As depicted in the synthesis pathways for gangliosides, the epitope neighborhood for GD2 could be clearly defined. For example, GD3 and GD1b are the most common cross-reactive gangliosides recognized by anti-GD2 antibodies. A GD2-derivative with a 9-O-acetyl modification on the terminal sialic acid is called O-acetyl-GD2. While most anti-GD2 antibodies cross-react with O-GD2, some do not. Anti-O-GD2 antibodies with no cross-reactivity with GD2 had less cross-reactivity with normal neurons. Gangliosides are found on the cell surface of the nervous system in vertebrates. Lower vertebrates like fish and amphibian have more

polysialo-gangliosides, containing four to five NANA residues, whereas gangliosides in higher vertebrates, including reptiles, birds and mammals, have only one to three NANA residues (MAYA SUZUKI ET AL., Disialoganglioside GD2 as a therapeutic target for human diseases, Expert Opinion on Therapeutic Targets, 2015, v. 15, pages 349-362, PMID: 25604432, DOI: 10.1517/14728222.2014.986459).

GD2 is expressed on neural stem cells, mesenchymal stem cells (MSCs) and peripheral sympathoadrenergic progenitors, and it is involved in neural differentiation and proliferation. While the role of polysialic acid in neuronal development has been extensively studied, the precise functions of gangliosides, and specifically of GD2, remain unknown. After birth, GD2 expression is restricted to the CNS, predominantly in neuronal cell bodies, and MSCs, as well as peripheral nerves and skin melanocytes at low levels. GD2 is thought to play a role in the maintenance and repair of nervous tissues, which undergo continually progressive degenerative changes through the regulation of complement activation and subsequent inflammation, although the exact immunologic mechanism remains obscure. It should be noted that GD2 (+) MSCs have the potentials to differentiate into multiple clones, including neurons (MAYA SUZUKI ET AL., Disialoganglioside GD2 as a therapeutic target for human diseases, Expert Opinion on Therapeutic Targets, 2015, v. 15, pages 349-362, PMID: 25604432, DOI: 10.1517/14728222.2014.986459).

GD2 is hyperexpressed in a variety of embryonal cancers (neuroblastoma, brain tumors, retinoblastoma, Ewing's sarcoma, rhabdomyosarcoma), bone tumors (osteosarcoma, Ewing's sarcoma), soft tissue sarcomas (leiomyosarcoma, liposarcoma, fibrosarcoma), lung cancer, melanoma, and breast cancer.

Tumor monoclonal antibodies (mAbs) have demonstrated clinical efficacy, thus becoming an important method for cancer immunotherapy. Due to its limited expression in normal tissue, the disialoganglioside GD2 expressed on neuroblastoma cells is an excellent candidate for mAb therapy.

The international application WO2005070967A2 discloses an antibody to GD2.

To date, there are only 2 antibodies to GD2 in the world that are approved for therapeutic use (dinutuximab and naxitamab). In connection with the above, there is a need for creation of novel antagonistic antibodies that specifically bind to GD2.

Description of the invention

Brief description of the invention

The authors of the present group of inventions have developed antibodies that specifically bind to GD2, and also have a degree of humanization of at least 80 % in variable domains. The subject antibodies have high thermal stability.

In one aspect, the present invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 (ganglioside GD2), wherein the antibody or antigen-binding fragment thereof includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 with an amino acid sequence selected from the group: GHNMN (SEQ ID NO: 1) or GKNMN (SEQ ID NO: 2),
 - (ii) CDR2 with the amino acid sequence AIDPFYGGTSYNQKFKG (SEQ ID NO: 3),
 - (iii) CDR3 with an amino acid sequence selected from the group: GMIY (SEQ ID NO: 4), GMFY (SEQ ID NO: 5), GMYI (SEQ ID NO: 6) or GMLY (SEQ ID NO: 7); and
- (b) a light chain variable domain comprising:
 - (i) CDR1 with an amino acid sequence selected from the group: RSSRSLVHRNGNTYLH (SEQ ID NO: 8) or RSSQNLVHRNGNTYLH (SEQ ID NO: 9),
 - (ii) CDR2 with an amino acid sequence selected from the group: KVSNRFG (SEQ ID NO: 10) or KVNNRFS (SEQ ID NO: 11),
 - (iii) CDR3 with an amino acid sequence selected from the group: GQSTHVPPLT (SEQ ID NO: 12) or SQSTHVPPLS (SEQ ID NO: 13).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises:

- (i) FR1 with the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKASGSSFT (SEQ ID NO: 42),
- (ii) FR2 with the amino acid sequence WVRQNIGQGLEWMG (SEQ ID NO: 43),
- (iii) FR3 with the amino acid sequence RVTLTVDKSISTAYMELSRLRSDDTAVYYCVS (SEQ ID NO: 44) and
- (iv) FR4 with the amino acid sequence WGQGTTLVTVSS (SEQ ID NO: 45).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises:

- (i) FR1 with the amino acid sequence DIVMTQTPLSLSVTPGERASLSC (SEQ ID NO: 46),
- (ii) FR2 with an amino acid sequence selected from the group: WYLQKPGQSPKLLIH (SEQ ID NO: 47) or WYLQKPGQSPQLLIH (SEQ ID NO: 48),
- (iii) FR3 with the amino acid sequence GVPDRFSGSGSGTDFTLKISRVEAEDVGVYFC (SEQ ID NO: 49) and
- (iv) FR4 with the amino acid sequence FGQGTKLELK (SEQ ID NO: 50).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

a) a heavy chain variable domain that comprises:

(i) FR1 with the amino acid sequence QVQLVQSGAEVKKPGASVKVSCASGSSFT (SEQ ID NO: 42),

(ii) FR2 with the amino acid sequence WVRQNIGQGLEWMG (SEQ ID NO: 43),

(iii) FR3 with the amino acid sequence RVTLTVDKSISTAYMELSRLSDDTAVYYCVS (SEQ ID NO: 44) and

(iv) FR4 with the amino acid sequence WGQGTLVTVSS (SEQ ID NO: 45), and, wherein

b) a light chain variable domain that comprises:

(i) FR1 with the amino acid sequence DIVMTQTPLSLSVTPGERASLSC (SEQ ID NO: 46),

(ii) FR2 with an amino acid sequence selected from the group: WYLQKPGQSPKLLIH (SEQ ID NO: 47) or WYLQKPGQSPQLLIH (SEQ ID NO: 48),

(iii) FR3 with the amino acid sequence GVPDRFSGSGSGTDFTLKISRVEAEDVGVYFC (SEQ ID NO: 49) and

(iv) FR4 with the amino acid sequence FGQGTLKLELK (SEQ ID NO: 50).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 2,

(ii) CDR2 with the amino acid sequence of SEQ ID NO: 3,

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 5.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 2,

(ii) CDR2 with the amino acid sequence of SEQ ID NO: 3,

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 4.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 9,

(ii) CDR2 with the amino acid sequence of SEQ ID NO: 11,

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 12.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 8,

(ii) CDR2 with the amino acid sequence of SEQ ID NO: 10,

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 12.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 or SEQ ID NO: 21.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17;

(b) a light chain variable domain that comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21;

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

(b) a light chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 or SEQ ID NO: 21.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 16;

(b) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 17;

(b) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 21.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is a full-length IgG antibody.

In some embodiments of the invention, the isolated monoclonal antibody is a full-length IgG antibody that is of human IgG1, IgG2, IgG3 or IgG4 isotype.

In some embodiments of the invention, the isolated monoclonal antibody is a full-length IgG antibody that is of human IgG1 isotype.

In some embodiments of the invention, the isolated monoclonal antibody comprises YTE mutations (M252Y, S254T, T256E) and/or K322A in the Fc fragment as compared to the naturally-occurring sequence of the Fc fragment.

In some embodiments of the invention, the isolated monoclonal antibody includes a heavy chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 or SEQ ID NO: 37.

In some embodiments of the invention, the isolated monoclonal antibody includes a light chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

In some embodiments of the invention, the isolated monoclonal antibody includes:

(a) a heavy chain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 or SEQ ID NO: 37, and

(b) a light chain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

In some embodiments of the invention, the isolated monoclonal antibody includes:

(a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 32; and

(b) a light chain that comprises the amino acid sequence of SEQ ID NO: 39.

In some embodiments of the invention, the isolated monoclonal antibody includes:

(a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 33; and

(b) a light chain that comprises the amino acid sequence of SEQ ID NO: 41.

In one aspect, the present invention relates to an isolated nucleic acid that encodes any above antibody or antigen-binding fragment thereof.

In some embodiments of the invention, the isolated nucleic acid is DNA.

In one aspect, the present invention relates to an expression vector that comprises any of the above nucleic acids.

In one aspect, the present invention relates to a method for producing a host cell to produce any above antibody or antigen-binding fragment thereof, and comprises transformation of the cell with the above vector.

In one aspect, the present invention relates to a host cell for producing any above antibody or antigen-binding fragment thereof, the host cell comprising any of the above nucleic acids.

In one aspect, the present invention relates to a method for producing any above antibody or antigen-binding fragment thereof, which comprises culturing said host cell in a growth medium under conditions sufficient to produce said antibody, if necessary, followed by isolation and purification of the resulting antibody.

In one aspect, the present invention relates to a pharmaceutical composition used for treating a disease or disorder mediated by GD2, which comprises any above antibody or antigen-binding fragment thereof in a therapeutically effective amount in combination with one or more pharmaceutically acceptable excipients.

In some embodiments of the pharmaceutical composition, the disease or disorder mediated by GD2 is selected from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

In one aspect, the present invention relates to a pharmaceutical composition for treating a disease or disorder mediated by GD2, the pharmaceutical combination comprising any above antibody or antigen-binding fragment thereof and at least one other therapeutically active compound.

In some embodiments of the pharmaceutical composition, the disease or disorder mediated by GD2 is selected from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

In some embodiments of the pharmaceutical composition, the other therapeutically active compound is an antibody, chemotherapeutic agent, or hormone therapy agent.

In some embodiments of the pharmaceutical composition, the other therapeutically active compound is an immune checkpoint inhibitor.

In some embodiments of the pharmaceutical composition, the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor.

In some embodiments of the pharmaceutical composition, the PD-1 inhibitor is an antibody that specifically binds to PD-1.

In some embodiments of the pharmaceutical composition, the antibody that specifically binds to PD-1 is selected from the group: prololigimab, pembrolizumab, nivolumab.

In some embodiments of the pharmaceutical composition, the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

In some embodiments of the pharmaceutical composition, the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

In some embodiments of the pharmaceutical composition, the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

In some embodiments of the pharmaceutical composition, the antibody that specifically binds to PD-L1 is selected from the group: durvalumab, avelumab, atezolizumab, manelimab.

In some embodiments of the pharmaceutical composition, the other therapeutically active compound is selected from the group: IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

In one aspect, the present invention relates to a method for inhibiting the biological activity of GD2 in a subject in need of such inhibition, comprising administering an effective amount of any above antibody or antigen-binding fragment thereof.

In one aspect, the present invention relates to a method for treatment of a disease or disorder mediated by GD2, which comprises administering in a subject in need of such treatment any above antibody or antigen-binding fragment thereof or said pharmaceutical composition, in a therapeutically effective amount.

In one aspect, the present invention relates to a method for treating a disease or disorder mediated by GD2, comprising administering in a subject in need of such treatment any above antibody or antigen-binding fragment thereof, and selected from the group:

- a) administration of at least one other therapeutically active compound,
- b) radiotherapy,
- c) hematopoietic stem cell transplantation,
- d) surgical treatment and, if necessary, adjuvant therapy, or
- e) any combination of the above a) to d).

In some embodiments of the method of treatment, the disease or disorder mediated by GD2 is selected from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

In some embodiments of the method of treatment, other therapeutically active compound is an antibody, chemotherapeutic agent, or hormone therapy agent.

In some embodiments of the method of treatment, the other therapeutically active compound is an immune checkpoint inhibitor.

In some embodiments of the method of treatment, the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor.

In some embodiments of the method of treatment, the PD-1 inhibitor is an antibody that specifically binds to PD-1.

In some embodiments of the method of treatment, the antibody that specifically binds to PD-1 is selected from the group comprising prolglumab, pembrolizumab, nivolumab.

In some embodiments of the method of treatment, the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

In some embodiments of the method of treatment, the antibody that specifically binds to CTLA-4 is ipilimumab or nivolumab.

In some embodiments of the method of treatment, the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

In some embodiments of the method of treatment, the antibody that specifically binds to PD-L1 is selected from the group: durvalumab, avelumab, atezolizumab, nivolumab.

In some embodiments of the method of treatment, the other therapeutically active compound is selected from the group: IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

In one aspect, the present invention relates to the use of the above antibody or antigen-binding fragment thereof or the above pharmaceutical composition for treating in a subject in need of such treatment a disease or disorder mediated by GD2.

In one aspect, the present invention relates to the use of any of the above antibody or antigen-binding fragment thereof and at least one of the group:

- a) other therapeutically active compound,
- b) radiotherapy,
- c) hematopoietic stem cell transplantation or
- d) surgical treatment and, if necessary, adjuvant therapy,

for treating a disease or disorder mediated by GD2.

In some embodiments of the use, the disease or disorder mediated by GD2 is selected from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

In some embodiments of the use, the other therapeutically active compound is an immune checkpoint inhibitor.

In some embodiments of the use, the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor.

In some embodiments of the use, the PD-1 inhibitor is an antibody that specifically binds to PD-1.

In some embodiments of the use, the antibody that specifically binds to PD-1 is selected from the group: prololigimab, pembrolizumab, nivolumab.

In some embodiments of the use, the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

In some embodiments of the use, the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

In some embodiments of the use, the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

In some embodiments of the use, the antibody that specifically binds to PD-L1 is selected from the group: durvalumab, avelumab, atezolizumab, manelimab.

In some embodiments of the use, the other therapeutically active compound is selected from the group: IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

Brief description of drawings

Figure 1 is the structure of the Fab fragment in complex with the GD2 target.

Figure 2 is a map of vector bearing the heavy chain genetic sequence of anti-GD2 antibody.

Figure 3 is a map of vector bearing the light chain genetic sequence of anti-GD2 antibody.

With respect to Figures 2-3:

Name	Definition
CMV-promotor	Eukaryotic CMV promoter
TPL	5'-untranslated tripartite leader sequence of adenovirus

E_MLP	Enhancer element of the adenovirus major late promoter
Intron Acceptor	Acceptor site
Kozak sequence	GCCGCCACC
Leader IgK	Murine IgK signal leader peptide
Anti-GD2_VH	Heavy chain variable domain gene of aGD2 antibody. Anti-GD2_VH may refer to the heavy chain variable domain of aGD2 antibody according to the invention, for example, which is selected from the group of antibodies to GD2: 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041
Anti-GD2_VL	Light chain variable domain gene of aGD2 antibody. Anti-GD2_VL may refer to the light chain variable domain of aGD2 antibody according to the invention, for example, which is selected from the group of antibodies to GD2: 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041
HumIgG1 CK	CK (kappa) light chain constant domain gene
HumIgG1 HC	HC heavy chain constant domain gene. HumIgG1 HC may refer to both a variant free of modifications and variants with point mutations to the antibody Fc fragment, which are selected from the group: M252Y, S254T, T256 (YTE), K322A or YTE + K322A
PolyA signal	Polyadenylation signal
EBV origin eukaryotic (OriP)	Eukaryotic origin of Epstein-Barr virus replication
pUC origin	Prokaryotic origin of replication
AmpR	Beta-lactamase gene that confers resistance to ampicillin. It enables selection of E.coli cell culture
STOP	Stop codon
START	Start codon

Figure 4 is an electrophoregram of 10-008 candidates under reducing and non-reducing conditions, by gradient gel 4-20% SDS-PAGE.

1. Molecular weight marker;

2. 10-008 1 μ g under non-reducing conditions;
3. 10-008 1 μ g under reducing conditions.

Figure 5 is a graph showing the presence of antibody-dependent cellular cytotoxicity of antibody 10-008 in an assay using SK-N-BE(2) target cells. Points free of antibody were used as a negative control.

Figure 6 is a graph showing the complement-dependent cytotoxicity of antibodies to GD2 according to the invention in an assay using SK-N-BE(2) target cells. The graph shows the fluorescence level of vital dye (used to show the number of living cells) vs. the concentration of antibodies upon addition of human serum. EC₅₀ values were obtained in the SigmaPlot 14.0 software, based on the logistic model.

Definitions and general methods

Unless defined otherwise herein, all technical and scientific terms used in connection with the present invention will have the same meaning as is commonly understood by those skilled in the art.

Furthermore, unless otherwise required by context, singular terms shall include plural terms, and the plural terms shall include the singular terms. Typically, the present classification and methods of cell culture, molecular biology, immunology, microbiology, genetics, analytical chemistry, organic synthesis chemistry, medical and pharmaceutical chemistry, as well as hybridization and chemistry of protein and nucleic acids described herein are well known by those skilled and widely used in the art. Enzyme reactions and purification methods are performed according to the manufacturer's guidelines, as is common in the art, or as described herein.

The term "K_a" as used herein is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term "K_D" or "K_d" is intended to refer to the dissociation rate of a particular antibody-antigen interaction.

"Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g. an antibody) and its binding partner (e.g. an antigen). Unless indicated otherwise, "binding affinity" refers to intrinsic (characteristic, true) binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g. antibody and antigen). The affinity of a molecule X for its binding partner Y can generally be represented by the dissociation constant (K_d). The preferred K_d value is about 200 nM, 150 nM, 100 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 8 nM, 6 nM, 4 nM, 2 nM, 1 nM, or less. Affinity can be measured by common methods known in the art, including those described in the present description. Low-affinity antibodies generally bind an antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind an antigen faster and tend to

remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for the purposes of the present invention.

The term "koff" or "kdis" refers to the off rate constant of a particular interaction between a binding molecule and antigen. The off rate constant koff can be measured using bio-layer interferometry, for example, using Octet™ system.

The term "kon" or "on-rate" refers to the association rate constant.

The term "off-rate screening" refers to screening in which candidates are examined only based on koff values.

The term "R²" refers to the coefficient of determination.

The term "Response" refers to the antibody-antigen binding signal.

The term "in vitro" refers to a biological entity, a biological process, or a biological reaction outside the body under artificial conditions. For example, a cell grown in vitro is to be understood as a cell grown in an environment outside the body, e.g. in a test tube, a culture vial, or a microtiter plate.

The term "IC₅₀" (inhibitory concentration 50%), as used herein, refers to concentrations of a formulation, at which a measurable activity or response, for example, growth/proliferation of cells such as tumor cells, is inhibited by 50%. IC₅₀ value can be calculated using appropriate dose-response curves, using special statistical software for curve fitting.

The term "ED₅₀" (EC₅₀) (50% effective dose/concentration) refers to concentrations of a formulation producing 50% biological effect (which may include cytotoxicity).

As used in the present description and claims that follow, unless otherwise dictated by the context, the words "have", "include," and "comprise" or variations thereof such as "has", "having," "includes", "including", "comprises," or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Detailed description of the invention

Antibody

The present invention relates to a monoclonal antibody or or antigen-binding fragment thereof that specifically binds to GD2 (ganglioside GD2).

The term "monoclonal antibody" or "mAb" refers to an antibody that is synthesized and isolated by a separate clonal population of cells.

The antibody of the invention is a recombinant antibody.

The term "recombinant antibody" refers to an antibody that is expressed in a cell or cell line comprising nucleotide sequence(s) encoding antibodies, wherein said nucleotide sequence(s) is (are) not associated with the cell in nature.

In one aspect, the present invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 (ganglioside GD2), wherein the antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain comprising:

(i) CDR1 with an amino acid sequence selected from the group: GHNMN (SEQ ID NO: 1) or GKNMN (SEQ ID NO: 2),

(ii) CDR2 with the amino acid sequence AIDPFYGGTSYNQKFKG (SEQ ID NO: 3),

(iii) CDR3 with an amino acid sequence selected from the group: GMIY (SEQ ID NO: 4), GMFY (SEQ ID NO: 5), GMY Y (SEQ ID NO: 6) or GMLY (SEQ ID NO: 7); and

(b) a light chain variable domain comprising:

(i) CDR1 with an amino acid sequence selected from the group: RSSRSLVHRNGNTYLH (SEQ ID NO: 8) or RSSQNLVHRNGNTYLH (SEQ ID NO: 9),

(ii) CDR2 with an amino acid sequence selected from the group: KVS NRFG (SEQ ID NO: 10) or KVNNRFS (SEQ ID NO: 11),

(iii) CDR3 with an amino acid sequence selected from the group: GQSTHVPPLT (SEQ ID NO: 12) or SQSTHVPPLS (SEQ ID NO: 13).

The term "isolated" used to describe various antibodies in this description refers to an antibody which has been identified and separated and/or regenerated from a cell or cell culture, in which the antibody is expressed. Impurities (contaminant components) from natural environment are materials which typically interfere with diagnostic or therapeutic uses of the polypeptide, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. The isolated polypeptide is typically prepared by at least one purification step.

Amplification of the GD2 gene and/or overexpression of protein thereof have been observed in many cancers, for example, in any of the diseases from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

The term "antibody" or "immunoglobulin" (Ig), as used in the present description, includes whole antibodies. The term "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding portion. Each heavy chain comprises a heavy chain variable region (abbreviated referred to in the present

description as VH) and a heavy chain constant region. Known are five types of mammalian antibody heavy chains denoted by Greek letters: α , δ , ϵ , γ and μ . (Janeway C.A., Jr. et al, Immunobiology, 5th ed., publ. by Garland Publishing, 2001). The type of a heavy chain present defines the class of an antibody; these chains are found in IgA, IgD, IgE, IgG, and IgM antibodies, respectively. (Rhoades R.A., Pflanzner R.G., Human Physiology, 4th ed., publ. by Thomson Learning, 2002). Distinct heavy chains differ in size and composition; α and γ contain approximately 450 amino acids, while μ and ϵ have approximately 550 amino acids. The constant region is identical in all antibodies of the same isotype, but differs in antibodies of different isotypes. Heavy chains γ , α and δ have a constant region composed of three constant domains CH1, CH2 and CH3 (in a line), and a hinge region for added flexibility (Woof J., Burton D., Nat Rev Immunol 4, 2004, cc.89-99); heavy chains μ and ϵ have a constant region composed of four constant domains CH1, CH2, CH3 and CH4 (Janeway C.A., Jr. et al, Immunobiology, 5th ed., publ. by Garland Publishing, 2001). In mammals, known are only two types of light chains denoted by lambda (λ) and kappa (κ). Each light chain consists of a light chain variable region (abbreviated referred to in the present description as VL) and light chain constant region. The approximate length of a light chain is 211 to 217 amino acids. Preferably the light chain is a kappa (κ) light chain, and the constant domain CL is preferably C kappa (κ).

"Antibodies" according to the invention can be of any class (e.g., IgA, IgD, IgE, IgG, and IgM, preferably IgG), or subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2, preferably IgG1).

VL and VH regions can be further subdivided into hyper-variability regions called complementarity determining regions (CDRs), interspersed between regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of antibodies may mediate the binding of immunoglobulin to host tissues or factors, including various cells of the immune system (e.g. effector cells) and the first component (C1q) of the classical complement system.

The term "antigen-binding portion" of an antibody or "antigen-binding fragment" (or simply "antibody portion" or "antibody fragment"), as used in this description, refers to one or more fragments of an antibody that retain the capability of specific binding to an antigen. It has been shown that the antigen-binding function of antibody can be performed by fragments of a full-length antibody. Examples of binding fragments which are included within the term "antigen-binding portion" of an antibody include (i) Fab-fragment, monovalent fragment, consisting of VL, VH, CL and CH1 domains; (ii) F(ab')₂ fragment, a bivalent fragment comprising two Fab-fragments linked by a disulfide bridge at the hinge region; (iii) Fd-fragment consisting of VH and

CH1 domains; (iv) Fv-fragment consisting of VL and VH domains of a single arm of an antibody; (v) dAb-fragment (Ward et al., (1989) *Nature* 341:544-546), which consists of a VH/VHH domain. In addition, two regions of the Fv-fragment, VL and VH, are encoded by different genes, they can be joined using recombinant methods using a synthetic linker that enables to receive them as a single protein chain in which the VL and VH regions are paired to form monovalent molecules (known as a single-chain Fv (scFv); see e.g. Bird et al. (1988) *Science* 242:423-426; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). It is assumed that such single-stranded molecules are also included within the term "antigen-binding portion" of antibody. Such antibody fragments are produced using conventional techniques known to those skilled in the art, and these fragments are screened in the same manner as intact antibodies are.

The term "variable domain" refers to the fact that certain portions of the variable domains greatly differ in sequence among antibodies. The V domain mediates antigen binding and determines specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of invariant fragments termed framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability termed "hypervariable regions" or CDRs. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a beta-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The hypervariable regions in each chain are held together in close proximity by FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., *Sequences of Proteins of Immunological Interest*. 5 th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding of antibody to antigen, but exhibit various effector functions, such as participation of antibody in antibody-dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" according to the present description refers to the amino acid residues of antibody which are responsible for antigen binding. The hypervariable region typically comprises amino acid residues from a "complementarity determining region" or "CDR" and/or those residues from a "hypervariable loop".

"Kabat numbering scheme" or "numbering according to Kabat" as used in this application refers to the system for numbering of amino acid residues that are more variable (i.e. hypervariable) than other amino acid residues in variable regions of heavy and light chains of the antibody (Kabat et al. *Ann. N.Y. Acad. Sci.*, 190:382-93 (1971); Kabat et al. *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242 (1991)).

The antibody of the present invention "which binds" a target antigen refers to an antibody that binds the antigen with sufficient affinity such that the antibody can be used as a diagnostic and/or therapeutic agent targeting a protein or cell or tissue expressing the antigen, and slightly cross-reacts with other proteins. According to analytical methods: fluorescence-activated cell sorting (FACS), radioimmunoassay (RIA) or ELISA, in such embodiments, the degree of antibody binding to a non-target protein is less than 10 % of antibody binding to a specific target protein. With regard to the binding of antibody to a target molecule, the term "specific binding" or "specifically binds to" or "is specific for" a particular polypeptide or an epitope on a particular target polypeptide means binding that is significantly (measurably) different from a non-specific interaction.

Specific binding may be measured, for example, by determining binding of a molecule as compared to binding of a control molecule. For example, specific binding may be determined by competition with another molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by the excess of unlabeled target. As used in the present description, the term "specific binding" or phrases "specifically binds to" or "is specific for" a particular polypeptide or an epitope on a particular target polypeptide may be described by example of a molecule having a K_d for the target of at least about 200 nM, or at least about 150 nM, or at least about 100 nM, or at least about 60 nM, or at least about 50 nM, or at least about 40 nM, or at least about 30 nM, or at least about 20 nM, or at least about 10 nM, or at least about 8 nM, or at least about 6 nM, or at least about 4 nM, or at least about 2 nM, or at least about 1 nM, or greater. In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or epitope on a polypeptide.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises:

- (i) FR1 with the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKASGSSFT (SEQ ID NO: 42),
- (ii) FR2 with the amino acid sequence WVRQNIGQGLEWMG (SEQ ID NO: 43),
- (iii) FR3 with the amino acid sequence RVTLTVDKSISTAYMELSRRLSDDTAVYYCVS (SEQ ID NO: 44) and
- (iv) FR4 with the amino acid sequence WGQGTLTVSS (SEQ ID NO: 45).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises:

(i) FR1 with the amino acid sequence DIVMTQTPLSLSVTPGERASLSC (SEQ ID NO: 46),

(ii) FR2 with an amino acid sequence selected from the group: WYLQKPGQSPKLLIH (SEQ ID NO: 47) or WYLQKPGQSPQLLIH (SEQ ID NO: 48),

(iii) FR3 with the amino acid sequence GVPDRFSGSGSGTDFTLKISRVEAEDVGVYFC (SEQ ID NO: 49) and

(iv) FR4 with the amino acid sequence FGQGTKLELK (SEQ ID NO: 50).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

a) a heavy chain variable domain that comprises:

(i) FR1 with the amino acid sequence QVQLVQSGAEVKKPGASVKVSCKASGSSFT (SEQ ID NO: 42),

(ii) FR2 with the amino acid sequence WVRQNIGQGLEWMG (SEQ ID NO: 43),

(iii) FR3 with the amino acid sequence RVTLTVDKSISTAYMELSRLSDDTAVYYCVS (SEQ ID NO: 44) and

(iv) FR4 with the amino acid sequence WGQGLTVTVSS (SEQ ID NO: 45), and, wherein

b) a light chain variable domain that comprises:

(i) FR1 with the amino acid sequence DIVMTQTPLSLSVTPGERASLSC (SEQ ID NO: 46),

(ii) FR2 with an amino acid sequence selected from the group: WYLQKPGQSPKLLIH (SEQ ID NO: 47) or WYLQKPGQSPQLLIH (SEQ ID NO: 48),

(iii) FR3 with the amino acid sequence GVPDRFSGSGSGTDFTLKISRVEAEDVGVYFC (SEQ ID NO: 49) and

(iv) FR4 with the amino acid sequence FGQGTKLELK (SEQ ID NO: 50).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 2,

(ii) CDR2 with the amino acid sequence of SEQ ID NO: 3,

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 5.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 2,

(ii) CDR2 with the amino acid sequence of SEQ ID NO: 3,

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 4.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises:

- (i) CDR1 with the amino acid sequence of SEQ ID NO: 9,
- (ii) CDR2 with the amino acid sequence of SEQ ID NO: 11,
- (iii) CDR3 with the amino acid sequence of SEQ ID NO: 12.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises:

- (i) CDR1 with the amino acid sequence of SEQ ID NO: 8,
- (ii) CDR2 with the amino acid sequence of SEQ ID NO: 10,
- (iii) CDR3 with the amino acid sequence of SEQ ID NO: 12.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises an amino acid sequence that is selected from the group:

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMYWYGQGLTV
TVSS (SEQ ID NO: 14),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGHNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMLYWYGQGLVT
VSS (SEQ ID NO: 15),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMIYWYGQGLVT
VSS (SEQ ID NO: 16)

or

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMFYWYGQGLVT
VSS (SEQ ID NO: 17).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises an amino acid sequence that is selected from the group:

DIVMTQTPLSLSVTPGERASLSCRSSRSLVHRNGNTYLHWYLQKPGQSPKLLIHK
VSNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCGQSTHVPPLTFGQGGTKLELK
(SEQ ID NO: 18),

DIVMTQTPLSLSVTPGERASLSCRSSRSLVHRNGNTYLHWYLQKPGQSPQLLIHK
VSNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCGQSTHVPPLTFGQGGTKLELK
(SEQ ID NO: 19),

DIVMTQTPLSLSVTPGERASLSCRSSRSLVHRNGNTYLHWYLQKPGQSPKLLIHK
VNNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCSQSTHVPPLSFGQGGTKLELK
(SEQ ID NO: 20)

or

DIVMTQTPLSLSVTPGERASLSCRSSQNLVHRNGNTYLHWYLQKPGQSPKLLIHK
VNNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCGQSTHVPPLTFGQGGTKLELK
(SEQ ID NO: 21).

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17;

(b) a light chain variable domain that comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21;

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

(b) a light chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 or SEQ ID NO: 21.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 16;

(b) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19.

In some embodiments of the invention, the isolated monoclonal antibody or antigen-binding fragment thereof includes:

(a) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 17;

(b) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 21.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is a full-length IgG antibody.

In some embodiments of the invention, the isolated monoclonal antibody is a full-length IgG antibody that is of human IgG1, IgG2, IgG3 or IgG4 isotype.

In some embodiments of the invention, the isolated monoclonal antibody is a full-length IgG antibody that is of human IgG1 isotype.

In some embodiments of the invention, the isolated monoclonal antibody comprises YTE mutations (M252Y, S254T, T256E) and/or K322A in the Fc fragment as compared to the naturally-occurring sequence of the Fc fragment.

The above mutations in the Fc fragment are numbered according to EU numbering for amino acid chains of antibodies (Edelman, G.M., et al., Proc. Natl. Acad. Sci. USA 63 (1969), pp. 78-85; Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD, (1991).

In some embodiments of the invention, the isolated monoclonal antibody includes a heavy chain comprising an amino acid sequence that is selected from the group:

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMYWVGQGLTV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYIT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 22),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGHNMNWRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMLYWVGQGLTV
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 23),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMIYWVGQGLTV

VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 24),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMFYWGQGTLLV
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 25),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMYWYGQGTLLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 26),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGHNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMLYWYGQGTLLV
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 27),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMIYWYGQGTLLV
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE

EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 28),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNVWRQNIQGLEWMGAIDPFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMFIYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSDDLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 29),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNVWRQNIQGLEWMGAIDPFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMFIYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSDDLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLTPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 30),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGHNMNVWRQNIQGLEWMGAIDPFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMFIYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSDDLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLTPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 31),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNVWRQNIQGLEWMGAIDPFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRRLSDDTAVYYCVSGMFIYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSDDLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLTPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 32),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRLSDDTAVYYCVSGMFYWGQGLTV
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTL
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 33),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRLSDDTAVYYCVSGMYWYGQGLTV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 34),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGHNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRLSDDTAVYYCVSGMLYWGQGLTV
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTL
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 35),

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRLSDDTAVYYCVSGMIYWGQGLTV
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTL
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 36)

or

QVQLVQSGAEVKKPGASVKVSCKASGSSFTGKNMNWVRQNIQGLEWMGAID
PFYGGTSYNQKFKGRVTLTVDKSISTAYMELSRLSDDTAVYYCVSGMFYWGQGLTV

VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLTP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 37).

In some embodiments of the invention, the isolated monoclonal antibody includes a light chain comprising an amino acid sequence that is selected from the group:

DIVMTQTPLSLSVTPGERASLSCRSSRSLVHRNGNTYLHWYLQKPGQSPKLLIHK
VSNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCGQSTHVPPLTFGQGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 38),

DIVMTQTPLSLSVTPGERASLSCRSSRSLVHRNGNTYLHWYLQKPGQSPQLLIHK
VSNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCGQSTHVPPLTFGQGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 39),

DIVMTQTPLSLSVTPGERASLSCRSSRSLVHRNGNTYLHWYLQKPGQSPKLLIHK
VNNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCGQSTHVPPLTFGQGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 40)

or

DIVMTQTPLSLSVTPGERASLSCRSSQNLVHRNGNTYLHWYLQKPGQSPKLLIHK
VNNRFGGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCGQSTHVPPLTFGQGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 41).

In some embodiments of the invention, the isolated monoclonal antibody includes:

(a) a heavy chain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 or SEQ ID NO: 37, and

(b) a light chain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

In some embodiments of the invention, the isolated monoclonal antibody includes:

(a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 32; and

(b) a light chain that comprises the amino acid sequence of SEQ ID NO: 39.

In some embodiments of the invention, the isolated monoclonal antibody includes:

- (a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 33; and
- (b) a light chain that comprises the amino acid sequence of SEQ ID NO: 41.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is antibody 07-006.

The antibody 07-006 includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 22; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-006 includes:

- (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 14;
- (b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 18.

The antibody 07-006 includes:

(a) a heavy chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 2,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 3,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 6, and

(b) a light chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 8,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 10,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 12.

The antibody 07-006 includes:

(a) a heavy chain variable domain comprising:

- (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 51,
- (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 53,
- (iii) CDR3 (Chothia) with the amino acid sequence of SEQ ID NO: 56, and

(b) a light chain variable domain comprising:

- (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 58,
- (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 60,
- (iii) CDR3 (Chothia) with the amino acid sequence SEQ ID NO: 62.

The antibody 07-006 includes:

(a) a heavy chain variable domain comprising:

- (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 64,
- (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 66,
- (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 69, and

(b) a light chain variable domain comprising:

- (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 71,
- (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 73,
- (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 75.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is antibody 07-015.

The antibody 07-015 includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 23; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-015 includes:

- (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 15;

- (b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 19.

The antibody 07-015 includes:

(a) a heavy chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 3,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 7, and

(b) a light chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 8,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 10,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 12.

The antibody 07-015 includes:

(a) a heavy chain variable domain comprising:

- (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 52,
- (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 53,
- (iii) CDR3 (Chothia) with the amino acid sequence of SEQ ID NO: 57, and

(b) a light chain variable domain comprising:

- (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 58,
- (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 60,
- (iii) CDR3 (Chothia) with the amino acid sequence SEQ ID NO: 62.

The antibody 07-015 includes:

(a) a heavy chain variable domain comprising:

- (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 65,
- (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 66,

(iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 70, and

(b) a light chain variable domain comprising:

(i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 71,

(ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 73,

(iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 75.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is antibody 07-016.

The antibody 07-016 includes:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 23; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-016 includes:

(a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 15;

(b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 18.

The antibody 07-016 includes:

(a) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 3,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 7, and

(b) a light chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 8,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 10,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 12.

The antibody 07-016 includes:

(a) a heavy chain variable domain comprising:

(i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 52,

(ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 53,

(iii) CDR3 (Chothia) with the amino acid sequence of SEQ ID NO: 57, and

(b) a light chain variable domain comprising:

(i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 58,

(ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 60,

(iii) CDR3 (Chothia) with the amino acid sequence SEQ ID NO: 62.

The antibody 07-016 includes:

(a) a heavy chain variable domain comprising:

(i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 65,

- (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 66,
- (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 70, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 71,
 - (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 73,
 - (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 75.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is antibody 07-028.

The antibody 07-028 includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 23; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 40.

The antibody 07-028 includes:

- (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 15;
- (b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 20.

The antibody 07-028 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 3,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 7, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 8,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 11,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 13.

The antibody 07-028 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 52,
 - (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 53,
 - (iii) CDR3 (Chothia) with the amino acid sequence of SEQ ID NO: 57, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 58,
 - (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 61,
 - (iii) CDR3 (Chothia) with the amino acid sequence SEQ ID NO: 63.

The antibody 07-028 includes:

- (a) a heavy chain variable domain comprising:

- (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 65,
- (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 66,
- (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 70, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 71,
 - (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 74,
 - (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 76.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is antibody 07-031.

The antibody 07-031 includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 24; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-031 includes:

- (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 16;
- (b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 19.

The antibody 07-031 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 2,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 3,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 4, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 8,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 10,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 12.

The antibody 07-031 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 51,
 - (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 53,
 - (iii) CDR3 (Chothia) with the amino acid sequence of SEQ ID NO: 54, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 58,
 - (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 60,
 - (iii) CDR3 (Chothia) with the amino acid sequence SEQ ID NO: 62.

The antibody 07-031 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 64,
 - (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 66,
 - (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 67, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 71,
 - (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 73,
 - (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 75.

In some embodiments of the invention, the isolated monoclonal antibody that specifically binds to GD2 is antibody 07-041.

The antibody 07-041 includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 25; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 41.

The antibody 07-041 includes:

- (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 17;
- (b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 21.

The antibody 07-041 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 2,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 3,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 5, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 9,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 11,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 12.

The antibody 07-041 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 51,
 - (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 53,
 - (iii) CDR3 (Chothia) with the amino acid sequence of SEQ ID NO: 55, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (Chothia) with the amino acid sequence of SEQ ID NO: 59,
 - (ii) CDR2 (Chothia) with the amino acid sequence of SEQ ID NO: 61,
 - (iii) CDR3 (Chothia) with the amino acid sequence SEQ ID NO: 62.

The antibody 07-041 includes:

- (a) a heavy chain variable domain comprising:
 - (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 64,
 - (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 66,
 - (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 68, and
- (b) a light chain variable domain comprising:
 - (i) CDR1 (IMGT) with the amino acid sequence of SEQ ID NO: 72,
 - (ii) CDR2 (IMGT) with the amino acid sequence of SEQ ID NO: 74,
 - (iii) CDR3 (IMGT) with the amino acid sequence of SEQ ID NO: 75.

Modification(s) of amino acid sequences of antibodies is (are) provided. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of antibody are prepared by introducing appropriate nucleotide changes into the nucleic acid encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions, and/or insertions and/or substitutions of residues within the amino acid sequences of antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes in the antibody, such as changing the number or position of glycosylation sites.

Variant of modification of amino acid sequences of antibodies using amino acid substitutions. Such a variant is substitution of at least one amino acid residue in the antibody molecule with a different residue. The sites of greatest interest for substitutional mutagenesis include hypervariable regions or CDRs, but FR or Fc alterations are also contemplated. Conservative substitutions are shown in Table A under the heading "preferred substitutions". If such substitutions cause alteration of the biological activity, further substantial changes can be made, which are denoted as "exemplary substitutions" set forth in Table A, or alterations described in more detail below when describing amino acid classes, and also product screening may be performed.

Table A		
Initial residue	Exemplary substitutions	Preferred substitutions
Ala (A)	Val; Leu; Ile	Val
Arg(R)	Lys; Gin; Asn	Lys

Asn(N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln(Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly(G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe(F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser(S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp(W)	Tyr; Phe	Tyr
Tyr(Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

In some embodiments of the invention, the antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041 include an Fc fragment that comprises YTE mutations (M252Y, S254T, T256E) and/or K322A as compared to the naturally-occurring sequence of the Fc fragment.

In some embodiments of the invention, the antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041 include an Fc fragment that comprises YTE mutations (M252Y, S254T, T256E) and K322A as compared to the naturally-occurring sequence of the Fc fragment.

In some embodiments of the invention, the antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041 include an Fc fragment that comprises YTE mutations (M252Y, S254T, T256E) as compared to the naturally-occurring sequence of the Fc fragment.

In some embodiments of the invention, the antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041 include an Fc fragment that comprises the K322A mutation as compared to the naturally-occurring sequence of the Fc fragment.

The antibody 07-006 with YTE and K322A mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 30; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-015 with YTE and K322A mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 31; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-016 with YTE and K322A mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 31; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-028 with YTE and K322A mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 31; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 40.

The antibody 07-031 with YTE and K322A mutations (or the antibody 10-02) includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 32; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-041 with YTE and K322A mutations (or the antibody 10-08) includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 33; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 41.

The antibody 07-006 with YTE mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 26; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-015 with YTE mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 27; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-016 with YTE mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 27; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-028 with YTE mutations includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 27; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 40.

The antibody 07-031 with YTE mutations (or the antibody 10-01) includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 28; and
- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-041 with YTE mutations (or the antibody 10-07) includes:

- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 29; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 41.

The antibody 07-006 with the K322A mutation includes:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 34; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-015 with the K322A mutation includes:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 35; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-016 with the K322A mutation includes:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 35; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 38.

The antibody 07-028 with the K322A mutation includes:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 35; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 40.

The antibody 07-031 with the K322A mutation (or the antibody 10-03) includes:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 36; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 39.

The antibody 07-041 with the K322A mutation (or the antibody 10-09) includes:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 37; and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 41.

In some embodiments of the invention, the antibodies according to the invention may be afucosylated antibodies.

In some embodiments of the invention, the antibodies according to the invention may be fucosylated antibodies.

The presence or absence of antibody fucosylation will depend on the cell culture that is used to produce antibodies according to the invention.

Antibody fragments

In certain circumstances, it is advisable to use antibody fragments rather than whole antibodies. The small sizes of the fragments contributes to rapid clearance thereof and may contribute to better penetration into dense tumors.

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see e.g. Morimoto et al, Journal of Biochemical and Biophysical Methods, 24, 1992, pp. 107-117 and Brennan et al, Science, 229, 1985, p. 81). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can be expressed in and secreted

from *E. coli*, thus allowing to facilitate the production of large amounts of these fragments. Antibody fragments may be isolated from the antibody phage libraries. According to another embodiment, Fab'-SH fragments can be directly isolated from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter et al., *Bio/Technology* 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture Fab and F(ab')₂ fragment with increased in vivo half-life retaining epitope binding receptor residues are described in US 5869046. Other techniques for the production of antibody fragments will be apparent to those skilled in the art. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv) (see WO 93/16185; US 5571894 and US 5587458). Fv and scFv are the only species with intact binding sites that are devoid of constant regions; as a result, they are suitable for reduced nonspecific binding during in vivo use. scFv fusion proteins may be constructed to yield fusion of an effector protein at either N- or C-terminus of an scFv (see *Antibody Engineering*, ed. Borrebaeck, above). The antibody fragment may also be a "linear antibody", e.g. as described in U.S. 5641870.

Nucleic acid molecule

In one aspect, the present invention relates to an isolated nucleic acid that encodes any above antibody or antigen-binding fragment thereof that specifically binds to GD2.

In any of the above embodiments, the nucleic acid molecules may be isolated.

The terms "nucleic acid", "nucleic sequence", "nucleic acid sequence", "polynucleotide", "oligonucleotide", "polynucleotide sequence" and "nucleotide sequence", used interchangeably in the present description, mean a precise sequence of nucleotides, modified or not, determining a fragment or a region of a nucleic acid, containing unnatural nucleotides or not, and being either a double-strand DNA or RNA, a single-strand DNA or RNA, or transcription products of said DNAs.

It should also be included here that the present invention does not relate to nucleotide sequences in their natural chromosomal environment, i.e. in a natural state. The sequences of the present invention have been isolated and/or purified, i.e., they were sampled directly or indirectly, for example by copying, their environment having been at least partially modified. Thus, isolated nucleic acids obtained by recombinant genetics, by means, for example, of host cells, or obtained by chemical synthesis should also be mentioned here.

A reference to a nucleotide sequence encompasses the complement thereof unless otherwise specified. Thus, a reference to a nucleic acid having a particular sequence should be understood as one which encompasses the complementary strand thereof with the complementary sequence thereof.

An "isolated" nucleic acid molecule is one which is identified and separated from at least one nucleic acid molecule-impurity, which the former is bound to in the natural source of antibody nucleic acid. An isolated nucleic acid molecule is different from the form or set in which it is found under natural conditions. Thus, an isolated nucleic acid molecule is different from a nucleic acid molecule that exists in cells under natural conditions.

In one aspect, the present invention relates to a nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from SEQ ID NOs: 1-76. A nucleic acid molecule can also comprise any combination of said nucleotide sequences.

In some embodiments of the invention, the isolated nucleic acid is DNA.

The nucleic acid molecule of the invention may be isolated from any source that produces the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2. In certain embodiments, the nucleic acid molecule of the invention may be synthesized, rather than isolated.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-006, and includes a nucleotide sequence with SEQ ID NO: 77.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-006, and includes a nucleotide sequence with SEQ ID NO: 78.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-015, and includes a nucleotide sequence with SEQ ID NO: 79.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-015, and includes a nucleotide sequence with SEQ ID NO: 80.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-016, and includes a nucleotide sequence with SEQ ID NO: 81.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-016, and includes a nucleotide sequence with SEQ ID NO: 82.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-028, and includes a nucleotide sequence with SEQ ID NO: 83.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-028, and includes a nucleotide sequence with SEQ ID NO: 84.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-031, and includes a nucleotide sequence with SEQ ID NO: 85.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-031, and includes a nucleotide sequence with SEQ ID NO: 86.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-041, and includes a nucleotide sequence with SEQ ID NO: 87.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-041, and includes a nucleotide sequence with SEQ ID NO: 88.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of the antibody 10-001, and includes a nucleotide sequence with SEQ ID NO: 89.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of the antibody 10-001, and includes a nucleotide sequence with SEQ ID NO: 90.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of the antibody 10-002, and includes a nucleotide sequence with SEQ ID NO: 91.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of the antibody 10-002, and includes a nucleotide sequence with SEQ ID NO: 92.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of the antibody 10-003, and includes a nucleotide sequence with SEQ ID NO: 93.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of the antibody 10-003, and includes a nucleotide sequence with SEQ ID NO: 94.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of the antibody 10-007, and includes a nucleotide sequence with SEQ ID NO: 95.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of the antibody 10-007, and includes a nucleotide sequence with SEQ ID NO: 96.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of the antibody 10-008, and includes a nucleotide sequence with SEQ ID NO: 97.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of the antibody 10-008, and includes a nucleotide sequence with SEQ ID NO: 98.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of the antibody 10-009, and includes a nucleotide sequence with SEQ ID NO: 99.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of the antibody 10-009, and includes a nucleotide sequence with SEQ ID NO: 100.

The nucleic acid molecules may be used to express the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2.

Vector

In one aspect, the present invention relates to an expression vector comprising the above isolated nucleic acid. The present invention relates to a vector suitable for the expression of any of nucleotide sequences described herein.

The term "vector" as used herein means a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. In some embodiments of the invention, the vector is a plasmid, i.e., a circular double stranded piece of DNA into which additional DNA segments may be ligated. In some embodiments of the invention, the vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. In some embodiments of the invention, vectors are capable of autonomous replication in a host cell into which they are introduced (e.g. bacterial vectors having a bacterial origin site of replication and episomal mammalian vectors). In further embodiments of the invention, vectors (e.g. non-episomal mammalian vectors) may be integrated into the genome of a host cell upon introduction into a host cell, and thereby are replicated along with the host gene. Moreover, certain vectors are capable of

directing the expression of genes to which they are operably linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors").

The present invention relates to vectors comprising nucleic acid molecules that encode any of the amino acid sequences of a monoclonal antibody that specifically binds to GD2 or portions thereof (e.g. heavy chain and/or light chain binding domain sequences), as described herein. The invention further relates to vectors comprising nucleic acid molecules encoding the antibodies or fragments thereof.

Expression vectors include plasmids, retroviruses, adenoviruses, adeno-associated viruses (AAVs), plant viruses, such as cauliflower mosaic virus, tobacco mosaic virus, cosmids, YACs, EBV derived episomes, and the like. DNA molecules may be ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the DNA. An expression vector and expression control sequences may be chosen to be compatible with the expression host cell used. DNA molecules partially or fully encoding the sequences of first and second binding domains (for example, heavy and light chain sequences where a binding domain comprises a heavy and light chain sequence) can be introduced into individual vectors. In one embodiment, any combination of said DNA molecules is introduced into the same expression vector. DNA molecules may be introduced into an expression vector by standard methods (e.g. ligation of complementary restriction sites on an antibody gene fragment and vector, or blunt end ligation if no restriction sites are present).

In some embodiments of the invention, a suitable vector is one that includes restriction sites such that any VH or VL sequence can easily be inserted and expressed, as described above. Polyadenylation and transcription termination may occur at a native chromosomal site downstream of coding regions. A recombinant expression vector can also encode a signal peptide that facilitates secretion of an antibody chain from a host cell. An antibody chain gene may be cloned into a vector such that the signal peptide is linked in-frame to the amino terminus of an immunoglobulin chain. The signal peptide may be an immunoglobulin signal peptide or a heterologous signal peptide (i.e. a signal peptide from a non-immunoglobulin protein).

In some embodiments of the invention, in addition to antibody chain genes, the recombinant vector expression of the invention can carry regulatory sequences that control the expression of antibody chain genes in a host cell. It will be understood by those skilled in the art that the design of an expression vector, including the selection of regulatory sequences, may depend on such factors as the choice of a host cell to be transformed, the level of expression of a desired protein, and so forth. Preferred control sequences for an expression host cell in mammals include viral elements that ensure high levels of protein expression in mammalian cells, such as

promoters and/or enhancers derived from a retroviral LTR, cytomegalovirus (CMV) (such as a CMV promoter/enhancer), simian virus 40 (SV40) (such as a SV40 promoter/enhancer), adenovirus, (e.g. the major late promoter adenovirus (AdMLP)), polyomavirus and strong mammalian promoters such as native immunoglobulin promoter or actin promoter. Methods for expressing polypeptides in bacterial cells or fungal cells, e.g. yeast cells, are also well known in the art.

In some embodiments of the invention, in addition to antibody chain genes and regulatory sequences, the recombinant expression vectors of the invention may carry additional sequences, such as sequences that regulate replication of a vector in host cells (e.g. origins of replication) and selectable marker genes. The selectable marker gene facilitates the selection of host cells into which a vector has been introduced.

In some embodiments of the invention, the vector may include an expression control sequence. The term "expression control sequence" as used in the present description refers to polynucleotide sequences that are necessary to effect the expression and processing of coding sequences to which they are ligated. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (i.e., Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include the promoter of ribosome binding site, and transcription termination sequences; in eukaryotes, typically, such control sequences include promoters and transcription termination sequences. The term "control sequences" includes at least all components, the presence of which is essential for expression and processing, and can also include additional components, the presence of which is advantageous, for example, leader sequences and fusion partner sequences.

Host cell

In one aspect, the present invention relates to a method for producing a host cell to produce any above antibody or antigen-binding fragment thereof that specifically binds to GD2, and comprises transformation of the cell with the above vector.

In one aspect, the present invention relates to a host cell for producing any above antibody or antigen-binding fragment thereof that specifically binds to GD2, the host cell comprising any of the above nucleic acids.

The term "recombinant host cell" (or simply "host cell") as used herein refers to a cell into which a recombinant expression vector has been introduced. The present invention relates to host cells, which may include, for example, a vector according to the invention described above. The present invention also relates to host cells that comprise, for example, a nucleotide sequence encoding a heavy chain or antigen-binding portions thereof, a light chain-encoding nucleotide sequence or antigen-binding portions thereof, or both, of the binding domain of the binding molecule of the invention. It should be understood that "recombinant host cell" and "host cell" refer not only to a particular subject cell but to the progeny of such a cell as well. Since modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to a parental cell; however, such cells are still included within the scope of the term "host cell" as used herein.

Nucleic acid molecules encoding the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention and vectors comprising these nucleic acid molecules may be used for transfection of a suitable mammalian or cell thereof, plant or cell thereof, bacterial or yeast host cell. Transformation may be carried out by any known technique of introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, cationic polymer-nucleic acid complex transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors.

Mammalian cell lines used as hosts for transformation are well known in the art and include a plurality of immortalized cell lines available. These include, e.g., Chinese hamster ovary (CHO) cells, NS0 cells, SP2 cells, HEK-293T cells, FreeStyle 293 cells (Invitrogen), NIH-3T3 cells, HeLa cells, baby hamster kidney (BHK) cells, African green monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), A549 cells, and a number of other cell lines. Cell lines are selected by determining which cell lines have high expression levels and provide for necessary characteristics of the protein produced. Other cell lines that may be used are insect cell lines, such as Sf9 or Sf21 cells. When recombinant expression vectors encoding the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 are introduced into mammalian host cells, the antibodies or fragments thereof are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibodies or fragments thereof in host cells or, more preferably, secretion of the antibodies or fragments thereof into the culture medium in which the host cells are grown. The monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 may be isolated from culture medium using standard protein

purification techniques. Plant host cells include e.g. *Nicotiana*, *Arabidopsis*, duckweed, corn, wheat, potato, etc. Bacterial host cells include *Escherichia* and *Streptomyces* species. Yeast host cells include *Schizosaccharomyces pombe*, *Saccharomyces cerevisiae* and *Pichia pastoris*.

Furthermore, level of production of the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 from a production cell line may be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common approach for enhancing expression under certain conditions.

It is likely that the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 from various cell lines will have a different glycosylation profile as compared to each other. However, the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 encoded by nucleic acid molecules described herein, or comprising amino acid sequences provided herein are part of the present invention, regardless of the glycosylation of the binding molecules, and, in general, regardless of the presence or absence of post-translational modifications.

The above host cell does not refer to a host cell produced using human embryos.

The above host cell does not refer to a host cell produced by modifying the genetic integrity of human germline cells.

Method of obtaining the antibody

In one aspect, the present invention relates to a method for obtaining an antibody or antigen-binding fragment thereof that specifically binds to GD2, comprising culturing the above host cell in a growth medium under conditions sufficient to produce said antibody or fragment thereof, if necessary, followed by isolation and purification of the resulting antibody or fragment thereof.

The present invention relates to methods for obtaining the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 according to this invention. One embodiment of the invention relates to a method for producing monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2, as defined herein, which comprises the production of a recombinant host cell capable of expressing the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2, culturing of said host cell under conditions suitable for expression/production of the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2, and isolation of the resulting monoclonal antibody or fragment thereof that specifically binds to GD2. The monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2, produced by such expression in such recombinant host cells, is referred to herein as "recombinant monoclonal antibody that specifically binds to GD2" or "an

antigen-binding fragment of the recombinant monoclonal antibody that specifically binds to GD2". The invention also relates to the progeny from such host cells.

Pharmaceutical compositions

Another aspect of the invention is a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 as an active ingredient (or as the only active ingredient).

In one aspect, the present invention relates to a pharmaceutical composition used for treating a disease or disorder mediated by GD2, which comprises any of the above antibodies or antigen-binding fragments thereof in a therapeutically effective amount in combination with one or more pharmaceutically acceptable excipients.

"Pharmaceutical composition" refers to a composition comprising an antibody of the present invention and at least one of components selected from the group comprising pharmaceutically acceptable and pharmacologically compatible fillers, solvents, diluents, carriers, auxiliary, distributing and sensing agents, delivery agents, such as preservatives, stabilizers, filler, disintegrators, moisteners, emulsifiers, suspending agents, thickeners, sweeteners, flavouring agents, aromatizing agents, antibacterial agents, fungicides, lubricants, and prolonged delivery controllers, the choice and suitable proportions of which depend on the type and way of administration and dosage. Examples of suspending agents are ethoxylated isostearyl alcohol, polyoxyethene, sorbitol and sorbitol ether, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacant and their mixtures as well. Protection against action of microorganisms can be provided by various antibacterial and antifungal agents, such as, for example, parabens, chlorobutanol, sorbic acid, and similar compounds. The composition may also contain isotonic agents, such as, for example, sugars, polyols, sodium chloride, and the like. Prolonged action of the composition may be achieved by agents slowing down absorption of active ingredient, for example, aluminum monostearate and gelatine. Examples of suitable carriers, solvents, diluents and delivery agents are water, ethanol, polyalcohols and their mixtures, natural oils (such as olive oil) and organic esters (such as ethyl oleate) for injections. Examples of fillers are lactose, milk sugar, sodium citrate, calcium carbonate, calcium phosphate, and the like. Examples of disintegrators and distributors are starch, alginic acid and its salts, silicates and the like. Examples of lubricants are magnesium stearate, sodium lauryl sulfate, talc, and polyethylene glycol of high molecular weight as well. The pharmaceutical composition for peroral, sublingual, transdermal, intraocular, intramuscular, intravenous, subcutaneous, local or rectal administration of active ingredient, alone or in combination with another active compound may be administered to human and animals in a standard administration form, in a mixture with traditional

pharmaceutical carriers. Suitable standard administration forms include peroral forms such as tablets, gelatin capsules, pills, powders, granules, chewing-gums and peroral solutions or suspensions; sublingual and transbuccal administration forms; aerosols; implants; local, transdermal, subcutaneous, intramuscular, intravenous, intranasal or intraocular administration forms and rectal administration forms.

The term "excipient" or "auxiliary substance" is used herein to describe any ingredient other than the antibody of the present invention. These are substances of inorganic or organic nature which are used in the pharmaceutical production/manufacturing in order to give drug products the necessary physicochemical properties.

In some embodiments, compositions are intended to improve, prevent, or treat disorders that may be associated with GD2.

The term "disease or disorder mediated by GD2" refers to any disease or disorder that is either directly, or indirectly associated with GD2, including etiology, development, progression, persistence or pathology of a disease or disorder.

"Treat", "treating" and "treatment" refer to a method of alleviating or abrogating a biological disorder and/or at least one of its attendant symptoms. As used herein, to "alleviate" a disease, disorder or condition means reducing the severity and/or occurrence frequency of the symptoms of the disease, disorder, or condition. Further, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

In one aspect, the subject of treatment, or patient, is a mammal, preferably a human subject. Said subject may be either male or female, of any age.

The term "disorder" means any condition that would benefit from treatment with the compound of the present invention. This includes chronic and acute disorders or diseases including those pathological conditions that predispose the mammal to the disorder in question.

"Therapeutically effective amount" refers to that amount of the therapeutic agent being administered during treatment which will relieve to some extent one or more of the symptoms of the disease being treated.

In some embodiments of the invention of the pharmaceutical composition, the disease or disorder mediated by GD2 is selected from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

The pharmaceutical compositions of the present invention and methods of preparation thereof will be undoubtedly apparent to those skilled in the art. The pharmaceutical compositions should preferably be manufactured in compliance with the GMP (Good Manufacturing Practice) requirements. The composition may comprise a buffer composition, tonicity agents, stabilizers and solubilizers. Prolonged action of composition may be achieved by agents slowing down absorption of active pharmaceutical ingredient, for example, aluminum monostearate and gelatine. Examples of suitable carriers, solvents, diluents and delivery agents include water, ethanol, polyalcohols and their mixtures, oils, and organic esters for injections.

Any method for administering peptides, proteins or antibodies which is accepted in the art may be suitably employed for the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention.

The term "pharmaceutically acceptable" refers to one or more compatible liquid or solid components that are suitable for administration in a mammal, preferably a human.

The terms "buffer", "buffer composition", "buffering agent" refers to a solution, which is capable of resisting changes in pH by the action of its acid-base conjugate components, and which allows the product of antibody that specifically binds to GD2 to resist changes in pH. Generally, the pharmaceutical composition preferably has a pH in the range from 4.0 to 8.0. Examples of buffers used include, but are not limited to, acetate, phosphate, citrate, histidine, succinate, etc. buffer solutions.

The terms "tonic agent", "osmolyte" or "osmotic agent", as used herein, refer to an excipient that can increase the osmotic pressure of a liquid antibody formulation. "Isotonic" drug is a drug that has an osmotic pressure equivalent to that of human blood. Isotonic drugs typically have an osmotic pressure from about 250 to 350 mOsm/kg. Isotonic agents used include, but are not limited to, polyols, saccharides and sucrose, amino acids, metal salts, for example, sodium chloride, etc.

"Stabilizer" refers to an excipient or a mixture of two or more excipients that provide the physical and/or chemical stability of the active agent. Stabilizers may be amino acids, for example, but not limited to, arginine, histidine, glycine, lysine, glutamine, proline; surfactants, for example, but not limited to, polysorbate 20 (trade name: Tween 20), polysorbate 80 (trade name: Tween 80), polyethylene-polypropylene glycol and copolymers thereof (trade names: Poloxamer, Pluronic, sodium dodecyl sulfate (SDS); antioxidants, for example, but not limited to, methionine, acetylcysteine, ascorbic acid, monothioglycerol, sulfurous acid salts, etc.; chelating agents, for example, but not limited to, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), sodium citrate, etc.

The pharmaceutical composition according to the invention is a stable composition.

The pharmaceutical composition is "stable" if the active agent retains physical stability and/or chemical stability and/or biological activity thereof during the specified shelf life at storage temperature, for example, of 2-8 °C. Preferably, the active agent retains both physical and chemical stability, as well as biological activity. Storage period is adjusted based on the results of stability test in accelerated or natural aging conditions.

A pharmaceutical composition according to the invention may be manufactured, packaged, or widely sold in the form of a single unit dose or a plurality of single unit doses in the form of a ready formulation. The term "single unit dose" as used herein refers to discrete quantity of a pharmaceutical composition containing a predetermined quantity of an active ingredient. The quantity of the active ingredient typically equals the dose of the active ingredient to be administered in a subject, or a convenient portion of such dose, for example, half or a third of such dose.

The pharmaceutical compositions according to the present invention are typically suitable for parenteral administration as sterile formulations intended for administration in a human body through the breach in skin or mucosal barriers, bypassing the gastrointestinal tract by virtue of injection, infusion and implantation. In particular, it is contemplated that parenteral administration includes, inter alia, subcutaneous, intraperitoneal, intramuscular, intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intracranial, intrasynovial, transdermal injection or infusion, and kidney dialytic infusion techniques. Intra-tumor delivery, for example, intra-tumor injection, may also be employed. Regional perfusion is also contemplated. Preferred embodiments include intravenous and subcutaneous routes. Any method for administering peptides or proteins, which is accepted in the art may be suitably employed for the antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention.

Injectable formulations may be prepared, packaged, or sold, without limitation, in unit dosage form, such as in ampoules, vials, in plastic containers, pre-filled syringes, autoinjection devices. Formulations for parenteral administration include, inter alia, suspensions, solutions, emulsions in oily or aqueous bases, pastes, and the like.

In another embodiment, the invention provides a composition for parenteral administration comprising a pharmaceutical composition which is provided in dry (i.e. powder or granular) form for reconstitution with a suitable base (e.g. sterile pyrogen-free water) prior to administration. Such medicinal formulation may be prepared by, for example, lyophilization, i.e. a process, which is known in the art as freeze drying, and which involves freezing a product followed by removal of solvent from frozen material.

The antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention may also be administered intranasally or by inhalation, either alone, as a mixture

with a suitable pharmaceutically acceptable excipient from an inhaler, such as a pressurised aerosol container, pump, spray, atomiser, or nebuliser, where a suitable propellant is used or not used, or as nasal drops, or spray.

Medicinal formulations for parenteral administration may be formulated to be immediate or modified release. Modified release medicinal formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In one aspect, the present invention relates to a pharmaceutical composition for treating a disease or disorder mediated by GD2, the pharmaceutical combination comprising any above antibody or antigen-binding fragment thereof and at least one other therapeutically active compound.

In some embodiments of the invention of the pharmaceutical composition, the other therapeutically active compound is an antibody, chemotherapeutic agent, or hormone therapy agent.

In some embodiments of the invention of the pharmaceutical composition, the other therapeutically active compound is an immune checkpoint inhibitor.

In some embodiments of the invention of the pharmaceutical composition, the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor.

In some embodiments of the invention of the pharmaceutical composition, the PD-1 inhibitor is an antibody that specifically binds to PD-1.

In some embodiments of the invention of the pharmaceutical composition, the antibody that specifically binds to PD-1 is selected from the group: prolgolimab, pembrolizumab, nivolumab.

In some embodiments of the invention of the pharmaceutical composition, the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

In some embodiments of the invention of the pharmaceutical composition, the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

In some embodiments of the invention of the pharmaceutical composition, the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

In some embodiments of the invention of the pharmaceutical composition, the antibody that specifically binds to PD-L1 is selected from the group: durvalumab, avelumab, atezolizumab, manelimab.

In some embodiments of the invention of the pharmaceutical composition, the other therapeutically active compound is selected from the group: IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

Therapeutic use of the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2

In one aspect, the antibody or antigen-binding fragment thereof that specifically binds to GD2 is used in the treatment of disorders mediated by GD2 activity.

In one aspect, the subject of treatment, or patient, is a mammal, preferably a human subject. Said subject may be either male or female, of any age.

In the case of a tumor (for example, cancer), the therapeutically effective amount of an antibody or fragment thereof (for example, an antibody or fragment thereof that specifically binds to GTR) may reduce the number of cancer cells; reduce the initial tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit to some extent tumor growth; and/or relieve to some extent one or more of the symptoms associated with the disorder. The antibody or fragment thereof may to some extent prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, in vivo efficacy can, for example, be measured by assessing survival, time to tumor progression (TTP), tumor response rate to treatment (RR), duration of response and/or quality of life.

The uses or methods used herein relating to the antibody or antigen-binding fragment thereof that specifically binds to GD2 with one or more other therapeutic agents are contemplated to mean, refer to and include the following:

1) simultaneous administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to GD2 and therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,

2) simultaneous administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to GD2 and therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,

3) sequential administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to GD2 and therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and

4) sequential administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to GD2 and therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner, whereupon they are concurrently, consecutively, or jointly released at the same and/or different times to said patient, where each portion may be administered by either the same or different routes.

The antibody or antigen-binding fragment thereof that specifically binds to GD2 may be administered without further therapeutic treatment, i.e. as an independent therapy.

In one aspect, the present invention relates to a method for inhibiting the biological activity of GD2 in a subject in need of such inhibition, comprising administering an effective amount of any above antibody or antigen-binding fragment thereof.

In one aspect, the present invention relates to a method for treatment of a disease or disorder mediated by GD2, which comprises administering in a subject in need of such treatment any above antibody or antigen-binding fragment thereof or said pharmaceutical composition, in a therapeutically effective amount.

In one aspect, the present invention relates to a method for treating a disease or disorder mediated by GD2, that comprises administering in a subject in need of such treatment any of the above antibodies or antigen-binding fragments thereof, and selected from the group:

- a) administration of at least one other therapeutically active compound,
- b) radiotherapy,
- c) hematopoietic stem cell transplantation,
- d) surgical treatment and, if necessary, adjuvant therapy, or
- e) any combination of the above a) to d).

In some embodiments of the method of treatment, the disease or disorder mediated by GD2 is selected from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

In some embodiments of the method of treatment, other therapeutically active compound is an antibody, chemotherapeutic agent, or hormone therapy agent.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of a malignant neoplasm. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide,

triethylenethiophosphoramidate and trimethylmelamine; acetogenins (e.g. bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopoletin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (e.g. cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g. calicheamicin, e.g. calicheamicin gamma II and calicheamicin omega II (see, e.g. Agnew, Chem. Intl. Ed. Engl., 33: 183-186 (1994))); dynemicin, including dynemicin A; esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HCl liposome injection (DOXOL®), liposomal doxorubicin TLC D-99 (MYOCET®), pegylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), epothilone and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamideglycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS

Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (e.g. T-2 toxin, verracurin A, roridin A and anguidine); urethan; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, e.g. paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANE®), and docetaxel (TAXOTERE®); chlorambucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin, and carboplatin; vinca alkaloids, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), vincristine (ONCOVIN®), vindesine (ELDISINE®), FILDESIN®, and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid, including bexarotene (TARGRETIN®); biphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE- 58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAJX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, e.g. those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as for example, PKC- α , Raf, H-Ras, and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (e.g. LURTOTECAN®); rmRH (e.g., ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (Pfizer); perifosine, COX-2 inhibitor (e.g. celecoxib or etoricoxib), proteasome inhibitor (e.g. PS341); bortezomib (VELCADE®); CCI-779; tipifarnib (811577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors (see definition below); tyrosine kinase inhibitors (see definition below); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone, and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATINTM) combined with 5-FU and leucovorin.

Hormonal agents are agents that act to regulate or inhibit hormone action on tumors. Examples of such agents are anti-estrogens with mixed agonist/antagonist profile, including, tamoxifen (NOLVADEX®), 4-hydroxytamoxifen, toremifene (FARESTON®), idoxifene, droloxifene, raloxifene (EVTSTA®), trioxifene, keoxifene, and selective estrogen receptor modulators (SERMs), such as SERM3; pure anti-estrogens without agonist properties, such as fulvestrant (FASLODEX®), and EM800 (such agents may block estrogen receptor (ER)

dimerization, inhibit DNA binding, increase ER turnover, and/or suppress ER levels); aromatase inhibitors, including steroidal aromatase inhibitors, such as formestane and exemestane (AROMASIN®), and nonsteroidal aromatase inhibitors, such as anastrozole (AREVIIDEX®), letrozole (FEMARA®) and aminoglutethimide, and other aromatase inhibitors including vorozole (RIVISOR®), megestrol acetate (MEGASE®), fadrozole, imidazole; lutenizing hormone-releasing hormone agonists, including leuprolide (LUPRON® and ELIGARD®), goserelin, buserelin, and triptorelin; sex steroids, including progestins, such as megestrol acetate and medroxyprogesterone acetate, estrogens, such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretinoic acid and fenretinide; onapristone; anti-progestones; estrogen receptor down-regulators (ERDs); anti-androgens, such as flutamide, nilutamide and bicalutamide; testolactone; and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above.

In some embodiments of the method of treatment, the other therapeutically active compound is an immune checkpoint inhibitor.

The term “immune checkpoint inhibitor” (or “checkpoint inhibitor”) refers to compounds that inhibit the activity of immune checkpoints. Inhibition includes reduction of function and full blockade. Examples of inhibitory checkpoint molecules include B7-H3, B7-H4, BTLA, CTLA-4, KIR, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, TIGIT, and VISTA. In some embodiments of the invention, the immune checkpoint inhibitor is an antibody that specifically recognizes an immune checkpoint protein. A number of immune checkpoint inhibitors are known and in analogy of these known immune checkpoint protein inhibitors, alternative immune checkpoint inhibitors may be developed in the near future. The immune checkpoint inhibitors include, but are not limited to, peptides, antibodies, nucleic acid molecules, and low molecular weight compounds.

In some embodiments of the method of treatment, the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor.

In some embodiments of the method of treatment, the PD-1 inhibitor is an antibody that specifically binds to PD-1.

In some embodiments of the invention, the PD-1 inhibitor is an antibody that specifically binds to PD-1. Examples of antibodies that specifically bind to PD-1 include pembrolizumab, nivolumab, prololizumab, toripalimab, cemiplimab, sintilimab and others. The most preferred ones are prololizumab, pembrolizumab, nivolumab.

In some embodiments of the method of treatment, the antibody that specifically binds to PD-1 is selected from the group comprising prololizumab, pembrolizumab, nivolumab.

In some embodiments of the method of treatment, the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

In some embodiments of the invention, the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4. Examples of antibodies that specifically bind to CTLA4 include ipilimumab, tremelimumab, zalifrelimab, nurulimab and others. The most preferred ones are ipilimumab or nurulimab.

In some embodiments of the method of treatment, the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

In some embodiments of the method of treatment, the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

In some embodiments of the method of treatment, the antibody that specifically binds to PD-L1 is selected from the group: durvalumab, avelumab, atezolizumab, manelimumab.

In some embodiments of the method of treatment, the other therapeutically active compound is selected from the group: IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

In one aspect, the present invention relates to the use of the above antibody or antigen-binding fragment thereof or the above pharmaceutical composition for treating in a subject in need of such treatment a disease or disorder mediated by GD2.

In one aspect, the present invention relates to the use of any of the above antibody or antigen-binding fragment thereof and at least one of the group:

- a) other therapeutically active compound,
 - b) radiotherapy,
 - c) hematopoietic stem cell transplantation or
 - d) surgical treatment and, if necessary, adjuvant therapy,
- for treating a disease or disorder mediated by GD2.

In some embodiments of the use, the disease or disorder mediated by GD2 is selected from the group: brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

In some embodiments of the use, the other therapeutically active compound is an immune checkpoint inhibitor.

In some embodiments of the use, the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor.

In some embodiments of the use, the PD-1 inhibitor is an antibody that specifically binds to PD-1.

In some embodiments of the use, the antibody that specifically binds to PD-1 is selected from the group: prolgolimab, pembrolizumab, nivolumab.

In some embodiments of the use, the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

In some embodiments of the use, the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

In some embodiments of the use, the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

In some embodiments of the use, the antibody that specifically binds to PD-L1 is selected from the group: durvalumab, avelumab, atezolizumab, manelimab.

In some embodiments of the use, the other therapeutically active compound is selected from the group: IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

Doses and routes of administration

The monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention will be administered in an amount that is effective in treatment of the condition in question, i.e. in doses and during the periods of time required to achieve the desired result. A therapeutically effective amount may vary according to factors such as the particular condition being treated, the age, sex and weight of the patient, and whether the monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 is being administered as a stand-alone treatment or in combination with one or more additional drugs or treatments.

Dosage regimens may be adjusted to provide the optimum desired response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in a unit dosage form for ease of administration and uniformity of dosage. A unit dosage form as used herein refers to physically discrete units suited as unitary dosages for patients/subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the desired pharmaceutical carrier. Specification for the unit dosage forms of the invention is typically dictated by and directly dependent on (a) the unique characteristics of a therapeutic agent and particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in subjects.

Thus, a skilled artisan would appreciate, based upon the disclosure provided herein, that the doses and dosage regimen are adjusted in accordance with methods well-known in the therapeutic arts. That is, the maximum tolerable dose can be readily established, and the effective amount providing a detectable therapeutic effect to a patient may also be determined, as can the temporal requirements for administering each agent to provide a detectable therapeutic effect to a patient. Thus, while certain doses and administration regimens are exemplified herein, these examples in no way limit the doses and administration regimens that may be provided to a patient in practicing the embodiments of the invention.

It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated, and may include single or multiple doses. Furthermore, it is to be understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the judgment of a medical professional administering or supervising the administration of the compositions, and that dosage ranges set forth in the present description are exemplary only and are not intended to limit the scope or practice of the claimed compositions. Further, the dosage regimen with the compositions of this invention may be based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. For example, doses may be adjusted based on pharmacokinetic and pharmacodynamic parameters, which may include clinical effects such as toxic effects or laboratory values. Thus, the present invention encompasses intra-patient dose-escalation as determined by one skilled in the art. Methods for determining appropriate dosage and regimen are well-known in the art and would be understood by a skilled artisan once provided the ideas disclosed herein.

Examples of suitable administration methods are provided above.

It is believed that a suitable dose of a monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention will be in the range of 0.1-200 mg/kg, preferably 0.1-100 mg/kg, including about 0.5-50 mg/kg, for example about 1-20 mg/kg. The monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 may be administered, e.g. in a dose of at least 0.25 mg/kg, such as at least 0.5 mg/kg, including at least 1 mg/kg, e.g. at least 1.5 mg/kg, such as at least 2 mg/kg, e.g. at least 3 mg/kg, including at least 4 mg/kg, e.g. at least 5 mg/kg; and for example up to a maximum of 50 mg/kg, including up to a maximum of 30 mg/kg, e.g. up to a maximum of 20 mg/kg, including up to a maximum of 15 mg/kg. The administration will typically be repeated in appropriate time intervals, such as once a week, once every two weeks, once every three weeks or once every four weeks, and for as long as

deemed appropriate by a responsible physician, who may, in some cases, increase or reduce the dose if necessary.

Diagnostic use of the antibody that specifically binds to GD2

The monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention are also used in diagnostic purposes (e.g. in vitro, ex vivo). For example, the present monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 according to the invention may be used for detecting or measuring the level of GD2 in samples obtained from a patient (e.g. tissue sample or a sample of body fluid, such as an inflammatory exudate, blood, serum, intestinal fluid, saliva or urine). Suitable methods for detection and measurement include immunoassays, such as flow cytometry, enzyme-linked immunosorbent assay (ELISA), chemiluminescent assay, radioimmunoassay, and immunohistology.

Examples

The following examples are provided for better understanding of the invention. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

All publications, patents, and patent applications cited in this specification are incorporated herein by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended embodiments.

Materials and general methods

General information regarding the nucleotide sequences of human immunoglobulin light and heavy chains is given in: Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991). Amino acids of antibody chains are numbered according to EU numbering (Edelman, G.M., et al., Proc. Natl. Acad. Sci. USA 63 (1969) 78-85; Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD, (1991).

Recombinant DNA techniques

Standard methods were used to manipulate DNA as described in Sambrook, J. et al, Molecular cloning: A laboratory manual; Cold Spring Harbor Laboratory Press, Cold Spring

Harbor, New York, 1989. The molecular biological reagents were used according to the manufacturer protocols.

Gene synthesis

Desired gene segments were prepared from oligonucleotides made by chemical synthesis. The gene segments of 300-1400 bp long, which were flanked by singular restriction sites, were assembled by annealing and ligation of oligonucleotides including PCR amplification and subsequently cloned via the restriction sites. The DNA sequences of the subcloned gene fragments were confirmed by DNA sequencing.

DNA sequence determination

DNA sequences were determined by Sanger sequencing.

DNA and protein sequence analysis and sequence data management

The Unipro's UGENE suite version 1.29 and SnapGene Viewer were used for sequence creation, mapping, analysis, annotation and illustration.

Expression vectors

For the expression of the antibodies described in the application materials, variants of expression plasmids intended for expression of antibodies in prokaryotic cells (E.coli), transient expression in eukaryotic cells (e.g., in CHO cells) were applied. Beside the antibody expression cassette the vectors contained: an origin of replication which allows replication of said plasmid in E. coli, genes which confer resistance in E. coli to various antibiotics (e.g. to ampicillin, kanamycin).

The fusion genes comprising the described antibody chains as described below were generated by PCR and/or gene synthesis and assembled with known recombinant methods and techniques by connection of the according nucleic acid segments, e.g. using unique restriction sites in the corresponding vectors. The subcloned nucleic acid sequences were verified by DNA sequencing. For transient transfections, larger quantities of the plasmids were prepared by plasmid preparation from transformed E. coli cultures.

Example 1

Selection of anti-GD2 antibody sequences

Anti-GD2 antibody molecules were created using structural data obtained in silico. In silico scaffolding was performed using the internal algorithm of JSC "Biocad". The PrepWizard

instrument from Schrodinger Suite 2017-2 was employed to prepare the structures. It was followed by folding using the Prime instrument from Schrodinger Suite 2017-2.

The approach of sequential modification of the amino acid composition of variable domains was applied.

The antibodies were optimized in silico to thereby produce antibody candidates for further study, the antibody candidates are indicated in Table 1.

Table 1. Antibody candidates for further study

Name of antibody to GD2
07-001
07-002
07-003
07-004
07-005
07-006
07-007
07-008
07-009
07-010
07-011
07-012
07-013
07-014
07-015
07-016
07-017
07-019
07-028
07-029
07-030
07-031
07-032
07-033
07-041

07-042
07-043
07-044

6 leader antibodies were selected from Table 1 as follows: 07-006, 07-015, 07-016, 07-028, 07-031, 07-041; these antibodies surprisingly showed the best parameters (see examples below).

Example 2

Identity/humanization analysis for the light/heavy chain variable fragments of anti-GD2 antibodies 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041

Table 2 shows the identity analysis for the heavy chain variable fragments of anti-GD2 antibodies 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041.

Table 2. % identity in antibody VHs

% identity in VHs	07-006	07-015	07-016	07-028	07-031	07-041
07-006	100	98	98	98	99	99
07-015	98	100	100	100	98	98
07-016	98	100	100	100	98	98
07-028	98	100	100	100	98	98
07-031	99	98	98	98	100	99
07-041	99	98	98	98	99	100

Thus, the heavy chain variable fragments of anti-GD2s according to the invention have at least 98 % identity to each other.

Table 3 shows the humanization analysis for the heavy chain variable fragments of anti-GD2 antibodies 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041.

Table 3. Degree of antibody VH humanization

Degree of VH humanization	
07-006	0.806
07-015	0.806
07-016	0.806
07-028	0.806
07-031	0.806

07-041	0.806
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Thus, the heavy chain variable fragments of anti-GD2 antibodies according to the invention have a degree of humanization of more than 80 %.

Table 4 shows the identity analysis for the light chain variable fragments of anti-GD2 antibodies 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041

Table 4. % identity in antibody VLs

% identity in VLs	07- 006	07- 015	07- 016	07- 028	07- 031	07- 041
07-006	100	99	100	96	99	96
07-015	99	100	99	96	100	96
07-016	100	99	100	96	99	96
07-028	96	96	96	100	96	96
07-031	99	100	99	96	100	96
07-041	96	96	96	96	96	100

Thus, the light chain variable fragments of anti-GD2 antibodies according to the invention have at least 96 % identity to each other.

Table 5 shows the humanization analysis for the light chain variable fragments of anti-GD2 antibodies 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041.

Table 5. Degree of VL humanization

Degree of antibody VL humanization	
07-006	0.8
07-015	0.81
07-016	0.8
07-028	0.8
07-031	0.81
07-041	0.8

Thus, the light chain variable fragments of candidate anti-GD2s according to the invention have a degree of humanization of more than 80 %.

Example 3

Production of sequences of anti-GD2 antibodies 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041

The genes of the heavy/light chain variable domains of the antibody to GD2 according to the invention that is selected from the group: 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041, were synthesized de novo. To this end, we synthesized oligonucleotides of 55-60 bp each forming a completely overlapping gene sequence. Each gene was assembled using two-round PCR, which resulted in production of fragments of 339 bp each. Fusion of the heavy chain variable domain gene and the Fc fragment of human IgG1, the light chain variable domain and CK were performed using PCR and/or gene synthesis and assembly using known recombination methods and processes by connecting the appropriate nucleic acid segments, for example, using SOE-PCR (Splicing by overlap extension).

The heavy and light chain genes of the antibody to GD2 according to the invention selected from the group: 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041 were cloned into PEE plasmids for producing protein in the IgG1 format in mammalian cells. The cloned nucleic acid sequences were verified by DNA sequencing. The desired quantities of the resulting plasmids (Figures 2 and 3) were produced in E.coli cells and purified using a commercial plasmid DNA isolation kit from Qiagen.

The resulting gene constructs were transferred for transient production of proteins in CHO cell line.

Example 4

Modification of the Fc heavy chain constant domain of a GD2 antibodies 07-006, 07-015, 07-016, 07-028, 07-031 or 07-041

To produce antibodies with improved properties, the Fc heavy chain constant domain was modified by introducing point mutations M252Y, S254T, T256 (YTE) and/or K322A. The set of YTE mutations makes it possible to achieve prolonged pharmacokinetics, whereas the introduction of the K322A mutation reduces the complement-dependent cytotoxicity of the resulting antibodies. Also, due to the expression in the CHO-1g6-Fut8 cell line, the Fc portion of the antibody was afucosylated, thus leading to increased antibody-dependent cellular cytotoxicity. The resulting antibodies are shown in Table 6.

Table 6. Variants of antibodies to GD2 according to the invention

Name of initial antibody without modifications to Fc fragment	Name of antibody with mutations M252Y, S254T,	Name of antibody with K322A mutation in Fc fragment	Name of antibody with mutations M252Y, S254T, T256E (YTE) + K322A in Fc fragment
---	---	---	--

	T256E (YTE) in Fc fragment		
07-006	07-006 + YTE	07-006 + K322A	07-006 + YTE + K322A
07-015	07-015 + YTE	07-015 + K322A	07-015 + YTE + K322A
07-016	07-016 + YTE	07-016 + K322A	07-016 + YTE + K322A
07-028	07-028 + YTE	07-028 + K322A	07-028+ YTE+ K322A
07-031	10-001	10-003	10-002
07-041	10-007	10-009	10-008

Assembly of genetic constructs included the fusion of the heavy chain variable domain gene and the Fc of human IgG1, into which point mutations were pre-introduced.

Heavy chain genes with substitutions were cloned into pEE plasmids for producing protein together with the already produced light chain constructs, in the IgG1 format in the CHO-1g6-Fut8 cell line. The cloned nucleic acid sequences were verified by DNA sequencing. The required quantities of the resulting plasmids (Figures 2, 3) were cultured in E.coli cells and purified using Qiagen kit.

The resulting gene constructs were transferred for transient production of proteins in CHO-1g6-Fut8 cell line.

Example 5

Production, isolation and purification of antibodies to GD2 from suspension culture of mammalian cells.

Full-length antibodies were produced in the CHO cell growth medium, afucosylated forms of full-length antibodies were produced in the CHO-1g6-Fut8 cell growth medium. Following transfection of cells with expression vectors, orbital feed-batch cultivation was performed in serum-free medium for 7 days. Secretion of the antibodies in question was monitored using the Pall ForteBio's Octet RED96 system for molecular interactions analysis on protein A biosensors.

After culturing, cell culture was centrifuged under 2000 g for 20 min and filtered through 0.22 µm filter. The target proteins were isolated from the culture fluid by affinity chromatography on the Akta Pure 25 chromatography system using HiTrap rProtein A FF columns. The culture liquid was applied to the HiTrap rProtein A FF column; thereafter, the column was washed with PBS and the protein was eluted with a solution of 0.1 M glycine buffer pH 3; thereafter, the protein solution was neutralized by adding 1 M Tris-HCl pH8 at a ratio of 1/5 v/V. The protein was then transferred to PBS pH 7.4 by dialysis; thereafter, the resulting solution was filtered (0.22 µm). The product was stored at -70 °C. The purity of the resulting protein solution was evaluated by SDS gel electrophoresis (Fig. 4).

Example 6**Kinetic studies of affinity of antibodies to GD2 to ganglioside GD2 using Forte Bio OctetRed96.**

Binding of antibody to GD2 was evaluated by bio-layer interferometry on the OctetRed96 (Pall) instrument. AR2G sensors were coated with ganglioside GD2. The sensors with immobilized GD2 were then immersed in wells containing the antibody. Following the association of the antibody and ganglioside, the sensors were immersed in the working solution for the subsequent dissociation stage. The resulting sensograms, after subtracting a reference signal, were analyzed using Octet Data Analysis software (Version 8.2) in accordance with the standard procedure and using 1:1 interaction model. KDs for aGD2 antibodies according to the invention are shown in Table 7.

Table 7. Dissociation constants for antibodies to GD2

Name of antibody	KD, M
07-006	7,58E-10
07-015	4,49E-10
07-016	7,03E-10
07-028	6,13E-10
07-031	10,6E-10
07-041	8,41E-10
10-008	7,56 E-10

Thus, all test anti-GD2 antibodies specifically bind to the ganglioside GD2 (Table 7) with high affinity.

Example 7**Analysis of thermal stability of antibodies to GD2.**

Antibodies were heated in PBS pH 7.4 using an amplifier in plastic test tubes at 50°C for 48 hours, followed by a shift to +4°C. After the end of the program, the samples were analyzed before and following heating using analytical gel chromatography on a TSK Gel G3000 SWxl column. The areas of the target peaks of the samples before and following heating were compared. A less than 5% change in the area of the monomer peak following heating for 48 hours indicates the stability of the product and the possibility of long-term storage (Table 8).

Table 8. Ratios of peak areas on chromatograms of antibody products before and following heating.

Name of antibody	% ratio of peaks			
		Σ aggregates, %	monomer, %	Σ fragments, %
07-006	before heating	1.49	96.06	2.46
	following heating	1.30	94.81	3.88
07-015	before heating	1.81	95.64	2.55
	following heating	1.58	91.46	6.95
07-016	before heating	1.11	96.85	2.04
	following heating	1.14	92.32	6.54
07-028	before heating	1.41	96.50	2.08
	following heating	1.39	93.21	5.41
07-031	before heating	0.72	89.95	9.33
	following heating	0.65	89.68	9.67
07-041	before heating	0.86	97.50	1.64
	following heating	1.03	95.68	3.29
10-008	before heating	0.34	98.17	1.49
	following heating	0.65	96.12	3.23

Thus, all test anti-GD2 antibodies show high thermal stability (Table 8).

Example 8

Determination of antibody-dependent cellular cytotoxicity of antibodies to GD2

We used a reporter cell line based on the Jurkat cell line, stably expressing surface CD16 and comprising a gene encoding firefly luciferase under the control of NFAT promoter; SK-N-BE(2) was used as target cells. Jurkat-NFAT-Luc-CD16 cells were cultured at 37°C with 5% CO₂ on RPMI-1640 medium (10% FBS, 10 µg/ml gentamicin, 2mM L-glutamine, 0.3 µg/ml puromycin and 200 µg/ml hygromycin); SK-N-BE(2) was cultured under the same conditions in DMEM/F12 medium (10% FBS, 10 mcg/ml gentamicin and 2mM L-glutamine).

25,000 Jurkat-NFAT-Luc-CD16 effector cells and 25,000 SK-N-BE(2) target cells in a volume of 50 µl, as well as dilutions of antibodies at concentrations according to the graph in a volume of 50 µl were introduced into each well of a 96-well culture plate.

Points free of antibody were used as a negative control. The plates were incubated for 4 hours at 37°C, 5% CO₂; thereafter, luminescence intensity in the wells was measured using a luciferase substrate (JSC BIOCAD) on a Spark plate reader (Tecan), data processing and plotting were performed using SigmaPlot 14.0 software. EC₅₀ values for anti-GD2 antibody samples are shown in Table 9.

Table 9. EC₅₀ values for anti-GD2 antibody samples

Name of antibody	EC ₅₀ (ng/ml)
07-001	3.2
07-002	3.6
07-003	2.2±1.3
07-004	4.5
07-005	2.8
07-006	1.3±0.6
07-007	5.3
07-008	4
07-009	2.7±1.7
07-010	3.6
07-011	1.8
07-012	1.3±0.9
07-013	1
07-014	1
07-015	1.1
07-016	1
07-017	1.4

07-019	0.7
07-028	0.7
07-029	1.3
07-030	2.6
07-031	8.5±2.6
07-032	10.3
07-033	1.1
07-041	4.1±3.9
07-042	2.4
07-043	1.6
07-044	2.2
07-041-dFuc (afucosylated variant of 07-041)	0.9±0.3
10-007	0.7±0.2
10-008	1±0.7
10-009	0.6±0.1
10-010	13.6±0.7
10-011	19.8±9.3
10-012	3.3±1.6

Figure 5 shows that antibody 10-008 has antibody-dependent cellular cytotoxicity in an assay using the reporter Jurkat-NFAT-Luc-CD16 cell line.

Example 9

Analysis of complement dependent cellular cytotoxicity

The SK-N-BE (2) (human neuroblastoma) cell line was used as target cells for the analysis. The cells were grown in DMEM medium supplemented with 10% bovine serum. To perform the analysis, we prepared a suspension of cells in DMEM medium supplemented with 0.1% bovine serum albumin at a concentration of 1×10^6 cells/ml, and prepared a number of dilutions of the test antibody candidates.

50 µl of antibody dilutions, 50 µl of cell suspension and 50 µl of freshly isolated human serum from healthy donors were added to each well of a 96-well culture plate. The plate was incubated at 37 °C, 5% CO₂ for 3 hours. After incubation, 15 µl of "Alamar Blue" vital dye (Invitrogen) was added to all wells and the plate was incubated at 37 °C, 5% CO₂ for 18 hours.

The plate was shaken for 10-20 minutes at room temperature on an orbital shaker for stirring. Fluorescence readings were obtained using the TECAN Spark plate reader. The detected fluorescence signal is proportional to the number of viable cells. Excel and SigmaPlot 14.0 software were used for data processing and plotting.

The test antibodies 07-041dFuc ((afucosylated variant of 07-041)), 10-007, 10-008, 10-009 cause the death of target cells in the presence of human serum. Antibodies 10-008 and 10-009 have a decreased effect as compared to that of other antibodies (see Figure 6).

Sequence listing

<110> JSC "BIOCAD"

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<150> RU2021107773

<151> 24-03-2021

<160> 100

<170> BiSSAP 1.3.6

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10-002, 10-003, 10-007, 10-008, 10-009

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35          40          45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50          55          60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65          70          75          80
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Ser

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20          25          30
Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
35          40          45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50          55          60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65          70          75          80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85          90          95
Val Ser Gly Met Leu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100          105          110
Ser

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20           25           30
Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
35           40           45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50           55           60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65           70           75           80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85           90           95
Val Ser Gly Met Ile Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100           105           110
Ser

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
20           25           30
Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
35           40           45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50           55           60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65           70           75           80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85           90           95
Val Ser Gly Met Phe Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100           105           110
Ser

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 20 25 30
 Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe Gly Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
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 Thr His Val Pro Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
 100 105 110
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 20 25 30
 Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile His Lys Val Ser Asn Arg Phe Gly Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
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Lys 100 105 110

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 20 25 30
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 35 40 45
 Pro Lys Leu Leu Ile His Lys Val Asn Asn Arg Phe Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
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 Thr His Val Pro Pro Leu Ser Phe Gly Gln Gly Thr Lys Leu Glu Leu
 100 105 110
 Lys

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 of antibodies 07-041, 10-007, 10-008, 10-009

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 20 25 30
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 35 40 45
 Pro Lys Leu Leu Ile His Lys Val Asn Asn Arg Phe Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Gly Gln Ser
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 Thr His Val Pro Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
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 Lys

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 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Tyr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
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 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 245 250 255
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
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 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Leu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr

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                195                200                205
Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
                210                215                220
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225                230                235                240
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                245                250                255
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                260                265                270
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                275                280                285
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                290                295                300
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
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Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
                340                345                350
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
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Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                370                375                380
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385                390                395                400
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
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Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe

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50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Ile Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 245 250 255
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 25

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 07-041

<400> 25

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1          5          10          15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
          20          25          30
Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
          35          40          45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
          50          55          60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65          70          75          80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
          85          90          95
Val Ser Gly Met Phe Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
          100          105          110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
          115          120          125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
          130          135          140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145          150          155          160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
          165          170          175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
          180          185          190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
          195          200          205
Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
          210          215          220
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225          230          235          240
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
          245          250          255
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
          260          265          270
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
          275          280          285
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
          290          295          300
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305          310          315          320
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
          325          330          335
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
          340          345          350
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
          355          360          365

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Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 26

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 07-006 +
 YTE

<400> 26

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Tyr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr

245 250 255
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 27

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibodies 07-015 +
 YTE, 07-016 + YTE и 07-028 + YTE

<400> 27

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly His
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Leu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp

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      130              135              140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145              150              155              160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
      165              170              175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
      180              185              190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195              200              205
Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
210              215              220
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225              230              235              240
Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr
      245              250              255
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
      260              265              270
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
      275              280              285
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
      290              295              300
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305              310              315              320
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
      325              330              335
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
      340              345              350
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
      355              360              365
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
      370              375              380
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385              390              395              400
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
      405              410              415
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
      420              425              430
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
      435              440

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<210> 28

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 10-001

<400> 28

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1              5              10              15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys

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20							25					30				
Asn	Met	Asn	Trp	Val	Arg	Gln	Asn	Ile	Gly	Gln	Gly	Leu	Glu	Trp	Met	
		35					40					45				
Gly	Ala	Ile	Asp	Pro	Phe	Tyr	Gly	Gly	Thr	Ser	Tyr	Asn	Gln	Lys	Phe	
50						55					60					
Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr	
65					70					75					80	
Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Val	Ser	Gly	Met	Ile	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	
			100					105					110			
Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	
		115					120					125				
Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	
130						135					140					
Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	
145					150					155					160	
Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	
				165					170					175		
Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	
			180					185					190			
Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	
195						200					205					
Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	
210						215					220					
Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	
225					230					235					240	
Pro	Lys	Pro	Lys	Asp	Thr	Leu	Tyr	Ile	Thr	Arg	Glu	Pro	Glu	Val	Thr	
				245					250					255		
Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	
			260					265					270			
Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	
275						280					285					
Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	
290						295					300					
Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	
305					310					315			320			
Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	
			325					330					335			
Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	
		340					345					350				
Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	
355						360					365					
Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	
370						375					380					
Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	
385					390					395			400			
Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	
			405					410					415			
Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	
			420					425					430			
Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						

<210> 29
 <211> 443
 <212> PRT
 <213> Artificial sequence

<220>
 <223> amino acid sequence of the heavy chain of antibody 10-007

<400> 29
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Phe Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr
 245 250 255
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 30

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 07-006 +
 YTE + K322A

<400> 30

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Tyr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro

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      210              215              220
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225              230              235              240
Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr
      245              250              255
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
      260              265              270
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
      275              280              285
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
      290              295              300
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser
305              310              315              320
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
      325              330              335
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
      340              345              350
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
      355              360              365
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
      370              375              380
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385              390              395              400
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
      405              410              415
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
      420              425              430
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
      435              440

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<210> 31

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibodies 07-015 +
 YTE + K322A, 07-016 + YTE + K322A and 07-028 + YTE + K322A

<400> 31

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1              5              10              15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly His
      20              25              30
Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
      35              40              45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
      50              55              60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65              70              75              80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
      85              90              95

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Val Ser Gly Met Leu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr
 245 250 255
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 32

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 10-002

<400> 32

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Ile Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr
 245 250 255
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly

				405					410					415	
Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr
			420					425					430		
Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys					
		435					440								

<210> 33

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 10-008

<400> 33

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Ser	Ser	Phe	Thr	Gly	Lys
			20					25					30		
Asn	Met	Asn	Trp	Val	Arg	Gln	Asn	Ile	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Ala	Ile	Asp	Pro	Phe	Tyr	Gly	Gly	Thr	Ser	Tyr	Asn	Gln	Lys	Phe
	50					55				60					
Lys	Gly	Arg	Val	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
65				70					75					80	
Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Val	Ser	Gly	Met	Phe	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser
			100					105						110	
Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser
			115				120					125			
Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp
	130					135					140				
Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr
145					150					155				160	
Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr
				165					170					175	
Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln
			180					185					190		
Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp
		195				200						205			
Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro
	210					215					220				
Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro
225					230					235				240	
Pro	Lys	Pro	Lys	Asp	Thr	Leu	Tyr	Ile	Thr	Arg	Glu	Pro	Glu	Val	Thr
				245					250					255	
Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn
			260					265					270		
Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg
	275					280						285			
Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val

```

      290              295              300
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser
305              310              315              320
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
      325              330              335
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
      340              345              350
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
      355              360              365
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
      370              375              380
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385              390              395              400
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
      405              410              415
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
      420              425              430
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
      435              440

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<210> 34

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 07-006 +
K322A

<400> 34

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1              5              10              15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
      20              25              30
Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
      35              40              45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
      50              55              60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65              70              75              80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
      85              90              95
Val Ser Gly Met Tyr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
      100              105              110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
      115              120              125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
      130              135              140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145              150              155              160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
      165              170              175

```

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 245 250 255
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 35

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibodies 07-015 + K322A, 07-016 + K322A and 07-028 + K322A

<400> 35

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly His
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe

<210>	36
<211>	443
<212>	PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 10-003

<400> 36

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1          5          10          15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
          20          25          30
Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
          35          40          45
Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
          50          55          60
Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65          70          75          80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
          85          90          95
Val Ser Gly Met Ile Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
          100          105          110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
          115          120          125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
          130          135          140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145          150          155          160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
          165          170          175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
          180          185          190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
          195          200          205
Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
          210          215          220
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225          230          235          240
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
          245          250          255
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
          260          265          270
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
          275          280          285
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
          290          295          300
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser
305          310          315          320
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
          325          330          335
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
          340          345          350
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
          355          360          365

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Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 37

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the heavy chain of antibody 10-009

<400> 37

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Lys
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Ala Ile Asp Pro Phe Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Val Ser Gly Met Phe Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
 210 215 220
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 225 230 235 240
 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 245 250 255

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 260 265 270
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 275 280 285
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 290 295 300
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser
 305 310 315 320
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 325 330 335
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 340 345 350
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 370 375 380
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 405 410 415
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 420 425 430
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 38

<211> 220

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the light chain of antibodies 07-006,
 07-016

<400> 38

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
 1 5 10 15
 Glu Arg Ala Ser Leu Ser Cys Arg Ser Ser Arg Ser Leu Val His Arg
 20 25 30
 Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe Gly Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Gly Gln Ser
 85 90 95
 Thr His Val Pro Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
 100 105 110
 Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 115 120 125
 Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn

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      130              135              140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145              150              155              160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
      165              170              175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
      180              185              190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
      195              200              205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
      210              215              220

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<210> 39

<211> 220

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence of the light chain of antibodies 07-015,
07-031, 10-001, 10-002, 10-003

<400> 39

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Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1              5              10              15
Glu Arg Ala Ser Leu Ser Cys Arg Ser Ser Arg Ser Leu Val His Arg
      20              25              30
Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35              40              45
Pro Gln Leu Leu Ile His Lys Val Ser Asn Arg Phe Gly Gly Val Pro
      50              55              60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Gly Gln Ser
      85              90              95
Thr His Val Pro Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
      100             105             110
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
      115             120             125
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
      130             135             140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145             150             155             160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
      165             170             175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
      180             185             190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
      195             200             205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
      210             215             220

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<210> 40

<211> 220
 <212> PRT
 <213> Artificial sequence

<220>
 <223> amino acid sequence of the light chain of antibody 07-028

<400> 40
 Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
 1 5 10 15
 Glu Arg Ala Ser Leu Ser Cys Arg Ser Arg Ser Leu Val His Arg
 20 25 30
 Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Lys Leu Leu Ile His Lys Val Asn Asn Arg Phe Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Ser Gln Ser
 85 90 95
 Thr His Val Pro Pro Leu Ser Phe Gly Gln Gly Thr Lys Leu Glu Leu
 100 105 110
 Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 115 120 125
 Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 130 135 140
 Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 145 150 155 160
 Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 165 170 175
 Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 180 185 190
 Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 195 200 205
 Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215 220

<210> 41
 <211> 220
 <212> PRT
 <213> Artificial sequence

<220>
 <223> amino acid sequence of the light chain of antibodies 07-041,
 10-007, 10-008, 10-009

<400> 41
 Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
 1 5 10 15
 Glu Arg Ala Ser Leu Ser Cys Arg Ser Ser Gln Asn Leu Val His Arg
 20 25 30

```

Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
   35           40           45
Pro Lys Leu Leu Ile His Lys Val Asn Asn Arg Phe Ser Gly Val Pro
   50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
   65           70           75           80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Gly Gln Ser
           85           90           95
Thr His Val Pro Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
   100           105           110
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
   115           120           125
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
   130           135           140
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
   145           150           155           160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
           165           170           175
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
           180           185           190
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
           195           200           205
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
   210           215           220

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<210> 42

<211> 30

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence FR1 (Kabat) of the heavy chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
10-002, 10-003, 10-007, 10-008, 10-009

<400> 42

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1           5           10           15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr
           20           25           30

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<210> 43

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence FR2 (Kabat) of the heavy chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
10-002, 10-003, 10-007, 10-008, 10-009

<400> 43

Trp Val Arg Gln Asn Ile Gly Gln Gly Leu Glu Trp Met Gly
 1 5 10

<210> 44

<211> 32

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence FR3 (Kabat) of the heavy chain variable domain
 of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
 10-002, 10-003, 10-007, 10-008, 10-009

<400> 44

Arg Val Thr Leu Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr Met Glu
 1 5 10 15
 Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Val Ser
 20 25 30

<210> 45

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence FR4 (Kabat) of the heavy chain variable domain
 of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
 10-002, 10-003, 10-007, 10-008, 10-009

<400> 45

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 1 5 10

<210> 46

<211> 23

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence FR1 (Kabat) of the light chain variable domain
 of antibodies 07-006, 07-15, 007-16, 07-028, 07-031, 07-041, 10-001,
 10-002, 10-003, 10-007, 10-008, 10-009

<400> 46

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
 1 5 10 15
 Glu Arg Ala Ser Leu Ser Cys

20

<210> 47
 <211> 15
 <212> PRT
 <213> Artificial sequence

<220>
 <223> amino acid sequence FR2 (Kabat) of the light chain variable domain
 of antibodies 07-006, 07-016, 07-028, 07-041, 10-007, 10-008, 10-009

<400> 47
 Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile His
 1 5 10 15

<210> 48
 <211> 15
 <212> PRT
 <213> Artificial sequence

<220>
 <223> amino acid sequence FR2 (Kabat) of the light chain variable domain
 of antibodies 07-015, 07-031, 10-001, 10-002, 10-003

<400> 48
 Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile His
 1 5 10 15

<210> 49
 <211> 32
 <212> PRT
 <213> Artificial sequence

<220>
 <223> amino acid sequence FR3 (Kabat) of the light chain variable domain
 of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
 10-002, 10-003, 10-007, 10-008, 10-009

<400> 49
 Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1 5 10 15
 Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys
 20 25 30

<210> 50
 <211> 10
 <212> PRT
 <213> Artificial sequence

<220>

<223> amino acid sequence FR4 (Kabat) of the light chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
10-002, 10-003, 10-007, 10-008, 10-009

<400> 50

Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
1 5 10

<210> 51

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR1 (Chothia) of the heavy chain variable domain
of antibodies 07-006, 07-031, 07-041, 10-001, 10-002, 10-003, 10-007,
10-008, 10-009

<400> 51

Gly Ser Ser Phe Thr Gly Lys
1 5

<210> 52

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR1 (Chothia) of the heavy chain variable domain
of antibodies 07-015, 07-016, 07-028

<400> 52

Gly Ser Ser Phe Thr Gly His
1 5

<210> 53

<211> 6

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR2 (Chothia) of the heavy chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
10-002, 10-003, 10-007, 10-008, 10-009

<400> 53

Asp Pro Phe Tyr Gly Gly

1 5

<210> 54
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR3 (Chothia) of the heavy chain variable domain
of antibodies n 07-031, 10-001, 10-002, 10-003

<400> 54
Gly Met Ile Tyr
1

<210> 55
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR3 (Chothia) of the heavy chain variable domain
of antibodies 07-041, 10-007, 10-008, 10-009

<400> 55
Gly Met Phe Tyr
1

<210> 56
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR3 (Chothia) of the heavy chain variable domain
of antibody 07-006

<400> 56
Gly Met Tyr Tyr
1

<210> 57
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR3 (Chothia) of the heavy chain variable domain
of antibodies 07-015, 07-016, 07-028

<400> 57

Gly Met Leu Tyr

1

<210> 58

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR1 (Chothia) of the light chain variable domain of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 10-001, 10-002, 10-003

<400> 58

Arg Ser Leu Val His Arg Asn Gly Asn Thr Tyr Leu His

1

5

10

<210> 59

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR1 (Chothia) of the light chain variable domain of antibodies 07-041, 10-007, 10-008, 10-009

<400> 59

Gln Asn Leu Val His Arg Asn Gly Asn Thr Tyr Leu His

1

5

10

<210> 60

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR2 (Chothia) of the light chain variable domain of antibodies 07-006, 07-015, 07-016, 07-031, 10-001, 10-002, 10-003

<400> 60

Lys Val Ser Asn Arg Phe Gly

1

5

<210> 61

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR2 (Chothia) of the light chain variable domain of antibodies 07-028, 07-041, 10-007, 10-008, 10-009

<400> 61

Lys Val Asn Asn Arg Phe Ser
1 5

<210> 62

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR3 (Chothia) of the light chain variable domain of antibodies 07-006, 07-015, 07-016, 07-031, 07-041, 10-001, 10-002, 10-003, 10-007, 10-008, 10-009

<400> 62

Gly Gln Ser Thr His Val Pro Pro Leu Thr
1 5 10

<210> 63

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR3 (Chothia) of the light chain variable domain of antibody 07-028

<400> 63

Ser Gln Ser Thr His Val Pro Pro Leu Ser
1 5 10

<210> 64

<211> 8

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR1 (IMGT) of the heavy chain variable domain of antibodies 07-006, 07-031, 07-041, 10-001, 10-002, 10-003, 10-007, 10-008, 10-009

<400> 64

Gly Ser Ser Phe Thr Gly Lys Asn
1 5

<210> 65
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR1 (IMGT) of the heavy chain variable domain
of antibodies 07-015, 07-016, 07-028

<400> 65
Gly Ser Ser Phe Thr Gly His Asn
1 5

<210> 66
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR2 (IMGT) of the heavy chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 07-041, 10-001,
10-002, 10-003, 10-007, 10-008, 10-009

<400> 66
Ile Asp Pro Phe Tyr Gly Gly Thr
1 5

<210> 67
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR3 (IMGT) of the heavy chain variable domain
of antibodies 07-031, 10-001, 10-002, 10-003

<400> 67
Val Ser Gly Met Ile Tyr
1 5

<210> 68
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> amino acid sequence CDR3 (IMGT) of the heavy chain variable domain
of antibodies 07-041, 10-007, 10-008, 10-009

<400> 68

Val Ser Gly Met Phe Tyr
1 5

<210> 69

<211> 6

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR3 (IMGT) of the heavy chain variable domain
of antibody 07-006

<400> 69

Val Ser Gly Met Tyr Tyr
1 5

<210> 70

<211> 6

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR3 (IMGT) of the heavy chain variable domain
of antibody 07-015, 07-016, 07-028

<400> 70

Val Ser Gly Met Leu Tyr
1 5

<210> 71

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR1 (IMGT) of the light chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-028, 07-031, 10-001, 10-002,
10-003

<400> 71

Arg Ser Leu Val His Arg Asn Gly Asn Thr Tyr
1 5 10

<210> 72

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR1 (IMGT) of the light chain variable domain
of antibodies 07-041, 10-007, 10-008, 10-009

<400> 72

Gln Asn Leu Val His Arg Asn Gly Asn Thr Tyr
1 5 10

<210> 73

<211> 3

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR2 (IMGT) of the light chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-031, 10-001, 10-002, 10-003

<400> 73

Lys Val Ser
1

<210> 74

<211> 3

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR2 (IMGT) of the light chain variable domain
of antibodies 07-028, 07-041, 10-007, 10-008, 10-009

<400> 74

Lys Val Asn
1

<210> 75

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR3 (IMGT) of the light chain variable domain
of antibodies 07-006, 07-015, 07-016, 07-31, 07-041,
10-001, 10-002, 10-003, 10-007, 10-008, 10-009

<400> 75

Gly Gln Ser Thr His Val Pro Pro Leu Thr
1 5 10

<210> 76

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> amino acid sequence CDR2 (IMGT) of the light chain variable domain of antibody 07-028

<400> 76

Ser	Gln	Ser	Thr	His	Val	Pro	Pro	Leu	Ser
1			5					10	

<210> 77

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-006

<400> 77

caggtacaac	tcgtacaatc	tggggccgaa	gtgaagaaac	caggcgcttc	cgtaaagggtg	60
tcctgcaaag	ccagcgggag	ctcgttcaca	gggaagaaca	tgaattgggt	ccgacagaac	120
attggacagg	gattagaatg	gatgggcgct	atagatccct	tctatggagg	cacatcctac	180
aaccagaaat	tcaagggccg	cgttaccctc	acagtcgata	agtctatctc	taccgcatac	240
atggaactgt	cccgcttacg	gtcggatgat	acagcagtg	actattgtgt	tagtgggatg	300
tactactggg	gtcagggcac	tctggtgaca	gtgtcgagt			339

<210> 78

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-006

<400> 78

gatatcgtga	tgacacaaac	cccattgagc	ctgtccgtga	cgccaggaga	gcgcgctagt	60
ttaagttgtc	ggagttcaag	gtccctgggt	caccggaatg	gcaataccta	cttgactg	120
tacttgcaga	aacctgggca	gtcgccaaag	ctcctcatcc	acaaagtatc	caatagattc	180

ggcggcgtgc cagatagatt ctctggctct ggttctggta cagatTTTtac tctgaagatt 240
 tctcgggtgg aggccgagga cgtaggggtg tacttctgcg gccaaagtac acacgttcca 300
 cccctaacct ttggacaagg gaccaagtta gaactgaaa 339

<210> 79
 <211> 339
 <212> DNA
 <213> Artificial sequence

<220>
 <223> Nucleic acid that encodes the amino acid sequence of the
 heavy chain variable domain of the antibody 07-015

<400> 79
 caggtacaac tcgtacaatc tggggccgaa gtgaagaaac caggcgcttc cgtaaggtg 60
 tcctgcaaag ccagcgggag ctcgttcaca gggcacaaca tgaattgggt ccgacagaac 120
 attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac 180
 aaccagaaat tcaagggccg cgttacccctc acagtcgata agtctatctc taccgcatac 240
 atggaactgt cccgcttacg gtcggatgat acagcagtgt actatttgtt tagtgggatg 300
 ctgtactggg gtcagggcac tctggtgaca gtgtcgagt 339

<210> 80
 <211> 339
 <212> DNA
 <213> Artificial sequence

<220>
 <223> Nucleic acid that encodes the amino acid sequence of the
 light chain variable domain of the antibody 07-015

<400> 80
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 ttaagttgtc ggagttcaag gtccttggtt caccggaatg gcaataccta cttgcactgg 120
 tacttgcaaga aacctgggca gtcgccacaa ctctcatcc acaaagtatc caatagattc 180
 ggcggcgtgc cagatagatt ctctggctct ggttctggta cagatTTTtac tctgaagatt 240
 tctcgggtgg aggccgagga cgtaggggtg tacttctgcg gccaaagtac acacgttcca 300

cccctaacct ttggacaagg gaccaagtta gaactgaaa

339

<210> 81

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-016

<400> 81

caggtacaac tcgtacaatc tggggccgaa gtgaagaaac caggcgcttc cgtaaagggtg 60

tcctgcaaag ccagcgggag ctctgtcaca gggcacaaca tgaattgggt ccgacagaac 120

attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac 180

aaccagaaat tcaagggccg cgttaccctc acagtcgata agtctatctc taccgcatac 240

atggaactgt cccgcttacg gtcggatgat acagcagtgt actattgtgt tagtgggatg 300

ctgtactggg gtcagggcac tctggtgaca gtgtcgagt 339

<210> 82

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-016

<400> 82

gatatcgtga tgacacaaac ccattgagc ctgtccgtga cgccaggaga gcgcgctagt 60

ttaagttgtc ggagttcaag gtccctgggt caccggaatg gcaataccta cttgcactgg 120

tacttgcaga aacctgggca gtcgcaaag ctctcatcc acaaagtatc caatagattc 180

ggcggcgtgc cagatagatt ctctggctct ggttctggta cagatcttac tctgaagatt 240

tctcgggtgg aggccgagga cgtaggggtg tacttctgcg gccaaagtac acacgttcca 300

cccctaacct ttggacaagg gaccaagtta gaactgaaa 339

<210> 83

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-028

<400> 83

caggtacaac tcgtacaatc tggggccgaa gtgaagaaac caggcgcttc cgtaaagggtg	60
tcctgcaaag ccagcgggag ctcgttcaca gggcacaaca tgaattgggt ccgacagaac	120
attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac	180
aaccagaaat tcaagggccg cgttaccctc acagtcgata agtctatctc taccgcatac	240
atggaactgt cccgcttacg gtcggatgat acagcagtgt actattgtgt tagtgggatg	300
ctgtactggg gtcagggcac tctggtgaca gtgtcgagt	339

<210> 84

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-028

<400> 84

gatatcgtga tgacacaaac ccattgagc ctgtccgtga cgccaggaga gcgcgctagt	60
ttaagttgtc ggagttcaag gtccctgggt caccggaatg gcaataccta cttgcactgg	120
tacttgcaga aacctgggca gtcgccaaag ctctcatcc acaaagtaaa caatagattc	180
tccggcgtgc cagatagatt ctctggctct gggtctggta cagatcttac tctgaagatt	240
tctcgggtgg aggccgagga cgtaggggtg tacttctgct ctcaaagtac acacgttcca	300
cccctatctt ttggacaagg gaccaagtta gaactgaaa	339

<210> 85

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-031

<400> 85
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 tcctgcaaag ccagcgggag ctctgttcaca gggaagaaca tgaattgggt ccgacagaac 120
 attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac 180
 aaccagaaat tcaagggccg cgttaccctc acagtcgata agtctatctc taccgcatac 240
 atggaactgt cccgcttacg gtcggatgat acagcagtgt actattgtgt tagtgggatg 300
 atctactggg gtcagggcac tctggtgaca gtgtcgagt 339

<210> 86
 <211> 339
 <212> DNA
 <213> Artificial sequence

<220>
 <223> Nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 07-031

<400> 86
 gatatcgtga tgacacaaac cccattgagc ctgtccgtga cgccaggaga gcgcgctagt 60
 ttaagttgtc ggagttcaag gtccctgggt caccggaatg gcaataccta cttgcactgg 120
 tacttgcaga aacctgggca gtcgccacaa ctccatcatcc acaaagtatc caatagattc 180
 ggccggcgtgc cagatagatt ctctggctct ggttctggta cagatcttac tctgaagatt 240
 tctcgggtgg aggccgagga cgtaggggtg tacttctgcg gccaaagtac acacgttcca 300
 cccctaacct ttggacaagg gaccaagtta gaactgaaa 339

<210> 87
 <211> 339
 <212> DNA
 <213> Artificial sequence

<220>
 <223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 07-041

<400> 87
 caggtacaac tcgtacaatc tggggccgaa gtgaagaaac caggcgcttc cgtaaagggtg 60

tcctgcaaag ccagcgggag ctctgtcaca gggaagaaca tgaattgggt ccgacagaac 120
attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac 180
aaccagaaat tcaagggccg cgttaccctc acagtcgata agtctatctc taccgcatac 240
atggaactgt cccgcttacg gtcggatgat acagcagtgt actattgtgt tagtgggatg 300
ttctactggg gtcagggcac tctggtgaca gtgtcgagt 339

<210> 88

<211> 339

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the
light chain variable domain of the antibody 07-041

<400> 88

gatatcgtga tgacacaaac cccattgagc ctgtccgtga cgccaggaga gcgcgctagt 60
ttaagttgtc ggagttcaca gaacctggtt caccggaatg gcaataccta cttgcactgg 120
tacttgcaga aacctgggca gtcgcaaag ctctcatcc acaaagtaaa caatagattc 180
tccggcgtgc cagatagatt ctctggctct ggttcttgta cagattttac tctgaagatt 240
tctcgggtgg aggccgagga cgtaggggtg tacttctgcg gccaaagtac acacgttcca 300
cccctaacct ttggacaagg gaccaagtta gaactgaaa 339

<210> 89

<211> 1329

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the
heavy chain variable domain of the antibody 10-001

<400> 89

caggtacaac tcgtacaatc tggggccgaa gtgaagaaac caggcgcttc cgtaaagggtg 60
tcctgcaaag ccagcgggag ctctgtcaca gggaagaaca tgaattgggt ccgacagaac 120
attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac 180

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aaccagaaat tcaagggccg cgttacccctc acagtcgata agtctatctc taccgcatac      240
atggaactgt cccgcttacg gtcggatgat acagcagtgt actatttgtgt tagtgggatg      300
atctactggg gtcagggcac tctggtgaca gtgtcgagtg ctagcaccaa gggcccatcg      360
gtcttcccc tggcacccctc ctccaagagc acctctgggg gcacagcggc cctgggctgc      420
ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgccctgacc      480
agcggcgtgc acaccttccc ggctgtccta cagtcctcag gactctactc cctcagcagc      540
gtggtgaccg tggcctccag cagcttgggc acccagacct acatctgcaa cgtgaatcac      600
aagcccagca acaccaaggt ggacaagaga gttgagccca aatcttgtga caaaactcac      660
acatgcccac cgtgcccagc acctgaactc ctggggggac cgtcagtctt cctcttcccc      720
ccaaaacca aggacaccct ctacatcacc cgggagcctg aggtcacatg cgtggtggtg      780
gacgtgagcc acgaagacc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg      840
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc      900
gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc      960
aacaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga     1020
gaaccacagg tgtacaccct gccccatcc cgggacgagc tgaccaagaa ccaggtcagc     1080
ctgacctgcc tgggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat     1140
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc     1200
ttctctata gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca     1260
tgctccgtga tgcattgaggc tctgcacaac cactacacgc agaaaagcct ctccctgtcc     1320
ccgggtaaa                                     1329

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<210> 90

<211> 660

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the
light chain variable domain of the antibody 10-001

<400> 90

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gatatcgtga tgacacaaac ccattgagc ctgtccgtga cgccaggaga gcgcgctagt      60

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ttaagttgtc ggagttcaag gtccctgggt caccggaatg gcaataccta cttgcactgg 120
 tacttgacaga aacctgggca gtcgccacaa ctccatcatcc acaaagtatc caatagattc 180
 ggccggcgtgc cagatagatt ctctggctct ggttctggta cagattttac tctgaagatt 240
 tctcgggtgg aggccgagga cgtaggggtg tacttctgcg gccaaagtac acacgttcca 300
 cccctaacct ttggacaagg gaccaagtta gaactgaaac gtacgggtggc tgcaccatct 360
 gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420
 ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaagggtga taacgccctc 480
 caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540
 ctcagcagca ccctgacgct gagcaaaaga gactacgaga aacacaaagt ctacgcctgc 600
 gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

<210> 91

<211> 1329

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 10-002

<400> 91

caggtacaac tcgtacaatc tggggccgaa gtgaagaaac caggcgcttc cgtaaggtg 60
 tcctgcaaag ccagcgggag ctctgtcaca gggaagaaca tgaattgggt ccgacagaac 120
 attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac 180
 aaccagaaat tcaagggccg cgttaccctc acagtcgata agtctatctc taccgcatac 240
 atggaactgt cccgcttacg gtcggatgat acagcagtgt actatttgtt tagtgggatg 300
 atctactggg gtcagggcac tctggtgaca gtgtcgagtg ctagcaccaa gggcccatcg 360
 gtcttcccc tggcaccctc ctccaagagc acctctgggg gcacagcggc cctgggctgc 420
 ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgccctgacc 480
 agcggcgtgc acaccttccc ggctgtccta cagtcctcag gactctactc cctcagcagc 540
 gtggtgaccg tgccctccag cagcttgggc acccagacct acatctgcaa cgtgaatcac 600

aagcccagca acaccaaggt ggacaagaga gttgagccca aatcttgtga caaaactcac 660
acatgcccac cgtgcccagc acctgaactc ctggggggac cgtcagtctt cctcttcccc 720
ccaaaacca aggacaccct ctacatcacc cggggagcctg aggtcacatg cgtggtggtg 780
gacgtgagcc acgaagaccc tgagggtcaag ttcaactggt acgtggacgg cgtggaggtg 840
cataatgcc aagacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 900
gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg cgcggtctcc 960
aacaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1020
gaaccacagg tgtacaccct gccccatcc cgggacgagc tgaccaagaa ccaggtcagc 1080
ctgacctgcc tgggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat 1140
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ttcctctata gcaagctcac cgtggacaag agcagggtggc agcaggggaa cgtcttctca 1260
tgctccgtga tgcattgaggc tctgcacaac cactacacgc agaaaagcct ctccctgtcc 1320
ccgggtaaa 1329

<210> 92

<211> 660

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the light chain variable domain of the antibody 10-002

<400> 92

gatatcgtga tgacacaaac ccattgagc ctgtccgtga cgccaggaga gcgcgctagt 60
ttaagttgtc ggagttcaag gtccctgggt caccggaatg gcaataccta cttgcactgg 120
tacttgaga aacctgggca gtcgccacaa ctctcatcc acaaagtatc caatagattc 180
ggcggcgtgc cagatagatt ctctggctct ggttctggta cagattttac tctgaagatt 240
tctcgggtgg aggccgagga cgtaggggtg tacttctgcg gccaaagtac acacgttcca 300
cccctaacct ttggacaagg gaccaagtta gaactgaaac gtacgggtggc tgcacatct 360
gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420
ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaagggtgga taacgccctc 480

caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540
 ctacgcagca ccctgacgct gagcaaagca gactacgaga aacacaaaagt ctacgcctgc 600
 gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

<210> 93

<211> 1329

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 10-003

<400> 93

caggtacaac tcgtacaatc tggggccgaa gtgaagaaac caggcgcttc cgtaaggtg 60
 tcctgcaaag ccagcgggag ctctgtcaca gggaagaaca tgaattgggt ccgacagaac 120
 attggacagg gattagaatg gatgggcgct atagatccct tctatggagg cacatcctac 180
 aaccagaaat tcaagggccg cgttaccctc acagtcgata agtctatctc taccgcatac 240
 atggaactgt cccgcttacg gtcggatgat acagcagtgt actatttgtt tagtgggatg 300
 atctactggg gtcagggcac tctggtgaca gtgtcgagtg ctagcaccaa gggcccatcg 360
 gtcttcccc tggcacctc ctccaagagc acctctgggg gcacagcggc cctgggctgc 420
 ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgccctgacc 480
 agcggcgtgc acaccttccc ggctgtccta cagtccctag gactctactc cctcagcagc 540
 gtggtgaccg tgccctccag cagcttgggc acccagacct acatctgcaa cgtgaatcac 600
 aagcccagca acaccaagggt ggacaagaga gttgagccca aatcttgtga caaaactcac 660
 acatgcccac cgtgcccagc acctgaactc ctggggggac cgtcagtcct cctcttcccc 720
 ccaaaacca aggacaccct catgatctcc cggaccctg aggtcacatg cgtggtggtg 780
 gacgtgagcc acgaagacct tgaggtaag ttcaactggt acgtggacgg cgtggaggtg 840
 cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 900
 gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg cgcggtctcc 960
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 ttctctata gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1260
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<210> 94

<211> 660

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the
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<400> 94

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<210> 95

<211> 1329

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 10-007

<400> 95

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<210> 96

<211> 660
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<220>
 <223> Nucleic acid that encodes the amino acid sequence of the
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<210> 97
 <211> 1329
 <212> DNA
 <213> Artificial sequence

<220>
 <223> Nucleic acid that encodes the amino acid sequence of the
 heavy chain variable domain of the antibody 10-008

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<210> 98

<211> 660

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the
light chain variable domain of the antibody 10-008

<400> 98

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<210> 99

<211> 1329

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of the antibody 10-009

<400> 99

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<210> 100

<211> 660

<212> DNA

<213> Artificial sequence

<220>

<223> Nucleic acid that encodes the amino acid sequence of the
light chain variable domain of the antibody 10-009

<400> 100

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gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

Claims

1. An isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to GD2 (ganglioside GD2), comprising:

(a) a heavy chain variable domain comprising:

CDR1 with an amino acid sequence selected from the group of SEQ ID NO: 1 or SEQ ID NO: 2,

CDR2 with the amino acid sequence of SEQ ID NO: 3,

CDR3 with an amino acid sequence selected from the group of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7; and

(b) a light chain variable domain comprising:

(i) CDR1 with an amino acid sequence selected from the group of SEQ ID NO: 8 or SEQ ID NO: 9,

(ii) CDR2 with an amino acid sequence selected from the group of SEQ ID NO: 10 or SEQ ID NO: 11,

(iii) CDR3 with an amino acid sequence selected from the group of SEQ ID NO: 12 or SEQ ID NO: 13.

2. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises:

(i) FR1 with the amino acid sequence of SEQ ID NO: 42,

(ii) FR2 with the amino acid sequence of SEQ ID NO: 43,

(iii) FR3 with the amino acid sequence of SEQ ID NO: 44 and

(iv) FR4 with the amino acid sequence of SEQ ID NO: 45.

3. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises:

(i) FR1 with the amino acid sequence of SEQ ID NO: 46,

(ii) FR2 with an amino acid sequence selected from the group of SEQ ID NO: 47 or SEQ ID NO: 48,

(iii) FR3 with the amino acid sequence of SEQ ID NO: 49 and

(iv) FR4 with the amino acid sequence of SEQ ID NO: 50.

4. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein

a) the heavy chain variable domain comprises:

(i) FR1 with the amino acid sequence of SEQ ID NO: 42,

(ii) FR2 with the amino acid sequence of SEQ ID NO: 43,

(iii) FR3 with the amino acid sequence of SEQ ID NO: 44 and

- (iv) FR4 with the amino acid sequence of SEQ ID NO: 45, and, wherein
 - b) the light chain variable domain comprises:
 - (i) FR1 with the amino acid sequence of SEQ ID NO: 46,
 - (ii) FR2 with an amino acid sequence selected from the group of SEQ ID NO: 47 or SEQ ID NO: 48,
 - (iii) FR3 with the amino acid sequence of SEQ ID NO: 49 and
 - (iv) FR4 with the amino acid sequence of SEQ ID NO: 50.
- 5. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises:
 - (i) CDR1 with the amino acid sequence of SEQ ID NO: 2,
CDR2 with the amino acid sequence of SEQ ID NO: 3,
CDR3 with the amino acid sequence of SEQ ID NO: 5; or
 - (ii) CDR1 with the amino acid sequence of SEQ ID NO: 2,
CDR2 with the amino acid sequence of SEQ ID NO: 3,
CDR3 with the amino acid sequence of SEQ ID NO: 4.
- 6. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises:
 - (i) CDR1 with the amino acid sequence of SEQ ID NO: 9,
CDR2 with the amino acid sequence of SEQ ID NO: 11,
CDR3 with the amino acid sequence of SEQ ID NO: 12; or
 - (ii) CDR1 with the amino acid sequence of SEQ ID NO: 8,
CDR2 with the amino acid sequence of SEQ ID NO: 10,
CDR3 with the amino acid sequence of SEQ ID NO: 12.
- 7. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17.
- 8. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises an amino acid sequence that is selected from the group of SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17.
- 9. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21.
- 10. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises an amino acid sequence that is

selected from the group of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 or SEQ ID NO: 21.

11. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein:

(a) the heavy chain variable domain comprises an amino acid sequence that has at least 98 % identity to the amino acid sequence of SEQ ID NO: 17;

(b) the light chain variable domain comprises an amino acid sequence that has at least 96 % identity to the amino acid sequence of SEQ ID NO: 21.

12. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein:

(a) the heavy chain variable domain comprises an amino acid sequence that is selected from the group of SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

(b) the light chain variable domain comprises an amino acid sequence that is selected from the group of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20 or SEQ ID NO: 21.

13. The isolated monoclonal antibody or antigen-binding fragment thereof according to claim 14, wherein:

(i) (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 16; and

(b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 19; or

(ii) (a) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 17;

(b) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 21.

14. The isolated monoclonal antibody according to any of claims 1-13, wherein the antibody that specifically binds to GD2 is a full-length IgG antibody.

15. The isolated monoclonal antibody according to claim 14, wherein the full-length IgG antibody belongs to the human IgG1, IgG2, IgG3 or IgG4 isotype.

16. The isolated monoclonal antibody according to claim 1, wherein the antibody comprises YTE mutations (M252Y, S254T, T256E) and/or K322A mutation in the Fc fragment as compared to the natural sequence of the Fc fragment.

17. The isolated monoclonal antibody according to claim 1, including a heavy chain comprising an amino acid sequence selected from the group of SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID

NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 or SEQ ID NO: 37.

18. The isolated monoclonal antibody according to claim 1, including a light chain comprising an amino acid sequence selected from the group of SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

19. The isolated monoclonal antibody according to claim 1, including:

(a) a heavy chain comprising an amino acid sequence selected from the group of SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36 or SEQ ID NO: 37, and

(b) a light chain comprising an amino acid sequence selected from the group of SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

20. The isolated monoclonal antibody according to claim 1, including:

(i) (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 32, and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 39; or

(ii) (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 33, and

(b) a light chain comprising the amino acid sequence of SEQ ID NO: 41.

21. An isolated nucleic acid that encodes the antibody or antigen-binding fragment thereof according to any of claims 1-20.

22. The isolated nucleic acid according to claim 21, wherein the nucleic acid is DNA.

23. An expression vector comprising the nucleic acid according to any of claims 21-22.

24. A method for obtaining a host cell to obtain the antibody or antigen-binding fragment thereof according to any of claims 1-20, including cell transformation by the expression vector according to claim 23.

25. A host cell for obtaining the antibody or antigen-binding fragment thereof according to any of claims 1-20, comprising the nucleic acid according to any of claims 21-22.

26. A method for obtaining the antibody or antigen-binding fragment thereof according to any of claims 1-20, comprising culturing the host cell according to claim 25 in a growth medium under conditions sufficient to produce said antibody, if necessary, followed by isolation and purification of the resulting antibody.

27. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any of claims 1-20 in combination with one or more pharmaceutically acceptable excipients.

28. The pharmaceutical composition according to claim 27 for treating a disease or disorder mediated by GD2.

29. The pharmaceutical composition according to claim 28, wherein the disease or disorder mediated by GD2 is selected from the group of brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

30. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any of claims 1-20 and at least one other therapeutically active compound.

31. The pharmaceutical composition according to claim 30 for treating a disease or disorder mediated by GD2.

32. The pharmaceutical composition according to claim 31, wherein the disease or disorder mediated by GD2 is selected from the group of brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

33. The pharmaceutical composition according to claim 30, wherein the other therapeutically active compound is an antibody, chemotherapeutic agent, hormone therapy agent or an immune checkpoint inhibitor, or the other therapeutically active compound is selected from the group of IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

34. The pharmaceutical composition according to claim 33, wherein the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor or CTLA-4 inhibitor.

35. The pharmaceutical composition according to claim 34, wherein the PD-1 inhibitor is an antibody that specifically binds to PD-1.

36. The pharmaceutical composition according to claim 35, wherein the antibody that specifically binds to PD-1 is selected from the group of prolgolimab, pembrolizumab, nivolumab.

37. The pharmaceutical composition according to claim 34, wherein the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

38. The pharmaceutical composition according to claim 37, wherein the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

39. The pharmaceutical composition according to claim 34, wherein the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

40. The pharmaceutical composition according to claim 39, wherein the antibody that specifically binds to PD-L1 is selected from the group of durvalumab, avelumab, atezolizumab, manelimab.

41. A method for inhibiting the biological activity of GD2 in a subject in need of such inhibition, including administering an effective amount of the antibody or antigen-binding fragment thereof according to any of claims 1-20.

42. A method for treating a disease or disorder mediated by GD2, including administering to a subject in need of such treatment the antibody or antigen-binding fragment thereof according to any of claims 1-20 or the pharmaceutical composition according to any of claims 27 or 30 in a therapeutically effective amount.

43. The method according to claim 42, wherein the method additionally includes:

- a) administration of at least one other therapeutically active compound,
- b) radiotherapy,
- c) hematopoietic stem cell transplantation,
- d) surgical treatment and, if necessary, adjuvant therapy, or
- e) any combination of the above a) to d).

44. The method according to any of claims 42-43, wherein the disease or disorder mediated by GD2 is selected from the group of brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

45. The method according to claim 43, wherein the other therapeutically active compound is an antibody, chemotherapeutic agent, hormone therapy agent, or an immune checkpoint inhibitor; or

the other therapeutically active compound is selected from the group of IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

46. The method according to claim 45, wherein the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor or CTLA-4 inhibitor.

47. The method according to claim 46, wherein the PD-1 inhibitor is an antibody that specifically binds to PD-1.

48. The method according to claim 47, wherein the antibody that specifically binds to PD-1 is selected from the group of prolgolimab, pembrolizumab, nivolumab.

49. The method according to claim 46, wherein the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

50. The method according to claim 49, wherein the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

51. The method according to claim 46, wherein the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

52. The method according to claim 51, wherein the antibody that specifically binds to PD-L1 is selected from the group of durvalumab, avelumab, atezolizumab, manelimab.

53. Use of the antibody or antigen-binding fragment thereof according to any of claims 1-30 or the pharmaceutical composition according to any of claims 27 or 30 for treating a disease or disorder mediated by GD2 in a subject in need of such treatment.

54. The use according to claim 53, wherein the use of the antibody or antigen-binding fragment thereof according to any of claims 1-30 or the pharmaceutical composition according to any of claims 27 or 30 and at least one of the group of:

- a) other therapeutically active compound,
 - b) radiotherapy,
 - c) hematopoietic stem cell transplantation or
 - d) surgical treatment and, if necessary, adjuvant therapy,
- for treating a disease or disorder mediated by GD2.

55. The use according to claim 53, wherein the disease or disorder mediated by GD2 is selected from the group of brain tumor, neuroblastoma, glioblastoma, medulloblastoma, retinoblastoma, astrocytoma, melanoma, B-cell lymphoma, small cell lung cancer, renal carcinoma, desmoplastic small round cell fibroma, osteosarcoma, Ewing's sarcoma, breast cancer, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, or soft tissue sarcoma.

56. The use according to claim 54 wherein the other therapeutically active compound is an immune checkpoint inhibitor or

the other therapeutically active compound is selected from the group of IL-2, GM-CSF, isotretinoin, one or more other cytokines, or any combination of therapeutically active compounds from this group.

57. The use according to claim 56, wherein the immune checkpoint inhibitor is selected from a PD-1 inhibitor, PD-L1 inhibitor or CTLA-4 inhibitor.

58. The use according to claim 57, wherein the PD-1 inhibitor is an antibody that specifically binds to PD-1.

59. The use according to claim 58, wherein the antibody that specifically binds to PD-1 is selected from the group of prolgolimab, pembrolizumab, nivolumab.

60. The use according to claim 57, wherein the CTLA-4 inhibitor is an antibody that specifically binds to CTLA-4.

61. The use according to claim 60, wherein the antibody that specifically binds to CTLA-4 is ipilimumab or nurulimab.

62. The use according to claim 57, wherein the PD-L1 inhibitor is an antibody that specifically binds to PD-L1.

63. The use according to claim 62, wherein the antibody that specifically binds to PD-L1 and is selected from the group of durvalumab, avelumab, atezolizumab, manelimab.