

SUMMARY

This invention relates, *inter cilia*, to antibodies that bind FcRn, and methods of identifying and using such antibodies. Thus, in one aspect, the present invention refers to isolated antibody comprising a heavy chain (HC) immunoglobulin variable domain and a light chain (LC) immunoglobulin variable domain sequence, wherein the HC and LC immunoglobulin variable domain sequences form an antigen binding site that binds to human FcRn; and, wherein the antibody comprises: (i) a HC that comprises a HC CDR1 comprising an amino acid sequence RSWMN (SEQ ID NO: 11), a HC CDR2 comprising an amino acid sequence RIHPGDGDTNYNGKFKG (SEQ ID NO: 12), and a HC CDR3 comprising an amino acid sequence EGSPYFDY (SEQ ID NO: 13); and a LC that comprises a LC CDR1 comprising an amino acid sequence SASSSISSNYLH (SEQ ID NO: 8), a LC CDR2 comprising an amino acid sequence RTSNLA (SEQ ID NO: 9), and a LC CDR3 comprising an amino acid sequence QQGSNIPLT (SEQ ID NO: 10); or (ii) a HC that comprises a HC CDR1 comprising an amino acid sequence DYAMH (SEQ ID NO: 17), a HC CDR2 comprising an amino acid sequence VITNYYGDASYNQKFKG (SEQ ID NO: 18), and a HC CDR3 comprising an amino acid sequence GGYDGYVDFDY (SEQ ID NO: 19); and a LC that comprises a LC CDR1 comprising an amino acid sequence KASQDINNYIA (SEQ ID NO: 14), a LC CDR2 comprising an amino acid sequence YTSTLQP (SEQ ID NO: 15), and a LC CDR3 comprising an amino acid sequence LQYDNLLRT (SEQ ID NO: 16). In another aspect, the present invention refers to an isolated antibody, wherein the antibody binds to an FcRn epitope comprising an amino acid sequence selected from the group consisting of CSAFSFYPPQLRFLRNL (SEQ ID NO: 26), and APGTPAFWVSGWLGPQQYLS (SEQ ID NO: 27). In still another aspect, the present invention refers to a pharmaceutical composition comprising the antibody of the present invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention refers to a method of detecting an FcRn in a sample, the method comprising contacting the sample with the antibody of the present invention; and detecting an interaction between the antibody and the FcRn if present. In one aspect, the present invention refers to the use of the antibody of the present invention in the manufacture of a medicament for use in treating an autoimmune disorder and/or modulating symptoms of an autoimmune disorder.

Also disclosed herein is an isolated antibody comprising a heavy chain (HC) immunoglobulin variable domain sequence and a light chain (LC) immunoglobulin variable domain sequence,

wherein the heavy chain and light chain immunoglobulin variable domain sequences form an antigen binding site that binds to human FcRn; and wherein the antibody includes one or more of the following characteristics:

- (a) a human CDR or human framework region;

(b) the LC immunoglobulin variable domain sequence comprises one or more CDRs that are at least 85% identical to a CDR of a LC variable domain of M0171-A03, M0171-A01, M0159-A07, M0161-B04, M0090-F11 or DX2500;

(c) the HC immunoglobulin variable domain sequence comprises one or more CDRs that are at least 85% identical to a CDR of a HC variable domain of M0171-A03, M0171-A01, M0159-A07, M0161-B04, M0090-F11 or DX2500;

(d) the LC immunoglobulin variable domain sequence is at least 85% identical to a LC variable domain of M0171-A03, M0171-A01, M0159-A07, M0161-B04, M0090-F11 or DX2500;

(e) the HC immunoglobulin variable domain sequence is at least 85% identical to a HC variable domain of M0171-A03, M0171-A01, M0159-A07, M0161-B04 M0090-F11 or DX2500; and

(f) the antibody binds an epitope that overlaps with an epitope bound by M0171-A03, M0171-A01, M0159-A07, M0161-B04, M0090-F11 or DX2500.

In one example the disclosure provides an isolated antibody that is at least 85% identical to an antibody selected from the group consisting of M0171-A03, M0171-A01, M0159-A07, M0161-B04, M0090-F11 and DX2500.

In one example the disclosure provides an isolated antibody selected from the group consisting of M0171-A03, M0171-A01, M0159-A07, M0161-B04, M0090-F11 and DX2504.

In one example the disclosure provides an isolated antibody comprising the CDRs of M0161-B04. In one example the disclosure provides an isolated antibody that is at least 85% identical to M0161-B04. The CDRs of M0161-B04 are represented in Table 17A.

In one example the disclosure provides an isolated antibody comprising the CDRs of M0171-A03. In one example the disclosure provides an isolated antibody that is at least 85% identical to M0171-A03. The CDRs of M0171-A03 are represented in Table 17A.

In one example the disclosure provides an isolated antibody comprising the CDRs of M0171-A01. In one example the disclosure provides an isolated antibody that is at least 85% identical to M0171-A01. The CDRs of M0171-A01 are represented in Table 17A.

In one example the disclosure provides an isolated antibody comprising the CDRs of M0159-A07. In one example the disclosure provides an isolated antibody that is at least 85% identical to M0159-A07. The CDRs of M0159-A07 are represented in Table 17A.

In one example the disclosure provides an isolated antibody comprising the CDRs of M0090-F11. In one example the disclosure provides an isolated antibody that is at least 85% identical to M0090-F11. The CDRs of M0090-F11 are represented in Table 17A.

In one example the disclosure provides an isolated antibody comprising the CDRs of DX-2500. In one example the disclosure provides an isolated antibody that is at least 85% identical to DX-2500. The CDRs of DX-2500 are represented in Table 17A.

In some embodiments of the antibodies provided herein the HC variable domain sequence comprises a variable domain sequence of M0161-B04 and the LC variable domain sequence comprises a variable domain sequence of M0161-B04.

In some embodiments of the antibodies provided herein the HC variable domain sequence comprises a variable domain sequence of M0171-A03 and the LC variable domain sequence comprises a variable domain sequence of M0171-A03.

In some embodiments of the antibodies provided herein the HC variable domain sequence comprises a variable domain sequence of M0171-A01 and the LC variable domain sequence comprises a variable domain sequence of M0171-A01.

In some embodiments of the antibodies provided herein the HC variable domain sequence comprises a variable domain sequence of M0159-A07 and the LC variable domain sequence comprises a variable domain sequence of M0159-A07.

in some embodiments of the antibodies provided herein the HC variable domain sequence comprises a variable domain sequence of M0090-F11 and the LC variable domain sequence comprises a variable domain sequence of M0090-F11.

In some embodiments of the antibodies provided herein the HC variable domain sequence comprises a variable domain sequence of DX2500 and the LC variable domain sequence comprises a variable domain sequence of DX2500.

In some embodiments of the antibodies provided herein the antibody binds to an FcRn epitope bound by M0171-A03, M0171-A01, M0159-A07, M0161-804, M0090-F11 or DX2500.

In some embodiments of the antibodies provided herein the antibody competes with M0171-A03, M0171 AOI, M0159-A07, M0161-B04, M0090-F11 or DX2500 for binding to FcRn.

As used herein M0171-A03 is also referred to as M171-A03 and M00171-A03. As used herein M0171-A01 is also referred to as M171-A01 and M00171-A01. As used herein M0159-A07 is also referred to as M159-A07 and M00159-A07. As used herein M0161-B04 is also referred to as M161-B04, M00161 -B04 and DX-2504. As used herein M0090-F11 is also referred to as M090-F11 and M90-F11.

In one example the disclosure provides an isolated antibody, or a fragment thereof, which binds to human FcRn, wherein the antibody is generated against the heavy chain of human FcRn or a fragment thereof, wherein the antibody functions as a non-competitive inhibitor of IgG binding to human FcRn, and wherein the antibody does not bind 132-microglobulin.

In one example the disclosure provides an isolated antibody, or fragment thereof, that binds to human FcRn, wherein the antibody is generated against the heavy chain of human FcRn or a fragment thereof, wherein the antibody does not bind 132-microglobulin when it is not complexed with FcRn, and wherein the antibody is not produced from a FcRn -/knockout mouse.

In some of the embodiments of the antibodies provided herein the antibody is selected from the group consisting of 3B3.11, 31.1, 4B4.12, and 17D3.

In some of the embodiments of the antibodies provided herein the antibody binds human FcRn at about pH range 5-7.4 with a dissociation constant (K_D) of less than 100 nM.

In some of the embodiments of the antibodies provided herein the antigen binding site specifically binds to human FcRn.

In some of the embodiments of the antibodies provided herein the antibody binds a stable FcRn expressing cell line.

In some of the embodiments of the antibodies provided herein the antibody binds FcRn in endosomes or under endosomal conditions.

In some of the embodiments of the antibodies provided herein the antibody does not release FcRn at pH 7.5.

In some of the embodiments of the antibodies provided herein the antibody causes an amelioration of symptoms associated with an autoimmune disorder when administered to a subject.

In some of the embodiments of the antibodies provided herein the HC and LC variable domain sequences are components of the same polypeptide chain.

In some of the embodiments of the antibodies provided herein the HC and LC variable domain sequences are components of different polypeptide chains.

In some of the embodiments of the antibodies provided herein the antibody is a full-length antibody.

In some of the embodiments of the antibodies provided herein the antibody is a human or humanized antibody or is non-immunogenic in a human.

In some of the embodiments of the antibodies provided herein the antibody comprises a human antibody framework region.

In some of the embodiments of the antibodies provided herein the antibody comprises an Fc domain.

In some of the embodiments of the antibodies provided herein the antibody is a murine antibody.

In some of the embodiments of the antibodies provided herein the antibody is a monoclonal antibody.

In some of the embodiments of the antibodies provided herein the antibody is chimeric or humanized.

In some of the embodiments of the antibodies provided herein the antibody is selected from the group consisting of Fab, F(ab)'₂, Fv and ScFv.

In some of the embodiments of the antibodies provided herein the antibody binding to FcRn is independent of the pH over a pH range of 6.0 to 8.0.

In one example the disclosure provides a pharmaceutical composition comprising the any one of the antibodies provided herein and a pharmaceutically acceptable carrier.

In one example the disclosure provides an isolated nucleic acid comprising a sequence that encodes a polypeptide that includes a sequence at least 80% identical to the sequence of a variable domain of M0171-A03, M0171-A01, M0159-A07 or M0161-B04.

In one example the disclosure provides an isolated nucleic acid comprising a sequence that encodes a polypeptide comprising the first and/or the second immunoglobulin variable domain of the any one of the antibodies provided herein.

In one example the disclosure provides a vector or host cell comprising the nucleic acid sequence provided herein

In one example the disclosure provides a method of detecting an FcRn in a sample, the method comprising: contacting the sample with any one of the antibodies provided herein and detecting an interaction between the antibody and the FcRn if present. In some embodiments the antibody further comprises a detectable label.

In one example the disclosure provides a method of detecting FcRn in a subject, the method comprising: administering any one of the antibodies provided herein that further comprises a detectable label, to a subject; and detecting the label in the subject. In some embodiments detecting comprises imaging the subject.

In one example the disclosure provides a method of modulating an FcRn activity, the method comprising: contacting an FcRn with any one of the antibodies provided herein, thereby modulating the activity of the FcRn. In some embodiments the FcRn is in a human subject. In some embodiments the antibody prevents binding of the FcRn to an endogenous Ig. In some embodiments the antibody prevents binding of the FcRn to a therapeutic antibody. In some embodiments the FcRn is in an epithelial cell endosome. In some embodiments the FcRn is in an endothelial cell endosome. In some embodiments the FcRn is on the cell surface.

In one example the disclosure provides a method of treating an autoimmune disorder and/or modulating symptoms of an autoimmune disorder, the method comprising: administering any one of the antibodies provided herein in an amount sufficient to modulate the symptoms. In some embodiments the autoimmune disorder is a disorder selected from the group consisting of: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Myasthenia Gravis (MG), Graves Disease, Idiopathic Thrombocytopenia Purpura (ITP), Guillain-Barre Syndrome, autoimmune myocarditis, Membrane Glomerulonephritis, diabetes mellitus, Type I or Type II diabetes, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, gastritis, Celiac Disease, Vitiligo, Hepatitis, primary biliary cirrhosis, inflammatory bowel disease, spondyloarthropathies, experimental autoimmune encephalomyelitis, immune neutropenia, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines, T-lymphocytes typically found in tuberculosis, sarcoidosis, and polymyositis, polyarteritis, cutaneous vasculitis,

pemphigus, pemphigoid, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, and Sjogren's syndrome. In some embodiments the pemphigus is pemphigus vulgaris, pemphigus foliaceus or paraneoplastic pemphigus. In some embodiments the antibody decreases the half-life of endogenous IgG.

In one example the disclosure provides a method of modulating the half life/levels of circulating IgG, the method comprising: identifying a subject in need of modulated circulating IgG half life/levels; and administering the antibody of any one of the antibodies provided herein to the subject in amount effective to modulate the half life/levels of circulating IgG in the subject. In some embodiments the method reduces circulating IgG half life/levels. In some embodiments the subject is a human. In some embodiments the antibody is administered to decrease the half life/levels of circulating IgG and in combination with an anti-autoimmune disorder agent or therapy that is not any one of the antibodies provided herein. In some embodiments the anti-autoimmune disorder agent or therapy that is not any one of the antibodies provided herein comprises intravenous Ig therapy; nonsteroidal anti-inflammatory drugs (NSAID); corticosteroids; cyclosporins, rapamycins, ascomycins, or their immunosuppressive analogs, *e.g.*, cyclosporin A, cyclosporin G, FK-506, rapamycin, 40-0-(2-hydroxy)ethyl-rapamycin; cyclophosphamide; azathioprene; methotrexate; brequinar; FTY 720; leflunomide; mnizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; immunosuppressive monoclonal antibodies, *e.g.*, monoclonal antibodies to leukocyte receptors, *e.g.*, MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, or CD58 or their ligands; other immunomodulatory compounds, *e.g.* CTLA4Ig; or other adhesion molecule inhibitors, *e.g.*, mAbs or low molecular weight inhibitors including selectin antagonists and VLA-4 antagonists.

In one example the disclosure provides a method of treating or preventing an autoimmune disorder, the method comprising: administering any one of the antibodies provided herein to a subject having the disorder or at risk of developing the disorder. In some embodiments the autoimmune disorder is characterized by unwanted circulating IgG. In some embodiments the antibody decreases the half-life of endogenous IgG. In some embodiments the autoimmune disorder is a disorder selected from rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Myasthenia Gravis (MG), Graves Disease, Idiopathic Thrombocytopenia Purpura (ITP), Guillain-Barre Syndrome, autoimmune myocarditis, Membrane Glomerulonephritis, diabetes mellitus, Type I or Type II diabetes, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, gastritis, Celiac Disease, Vitiligo,

Hepatitis, primary biliary cirrhosis, inflammatory bowel disease, spondyloarthropathies, experimental autoimmune encephalomyelitis, immune neutropenia, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines, lymphocytes typically found in tuberculosis, sarcoidosis, and polymyositis, polyarteritis, cutaneous vasculitis, pemphigus, pemphigoid, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, and Sjogren's syndrome. In some embodiments the pemphigus is pemphigus vulgaris, pemphigus foliaceus or paraneoplastic pemphigus.

In one example the disclosure provides a method of treating or preventing an autoimmune disorder, the method comprising: administering any one of the antibodies provided herein, in combination with a second therapy for treating or preventing the disorder to a subject having the disorder or at risk of developing the disorder. In some embodiments the second therapy comprises intravenous Ig therapy; nonsteroidal anti-inflammatory drugs (NSAID); corticosteroids; cyclosporins, rapamycins, ascomycins, or their immunosuppressive analogs, *e.g.*, cyclosporin A, cyclosporin G, FK-506, rapamycin, 40-0-(2-hydroxy)ethyl-rapamycin; cyclophosphamide; azathioprene; methotrexate; brequinar; FTY 720; leflunomide; mnizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; immunosuppressive monoclonal antibodies, *e.g.*, monoclonal antibodies to leukocyte receptors, *e.g.*, MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, or CD58 or their ligands; other immunomodulatory compounds, *e.g.* CTLA4Ig; or other adhesion molecule inhibitors, *e.g.*, mAbs or low molecular weight inhibitors including selectin antagonists and VLA-4 antagonists.

In one example the disclosure provides a method of reducing the concentration of undesired antibodies in an individual comprising the steps of administering to the individual a therapeutically effective dose of any one of the antibodies or antibody fragments provided herein. In some embodiments the antibody or a fragment thereof is administered in a pharmaceutically acceptable carrier. In some embodiments the individual is a human. In some embodiments the antibody or fragment thereof is administered with an adjuvant. In some embodiments the undesired antibody is natalizumab. In some embodiments the undesired antibody is non-self Human Leukocyte Antigen. In some embodiments the administered antibody or fragment thereof is administered in connection with organ transplant.

In one example the disclosure provides a method of reducing the binding of IgG to FcRn in an individual comprising the steps of providing an antibody or a fragment thereof which

binds to human FcRn, is generated against the heavy chain of human FcRn or a fragment thereof, is a non-competitive inhibitor of IgG binding to human FcRn and does not bind 132-microglobulin; and administering the antibody or the fragment thereof to an individual in an amount sufficient to reduce the binding of IgG to FcRn in the individual. In some embodiments the individual has an autoimmune or alloimmune disease. In some embodiments the individual is an organ transplant recipient. In some embodiments the individual has been administered a therapeutic antibody. In some embodiments the autoimmune disease is immune thrombocytopenia. In some embodiments the autoimmune disease is immune pemphigus. In some embodiments the individual is a human. In some embodiments the antibody is administered at a dosage of 1 mg/kg to 2 g/kg. In some embodiments the antibody is administered at a dosage of 1 mg/kg to 200 mg/kg.

In one example the disclosure provides a method for suppressing the level of an IgG antibody in an individual comprising the steps of providing an antibody or a fragment thereof which binds to human FcRn, is generated against the heavy chain of human FcRn or a fragment thereof, is a non-competitive inhibitor of IgG binding to human FcRn and does not bind 132-microglobulin; and administering the antibody or the fragment thereof to an individual in an amount sufficient to suppress the level of an IgG antibody in an individual. In some embodiments the IgG antibody is a therapeutic IgG antibody. In some embodiments the therapeutic IgG antibody is natalizumab. In some embodiments the IgG antibody is non-self Human Leukocyte Antigen. In some embodiments the method further comprises a plasma exchange step.

In one example, the disclosure relates to antibodies which inhibit the constant region of an IgG molecule from binding to FcRn. The disclosure thus relates to an antibody comprising at least one variable region that specifically binds a FcRn molecule epitope. In some embodiments, the antibodies of the disclosure bind to human FcRn. In other embodiments, the antibodies bind to rodent or monkey FcRn. Some exemplary antibodies of the disclosure include, *e.g.*, 4B4.I2, 3B3.11, 31.1, and 17D3.

In one example, the disclosure features an antibody (*e.g.*, an isolated antibody) that includes a heavy chain (HC) immunoglobulin variable domain sequence and a light chain (LC) immunoglobulin variable domain sequence. The first and second immunoglobulin variable domain sequences form an antigen binding site that binds to FcRn (*e.g.*, human FcRn). In one embodiment, the antibody has one or more of the following characteristics:

M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11. In one embodiment, the antibody binds to an FcRn epitope bound by 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11. In one embodiment, the antibody competes with 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11 for binding to FcRn.

In one example, the disclosure relates to a method of making a monoclonal antibody comprising: immunizing a rodent with FcRn protein or at least one fragment thereof or with a polynucleotide sequence encoding a FcRn molecule or fragment thereof; obtaining 13 cells from said rodent; fusing said 13 cells with a myeloma cell line to obtain a hybridoma cell; culturing said hybridoma cell under conditions such that it secretes a monoclonal antibody, wherein said antibody comprises at least one variable region, which specifically binds to a FcRn molecule, wherein said FcRn molecule comprises a domain capable of binding at least a portion of an IgG constant region, wherein the binding of said antibody to said FcRn molecule inhibits said binding of the portion of an IgG constant region to said FcRn molecule; and isolating the antibody.

In one example, the disclosure features a method of identifying a antibody that binds to FcRn, *e.g.*, human FcRn, and includes: providing an FcRn antigen or a fragment thereof; providing a library of antibodies, *e.g.*, a display library; and identifying a member present in the library that binds to the FcRn antigen, where each member of the library displays a heterologous antibody component on its surface and each member includes a nucleic acid encoding the heterologous antibody component, the heterologous antibody component being a member of a set of diverse antibody components. The method can include isolating a nucleic acid molecule from the identified member and the nucleic acid molecule encodes the polypeptide that specifically binds to the FcRn antigen. In one embodiment, the antibody specifically binds human FcRn.

In one embodiment, the library is a phage library, *e.g.*, a phage display library. In one embodiment, the identified phage is eluted using a competitor ligand, *e.g.*, an IgG Fc that binds to FcRn and/or with a competing anti-human FcRn antibody.

In another example, the disclosure features a method of detecting an FcRn in a sample, the method includes: contacting the sample with a FcRn binding antibody (*e.g.*, a antibody described herein) and detecting an interaction between the antibody and an FcRn if present.

In one embodiment, the antibody includes a detectable label such as a fluorescent tag (*e.g.* bodipy, fluorescein-5-isothiocyanate, rhodamine, and peroxidase or alkaline phosphatase that are detected in the presence of chromogenic or chemiluminescent substrates).

In one example, the disclosure features a method of modulating an FcRn activity, the method includes: contacting an FcRn with a FcRn binding antibody (*e.g.*, a antibody described herein), thereby modulating the activity (*e.g.*, binding to IgG Fc) of the FcRn. In one embodiment, the FcRn is in a human subject; the FcRn can be in an epithelial or endothelial cell or in the blood (*e.g.*, soluble in the blood or in cells circulating in the blood) of a human subject. In one embodiment, the antibody prevents binding of the FcRn to a substrate, *e.g.*, an endogenous substrate such as IgG Fc and/or serum albumin. In one embodiment, the FcRn is in an epithelial or endothelial cell endosome.

In one example, the disclosure features a method of treating, preventing, and/or modulating symptoms of a disorder, *e.g.*, an autoimmune disorder or a disorder associated with aberrant FcRn activity. The method includes: administering a FcRn binding antibody (*e.g.*, antibody described herein) to a subject, *e.g.*, a subject having the disorder or at risk of developing the disorder. In one embodiment, the ligand is administered in an amount and/or for a time sufficient to modulate the symptoms of the disorder.

In one embodiment, the autoimmune disorder is a disorder selected from the group consisting of: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), myasthenia gravis (MG), Graves Disease, idiopathic thrombocytopenia purpura (ITP), Guillain-Barre Syndrome, autoimmune myocarditis, membrane glomerulonephritis, diabetes mellitus, Type I or Type II diabetes, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, gastritis, celiac disease, vitiligo, hepatitis, primary biliary cirrhosis, inflammatory bowel disease, immune neutropenia, spondyloarthropathies, experimental autoimmune encephalomyelitis, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines, T-lymphocytes typically found in tuberculosis, sarcoidosis, and polymyositis, polyarteritis, cutaneous vasculitis, pemphigus, pemphigoid, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, and Sjogren's syndrome.

In one embodiment, the antibodies of the disclosure may be used to inhibit the transport of IgG across the blood-brain barrier. In another embodiment, the antibodies of the disclosure may be used to treat brain tumors or Alzheimer's disease.

In one embodiment, the antibody decreases the half-life of endogenous IgG. In one embodiment, the autoimmune disorder is characterized by unwanted circulating IgG, *e.g.*, unwanted circulating pathogenic IgG.

In one example, the disclosure features a method of detecting FcRn in a subject, the method includes: administering a FcRn binding antibody (*e.g.*, antibody described herein) that includes a detectable label, to a subject; and detecting the label in the subject. The method can include imaging the subject, *e.g.*, using tomography, *e.g.*, MRI.

In one example, the disclosure features a method of modulating the half life/levels of circulating IgG, the method includes: identifying a subject, *e.g.*, a human, in need of modulated circulating IgG half life/levels; and administering a FcRn binding antibody (*e.g.*, antibody described herein) to the subject in amount effective to modulate the half life/levels of circulating IgG in the subject. In one embodiment, the method reduces circulating IgG half life/levels. In one embodiment, the antibody is administered to decrease the half life/levels of circulating IgG and in combination with another anti-autoimmune disorder agent or therapy. The combination of the administration of the FcRn antibody and the other anti-autoimmune disorder agent or therapy may result in a decrease in the level of other anti-autoimmune disorder agent or therapy needed to modulate or reduce the half life/level of circulating IgG.

In another example, the disclosure features an isolated nucleic acid that includes a first sequence that encodes a first polypeptide that includes a sequence at least 80, 85, 90, 92, 94, 95, 96, 97, 98, 99, or 100% identical to the sequence of a first variable domain sequence of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11, or a sequence that hybridizes (*e.g.*, under stringent conditions) to a nucleic acid encoding the sequence of a variable domain of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11. In one embodiment, the nucleic acid further includes a second sequence that encodes a second polypeptide that includes a second variable domain sequence (of a corresponding variable domain), *e.g.*, a sequence at least 80, 85, 90, 92, 94, 95, 96, 97, 98, 99, or 100% identical to the sequence of a second variable domain sequence of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11, or a sequence that

hybridizes (*e.g.*, under stringent conditions) to a nucleic acid encoding the sequence of a variable domain of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11. In one embodiment, the nucleic acid further includes regulatory sequences (*e.g.*, a promoter sequence, an untranslated 5' region, and an untranslated 3' region) and/or vector sequences. For example, the nucleic acid constitutes a vector.

In still another example, the disclosure features a host cell that can express an antibody. The host cell includes one or more nucleic acids that collectively include: (1) a first sequence that encodes a first variable domain sequence that includes a sequence at least 80, 85, 90, 92, 94, 95, 96, 97, 98, 99, or 100% identical to the sequence of a first variable domain sequence of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11, or a sequence that hybridizes (*e.g.*, under stringent conditions) to a nucleic acid encoding the sequence of a variable domain of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11 and (2) a second sequence that encodes a second variable domain sequence that includes a second variable domain sequence (of a corresponding variable domain), *e.g.*, a sequence at least 80, 85, 90, 92, 94, 95, 96, 97, 98, 99, or 100% identical to the sequence of a second variable domain sequence of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11, or a sequence that hybridizes (*e.g.*, under stringent conditions) to a nucleic acid encoding the sequence of a variable domain of 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-E10, or M0090-F11.

In one example, the disclosure features a method of treating or preventing an autoimmune disorder, the method comprising: administering a FcRn binding antibody (*e.g.*, a antibody described herein), *e.g.*, in combination with a second therapy, to a subject having an autoimmune disorder or at risk of developing the disorder. For example, the second therapy can be a therapy suitable for treating or preventing the disorder. In one embodiment, the second therapy can include: intravenous Ig therapy; nonsteroidal anti-inflammatory drugs (NSAID); corticosteroids; cyclosporins, rapamycins, ascomycins, or their immunosuppressive analogs, *e.g.* cyclosporin A, cyclosporin G, FK-506, rapamycin, 40-0-(2-hydroxy)ethyl-rapamycin; cyclophosphamide; azathioprine; methotrexate; brequinar; FTY

720; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, or CD58 or their ligands; other immunomodulatory compounds, e.g. CTLA4Ig; or other adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including selectin antagonists.

In another example, the disclosure features a method of treating a fetus, the method includes: conjugating a small molecule or macromolecular drug, e.g., an antibiotic or vaccine (e.g., viral vaccine), to a FcRn binding antibody; and administering the conjugate to a pregnant woman who bears the fetus *in utero*. In one embodiment, the fetus has a disorder or is at risk for a disorder. Exemplary disorders include an immunological disorder (e.g., an autoimmune disorder, a metabolic disorder, or an infectious disorder, e.g., a bacterial or viral infection, e.g., an enteric infection (e.g., *Helibacter pylori* infection).

In another example, the disclosure features a method of treating an infant, the method comprising: conjugating a small molecule or macromolecular drug to an antibody that binds to FcRn, e.g., a antibody described herein; and introducing the conjugated antibody into breast milk. The breast milk can be administered to the infant. In one embodiment, the conjugated antibody is administered to a woman and the woman is providing breast milk to the infant, directly, e.g., nursing, or indirectly.

Although the invention is discussed primarily in terms of a preferred embodiment of antibodies, one of ordinary skill in the art will readily recognize that binding proteins or ligands other than antibodies are within the scope of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the result of an ELISA analysis of antibodies in mouse sera obtained 56 days after immunization from animals immunized with DNA encoding hFcRn or GPI linked hFcRn; as well as with DNA encoding human 132M for reactivity with either hFcRn or human β 2M. Mice #180-184 were immunized with plasmid encoded hFcRn; Mice #185-189 with plasmid encoded hFcRn and plasmid encoded h β 2M; Mice #190-194 were immunized with plasmid encoded GPI-linked hFcRn; Mice #195-199 were immunized with plasmid encoded GPI-linked hFcRn and plasmid encoded h β 2M.