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 disclosure refers to an isolated monoclonal antibody,

wherein the antibody binds to an FcRn epitope having an amino acid sequence of SCPHRLREHLERGRGNLEWK (SEQ ID NO: 24), ERGRGNLEWKEPPSMRLKAR (SEQ ID NO: 25), CSAFSFYPPELQLRFLRNGL (SEQ ID NO: 26), or APGTPAFWVSGWLGPQQYLS (SEQ ID NO: 27), and

wherein the antibody inhibits IgG binding to FcRn by at least 90%.

In another aspect, the present disclosure refers to a method of modulating FcRn activity in vitro, the method comprising:

providing a biological sample containing FcRn; and

contacting the biological sample with the isolated monoclonal antibody as disclosed herein.

In another aspect, the present disclosure refers to a use of the isolated monoclonal antibody as disclosed herein in the manufacture of a medicament for treating an autoimmune disorder or modulating symptoms of an autoimmune disorder in a subject.

In yet another aspect, the present disclosure refers to a use of the isolated monoclonal antibody of any one of claims as disclosed herein in the manufacture of a medicament for reducing the risk of graft failure in an organ transplantation in a subject

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 Fcitn; 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-Fllor 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 M0161-804 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 n isolated antibody that is at least 85% identical to M0090-F11. The CDRs of M0090-F1 I 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 examples 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 examples 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 examples 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 examples 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 examples 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 examples 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 examples 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 examples 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 FeRn, 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 examples 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 examples 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 examples of the antibodies provided herein the antigen binding site specifically binds to human FcRn.

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

In some of the examples of the antibodies provided herein the antibody modulates *(e.g.,* inhibits) FcRn binding to an antibody/immunoglobulin constant region.

In some of the examples of the antibodies provided herein the antibody binds to the alpha subunit of FcRn.

In some of the examples of the antibodies provided herein the, antibody binds the al, a2, or a3 domain of the FcRn alpha chain.

In some of the examples of the antibodies provided herein the antibody does not bind a beta subunit of FcRn, *i.e.,* the protein only binds an alpha subunit.

In some of the examples of the antibodies provided herein the antibody binds to a beta subunit of FcRn, wherein the beta subunit is associated with an alpha subunit.

In some of the examples of the antibodies provided herein the alpha and beta subunit are correctly assembled into FcRn.

In some of the examples of the antibodies provided herein the antibody binds an FcRn that contains both an alpha subunit and a beta subunit and is correctly assembled.

In some of the examples of the antibodies provided herein the antibody inhibits the binding of IgG-Fc with an ICso of less than about 800 nM, less than about 600 nM, less than about 300 nM, less than about 100 nM, less than about 50, nM, less than about 25 nM, less than about IO nM, or less than about 5 nM at about pH 6.

In some of the examples of the antibodies provided herein the antibody is soluble Fab.

In some of the examples of the antibodies provided herein the antibody binds to FcRn through its antigen binding domain and also through its Fc region.

In some of the examples of the antibodies provided herein the binding of the antibody to FcRn is substantially pH independent in the range of 2-10.

In some of the examples of the antibodies provided herein the binding of the antibody to FcRn is substantially pH independent in the range of 6-8.

In some of the examples of the antibodies provided herein the antibody has a k_{off} of less than 0.01, 0.001, 0.0001, 0.00001 s^{-1} at pH 7.5.

In some of the examples of the antibodies provided herein the binding of the antibody to FcRn is substantially pH dependent.

In some of the examples of the antibodies provided herein the antibody preferentially binds human FcRn as compared to rat FcRn in a pH-dependent or pH-independent manner.

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

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

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

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

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

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

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

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

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

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

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

In some of the examples 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 examples of the 'antibodies provided herein the antibody binding to Fan is independent of the pH over a p1-1 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 examples 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 examples 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 examples the FcRn is in a human subject. In some examples the antibody prevents binding of the FcRn to an endogenous 1g. In some examples the antibody prevents binding of the FcRn to a therapeutic antibody. In some examples the FcRn is in an epithelial cell endosome. In some examples the FeRn is in an endothelial cell endosome. In some examples 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 examples 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, pemphigold, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, and Sjogren's syndrome. In some examples the pemphigus is pemphigus vulgaris, pemphigus foliaceus or paraneoplastic pemphigus.
In some examples 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 examples the method reduces circulating IgG half life/levels. In some examples the subject is a human. In some examples 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 examples 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 examples the autoimmune disorder is characterized by unwanted circulating IgG. In some examples the antibody decreases the half-life of endogenous IgG. In some examples 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, pemphigold, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, and Sjogren's syndrome. In some examples 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 theantibodies 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 examples 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 administrating to the individual a therapeutically effective dose of any one of the antibodies or antibody fragments provided herein. In some examples the antibody or a fragment thereof is administered in a pharmaceutically acceptable carrier. In some examples the individual is a human. In some examples the antibody or fragment thereof is administered with an adjuvant. In some examples the undesired antibody is natalizumab. In some examples the undesired antibody is non-self Human Leukocyte Antigen. In some examples 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 examples the individual has an autoimmune or alloimmune disease. In some examples the individual is an organ transplant recipient. In some examples the individual has been administered a therapeutic antibody. In some examples the autoimmune disease is immune thrombocytopenia. In some examples the autoimmune disease is immune pemphigus. In some examples the individual is a human. In some examples the antibody is administered at a dosage of 1 mg/kg to 2 *g/kg.* In some examples 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 examples the IgG antibody is a therapeutic IgG antibody. In some examples the therapeutic IgG antibody is natalizumab. In some examples n the IgG antibody is non-self Human Leukocyte Antigen. In some examples 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 examples, the antibodies of the disclosure bind to human FcRn. In other examples, 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 example, the antibody has one or more of the following characteristics:

(a) the LC immunoglobulin variable domain sequence is at least 85% identical to a LC variable domain of 3D3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-012, M0057-F02, M0062-009, M0064-H04, M0073-E10, or M0090-Fl 1, or one or more CDRs thereof;

(b) the HC immunoglobulin variable domain sequence is at least 85% identical to a HC variable domain of 3B3.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-012, M0057-F02, M0062-009, M0064-H04, M0073-E10, or M0090-F11, or one or more CDRs thereof; and

(c) the antibody binds an epitope that overlaps with an epitope bound by 3B3.11, 31.1, 532A- M0090-F09, M0084-303, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-009, M0064-H04, M0073-E10, or M0090-F11 .

In one example, the antibody binds FcRn *(e.g.,* human FcRn), *e.g.,* in about pH range 5-8, *e.g.,* with a dissociation constant (K_D) of less than 100, 50, 10, 5, 1, or 0.1 nM. In one example, the antigen binding site specifically binds to human FcRn. As used herein, "specific binding" or "specifically binds" refers to the ability of a FcRn binding antibody to preferentially bind to human FcRn, with an affinity that is at least two-fold, 10-fold, 50-fold, 100-fold, or better (smaller KO than its affinity for binding to a non-specific antigen *(e.g.,* actin, casein) other than FcRn. In one example, the antibody binds human FcRn with a k_{gr} of less than 0.01, 0.001, 0.0001, 0.00001 s^{-1}.

In one example, the antibody binds the extracellular domain of FcRn; for example, one of the alpha subunits of FcRn, *i.e.,* the al, a2, or a3 domain of the FcRn alpha chain. In one example, the antibody does not bind the beta (f32M) subunit of FcRn, *e.g.,* the antibody binds only the alpha subunit. In one example, the antibody does bind to the beta subunit of FcRn, but , only when P2M is in association with the alpha subunit. For example, the antibody does not bind to either alpha or beta subunit unless both are present and correctly assembled into FcRn. In one example, the antibody binds to the FcRn that contains both the alpha and beta subunits and is correctly assembled.

In one example, the antibody modulates *(e.g.,* inhibits) FcRn binding to an antibody/immunoglobulin constant region. For example, the antibody can have a Ki of better

than *(e.g.,* numerically less than) 5 nM, 500 pM, 200 pM, 150 pM, 100 pM, or 75 pM, *e.g.,* between 50 nM and 1pM, or 200 pM and 5 pM.

In one example, the antibody binds to FcRn and decreases or prevents FcRn binding to an antibody/immunoglobulin constant region. For example, the antibody can bind to FcRn *(e.g.,* human FcRn) with an affinity (K_D) of better than *(i.e.,* numerically smaller than) $1x10^4$ M. In one example, the antibody is a Fab that binds to FcRn in a substantially pH independent or substantially pH dependent manner and with a **K_D** in the range of about 3.0- 82 nM at pH 6. In one example, the antibody is a Fab that binds to FcRn in a substantially pH independent or substantially pH dependent manner and with a K_D in the range of about 9.7- about 39.7 nM at pH 7.5. In one example, the antibody is an IgG that binds to FcRn in a substantially p1-1 independent or substantially pH dependent manner and with a **K_D** in the range of about 0.409- about 29.5 nM, about 2.44- about 29.5 nM, about 0.13- about 1.03 nM, about 6.43- about 30,2 nM, about 0.2- about 2.87 nM, about 0.34- about 2.87 nM, or about 0.2- about 30.2 nM at pH 6. In one example, the antibody is an IgG that binds to FcRn in a substantially pH independent or substantially pH dependent manner and with a **K_D** in the range of about 0.675- 24.2 nM, 2.1- 24.2 nM, 0.158- 10 nM, or about 2.04- about 80 nM at pH 7.5.

In one example, the antibody inhibits the binding of FcRn to IgG-Fc with an ICso of less than 800 nM, 600 nM, or 300 nM, 200 **nM,** 100 nM, I nM, 50 pM at about pH 6. In one example, the antibody is a Fab that inhibits the binding of FcRn to IgG-Fc in a substantially pH independent or substantially pH dependent manner and with an ICso in the range of about 13-754 nM or about 13- 80 nM at pH 6. In one example, the antibody is an IgG that inhibits the binding of FcRn in a substantially pH independent or substantially pH dependent manner and with an ICs_o in the range of about 1.2- 36 nM, 36-120 nM, 120-562 nM, 1.5-5.4 nM, 5.4-50 nM, 51-161 nM at pH 6.

In one example, the antibody is, *e.g.,* a single chain antibody, a Fab, an sFab fragment, an F(ab')2, an Fd fragment, an Fv fragment, an scFv, or a dAb fragment.

In some examples, the antibody monospecific, *e.g.,* a monoclonal antibody or recombinant antibody. The term "monospecific antibody" refers to an antibody that displays a single binding specificity and affinity for a particular target, *e.g.,* epitope. This term includes a "monoclonal antibody" or "monoclonal antibody composition," which as used herein refer to a preparation of an antibody of a single molecular composition.

In one example, the antibody is a recombinant or modified anti-FcRn antibody, *e.g.,* a chimeric, a humanized, a deimmunized, or an *in vitro* generated antibody. The term "recombinant" or "modified" human antibody, as used herein, is intended to include all antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial antibody library, antibodies isolated from an animal *(e.g.,* a mouse) that is transgenic for human immunoglobulin genes or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant antibodies include humanized, CDR grafted, chimeric, deimmunized, in vitro generated antibodies, and may optionally include constant regions derived from human germline immunoglobulin sequences. In one example, the antibody does not elicit an anti-globulin response in a human.

Also disclosed are antibodies (including full length antibodies or antigen-binding fragments thereof) that bind overlapping epitopes 44 or competitively inhibit, the binding of the anti- FcRn antibodies disclosed herein to FeRn *e.g.,* antibodies which bind overlapping epitopes of, or competitively inhibit, the binding of sFabs 532A- M0090-F09, M0084-B03, M0056-G05, M0084-BI 1, M0092-D02, M0055-G12, M0057-F02, M0062-009, M0064-H04, M0073-E10, or M0090-F1 I to FcRn. It is also possible to use a combination of anti-FcRn antibodies, *e.g.,* two or more antibodies that bind to different regions of FcRn, *e.g.,* antibodies that bind to two different epitopes on the extracellular domain of FcRn. Alternatively, a bispecific antibody can be used. A bispecific antibody is a molecule with two variable heavy and two variable light domains so that the single molecule embodies two specific binding capabilities; one or more of the variable domains or specificities can be of an antibody described herein and bind to FcRn.

In one example, the anti- FcRn antibody *(e.g.,* a full length antibody or antigen-binding fragment thereof) includes at least one light or heavy chain variable domain sequence *(e.g.,* at least one light chain immunoglobulin and at least one heavy chain immunoglobulin). In some examples, each immunoglobulin includes a light or a heavy chain variable domain sequence having at least one, two or three complementarity determining regions (CDR's) substantially identical to a CDR from a light or heavy chain variable domain sequence of an antibody that interacts with FcRn, *e.g.,* an sFab described herein, *e.g.,* 532A-

M0090-F09, M0084-B03, M0056-G05, M00844111, M0092-D02, M0055-012, M0057-F02, M0062-009, M0064-H04, M0073-E10, or M0090-F11.

In one example, the antibody binds to FcRn using its antigen binding domain and also through its Fc region. In one example, the antibody binds to FcRn using only its antigen binding domain. For example, the antibody does not include an Fc region or includes a modified Fc region that does not interact with FcRn. In one example, the antibody binds to FcRn at least 1000-fold more tightly through its antigen-binding domains as through its Fc domains.

In one example, the binding of the antibody to FcRn is substantially pH independent in the range of 2-10, of 4-9, of 5-8, of 6-8, or of 6-7.5. The term "pH independent" refers to the ability of the antibody to bind and/or to remain bound to FcRn at a pH in the range of 2-10, 4-9, 5-8, 6-8, or 6-7.5. The affinity may vary at the various pH values. In some examples, the $Kr_)$ is no higher than 200 nM, 50 nM, 10 nM, 1 nM or 100 pM at any value within the range. For example, the antibody can bind FcRn at pH 6 and remain bound at pH 7.5. In one example, the binding of the antibody to FcRn is substantially pH dependent. The term "pH independent" refers to the ability of the antibody to bind/and or remain bound to FcRn at a first pH and the ability to bind or to remain bound to Fan at a second pH, where the second pH is within a given number of pH units (e.g., 6, 5, 4, 3, 2, 1.5 units) of the first pH. For example, the antibody can bind FcRn at pH 6 and can also bind or remain bound to FcRn at pH 7.5. The term "pH dependent" refers to the ability of the antibody to bind/and or remain bound to FcRn at a first pH and the lack of ability to bind or to remain bound to FcRn at a second pH, where the second pH is within a given number of pH units (e.g., 6, 5, 4, 3, 2, 1.5 units) of the first pH. For example, the antibody can bind FcRn at pH 6 and cannot bind or remain bound to FcRn at pH 7.5.

In one example, the antibody preferentially binds human FcRn as compared to rat or monkey FcRn in a pH-dependent or pH-independent manner. In one example, the antibody binds both human FcRn and the FcRn of a suitable experimental animal (e.g., rat or monkey) with affinities that differ by no more than two-, five- or ten-fold. In one example, the antibody binds both human FcRn and the FcRn of a suitable experimental animal with $K_D \leq 5$ nM in the pH range of 6.0-7.5. In one example, the antibody binds FcRn in endosomes or under endosomal conditions. For example, the antibody binds FcRn under acidic conditions, *e.g.,* pH 6. In one example, the antibody binds FcRn at pH 6,

e.g., at least 1.5, 2, 5, 8, 10, 20, or 50-fold better than at pH 7.5. In one example, the antibody releases FcRn at pH 7.5, *e.g.,* at least 1.5, 2, 5, 8, 10, 20, or 50-fold more rapidly than at pH 6. In one example, the antibody binds FcRn at pH 7.5, *e.g.,* at least 1.5, 2, 5, 8, 10, 20, or 50-fold better than at pH 6. In one example, the antibody releases FcRn at pH 6, *e.g.,* at least 1.5, 2, 5, 8, 10, 20, or 50-fold more rapidly than at pH 7.5. In one example, the antibody does not release $FcRt^{-}$, at pH 7.5. In one example, the antibody does not release FcRn at pH 6.

In one example, the interaction with FcRn extends the half-life of the antibody. In one example, the antibody causes the half-life of other IgG molecules to be diminished, e.g., *at* least 5, 10, 20, 40, 50, 60, 70, 80, or 90%. For example, a reduction of 90% would change the half-life of an antibody from 20 days to 2 days.

In one example, the antibody causes an amelioration of symptoms associated with an autoimmune disorder when administered to a subject. For example, the antibody can alleviate or decrease the severity of symptoms such as joint swelling, pain, or stiffness; levels of circulating antibodies such as auto-antibodies; achy joints (arthralgia); fever; extreme fatigue; skin rashes; anemia; pain in the chest or deep breathing; butterfly-shaped rash across the cheeks and nose; photosensitivity; hair loss; seizures; mouth or nose ulcers; Raynaud's phenomenon; mild erythema; neuropsychiatric manifestations; thrombocytopenia; and pleural effusion.

In one example, the HC and LC variable domain sequences are components of the same polypeptide chain, that is they are part of a single-chain antibody. In one example, HC and LC variable domain sequences are components of different polypeptide chains.

In one example, the antibody is a full-length antibody. For example, the antibody can be a human or humanized antibody and/or can be non-immunogenic in a human. In one example, the antibody comprises a human antibody framework region. In one example, the antibody comprises an Fc domain.

In one example, the HC variable domain sequence comprises a 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-Fll and the LC variable domain sequence comprises a 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. In one example, 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 example, 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 FeRn 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 example, the antibody specifically binds human FcRn.

In one example, the library is a phage library, *e.g.,* a phage display library. In one example, 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 example, 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 describedherein), thereby modulating the activity *(e.g.,* binding to IgG Fc) of the FcRn. In one example, 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 example, the antibody prevents binding of the FcRn to a substrate, *e.g.,* an endogenous substrate such as IgG Fe and/or serum albumin. In one example, 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 example, the ligand is administered in an amount and/or for a time sufficient to modulate the symptoms of the disorder.

In one example, 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 binary 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, pemphigold, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, and Sjogren's syndrome.

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

In one example, the antibody decreases the half-life of endogenous IgG. In one example, 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 example, the method reduces circulating IgG half life/levels. In one example, 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 example, 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 example, 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 383.11, 31.1, 532A- M0090-F09, M0084-B03, M0056-G05, M0084-B11, M0092-D02, M0055-G12, M0057-F02, M0062-C09, M0064-H04, M0073-EI0, 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 example, 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; letlunomide; 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 example, 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 example, 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 example 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 β2M. Mice #180-184 were immunized with plasrnid encoded hFcRn; Mice #185-189 with plasmid encoded hFcRn and plasmid encoded hβ2M; 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 hβ2M.

WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody,

wherein the antibody binds to an FcRn epitope having an amino acid sequence of SCPHRLREHLERGRGNLEWK (SEQ ID NO: 24), ERGRGNLEWKEPPSMRLKAR (SEQ ID NO: 25), CSAFSFYPPELQLRFLRNGL (SEQ ID NO: 26), or APGTPAFWVSGWLGPQQYLS (SEQ ID NO: 27), and

wherein the antibody inhibits IgG binding to FcRn by at least 90%.

2. The isolated monoclonal antibody of claim 1, wherein the antibody is an IgG1 antibody.

3. The isolated monoclonal antibody of claim 1 or claim 2, wherein the antibody is a human or humanized antibody.

4. The isolated monoclonal antibody of any one of claims 1-3, wherein the antibody is germlined.

5. A method of modulating FcRn activity in vitro, the method comprising:

providing a biological sample containing FcRn; and

contacting the biological sample with the isolated monoclonal antibody of any one of claims 1 to 4.

6. Use of the isolated monoclonal antibody of any one of claims 1 to 4 in the manufacture of a medicament for treating an autoimmune disorder or modulating symptoms of an autoimmune disorder in a subject.

7. The use of claim 6, wherein 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, immune responses associated with delayed hypersensitivity mediated by cytokines, tuberculosis, sarcoidosis, polymyositis, polyarteritis, cutaneous vasculitis, pemphigus, pemphigold, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, and Sjogren's syndrome.

8. The use of claim 6, wherein the subject is a human patient.

9. The use of claim 8, wherein the subject has been treated with natalizumab.

10. Use of the isolated monoclonal antibody of any one of claims 1 to 4 in the manufacture of a medicament for reducing the risk of graft failure in an organ transplantation in a subject.

11. The use of claim 10, wherein the subject is a human patient.

12. The use of claim 11, wherein the human patient has antibodies that bind a non-self human leukocyte antigen.

13. A pharmaceutical composition, comprising the isolated monoclonal antibody of any one of claims 1 to 4 and a pharmaceutically acceptable carrier.