ITP. Further, FcRn-deficient mice genetically predisposed to develop autoimmune disorder such as lupus or arthritis have significant reduction in severity of the disease.

## SUMMARY ~~OF THE INVENTION~~

The present disclosure provides isolated antibodies that bind the human Fc receptor, nucleic acids encoding such antibodies, and methods of using these antibodies to detect presence of FcRn, modulate Fc receptor activity, and treat autoimmune disorders.

Accordingly, ~~one aspect of~~ the present disclosure features an isolated antibody that binds to human FcRn. This anti-FcRn antibody comprises a light chain variable region ($V_L$) that comprises a $V_L$ CDR1, a $V_L$ CDR2 and a $V_L$ CDR3 region, wherein the $V_L$ CDR3 region has at least 85% (e.g., 90% or 95%) homology with the $V_L$ CDR3 region of SSYAGSGIYV (SEQ ID NO:12) or ASYAGSGIYV (SEQ ID NO:13). Optionally, the $V_L$ CDR1 and $V_L$ CDR2 of the anti-FcRn antibody have at least 85% (e.g., at least 90% or 95%) homology with the $V_L$ CDR1 region TGTGSDVGSYNLVS (SEQ ID NO:14) and $V_L$ CDR2 region GDSQRPS (SEQ ID NO:15), respectively. The anti-FcRn antibody does not have a cysteine at the first position of at least one CDR3 region, e.g., at least one of the $V_L$ CDR3 regions.

In a first aspect of the present disclosure, there is provided an isolated antibody comprising a light chain variable region (VL) and a heavy chain variable region (VII), wherein the antibody binds to human FcRn; and wherein the VL comprises:

(i) a VL CDR1 comprising the amino acid sequence TGTGSDVGSYNLVS (SEQ ID NO: 14);

(ii) a VL CDR2 comprising the amino acid sequence GDSQRPS (SEQ ID NO: 15), and

(iii) a VL CDR3 comprising the amino acid sequence SSYAGSGIYV (SEQ ID NO: 12) or ASYAGSGIYV (SEQ ID NO: 13); and

the VH comprises:

(i) a VH CDR1 comprising the amino acid sequence EYAMG (SEQ ID NO: 22);

(ii) a VH CDR2 comprising the amino acid sequence SIGSSGGQTKYADSVKG (SEQ ID NO: 23): and

(iii) a VH CDR3 comprising the amino acid sequence LAIGDSY (SEQ ID NO: 24).

In a second aspect of the present disclosure, there is provided an isolated antibody comprising a light chain variable region (VL), a heavy chain variable region (VH), and a heavy chain constant region (CH), wherein the antibody binds to human FcRn; and wherein the VL comprises:

(i) a VL CDR1 comprising the amino acid sequence TGTGSDVGSYNLVS (SEQ ID NO: 14);

(ii) a VL CDR2 comprising the amino acid sequence GDSQRPS (SEQ ID NO: 15): and

(iv) a VL CDR3 comprising the amino acid sequence CSYAGSGIYV (SEQ ID NO: 25), SSYAGSGIYV (SEQ ID NO: 12) or ASYAGSGIYV (SEQ ID NO: 13); and

the VH comprises:

(i) a VH CDR1 comprising the amino acid sequence EYAMG (SEQ ID NO: 22);

(ii) a VH CDR2 comprising the amino acid sequence SIGSSGGQTKYADSVKG (SEQ ID NO: 23); and

(iii) a VH CDR3 comprising the amino acid sequence LAIGDSY (SEQ ID NO: 24);

and the CH has a deletion corresponding to the C-terminal lysine residue at the last position of SEQ ID NO: 17.

In a third aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody as defined herein and a pharmaceutically acceptable carrier.

In a fourth aspect of the present disclosure, there is provided an isolated nucleic acid comprising a nucleotide sequence that encodes the antibody as defined herein.

In a fifth aspect of the present disclosure, there is provided a vector comprising the nucleic acid as defined herein.

In a sixth aspect of the present disclosure, there is provided a host cell comprising the vector as defined herein.

In a seventh aspect of the present disclosure, there is provided an *in vitro* method of detecting an FcRn in a sample, the method comprising:

contacting the sample with the antibody as defined herein, and

detecting an interaction between the antibody and the FcRn if present.

In an eighth aspect of the present disclosure, there is provided the antibody as defined herein, for use in detecting an FcRn in a subject.

In a ninth aspect of the present disclosure, there is provided the antibody as defined herein, for use in inhibiting binding of IgG to FcRn thereby treating an autoimmune or inflammatory disease or disorder characterized by the presence of inappropriately regulated IgG antibodies.

In a tenth aspect of the present disclosure, there is provided the antibody as defined herein, for use in treating an autoimmune disorder or an inflammatory disorder in a subject.

In an eleventh aspect of the present disclosure, there is provided the antibody as defined herein, for use in modulating the half life/levels of circulating IgG in a subject.

In some embodiments, the above-described anti-FcRn antibody comprises a $V_L$ CDR1 having at least 90% homology with TGTGSDVGSYNLVS (SEQ ID NO:14), a $V_L$ CDR2 having at least 90% homology with GDSQRPS (SEQ ID NO:15), and/or a $V_L$ CDR3 having at least 90% homology with SSYAGSGIYV (SEQ ID NO:12) or ASYAGSGIYV (SEQ ID NO:13). In one example, the anti-FcRn antibody comprises the $V_L$ CDR1 region TGTGSDVGSYNLVS (SEQ ID NO:14), the $V_L$ CDR2 region GDSQRPS (SEQ ID NO:15), and/or the $V_L$ CDR3 region SSYAGSGIYV (SEQ ID NO:12) or ASYAGSGIYV (SEQ ID NO:13).

In other embodiments, the isolated anti-FcRn antibody disclosed herein comprises a $V_L$ that comprises an amino acid sequence having at least 85% (e.g., at least 90%, 95% or 98%) homology with SEQ ID NO:10 or SEQ ID NO:11. In one example, the $V_L$ of the isolated antibody comprises the amino acid sequence of SEQ ID NO:10 or SEQ ID NO:11.

T~~Another aspect of the~~ present disclosure features an isolated anti-FcRn antibody comprising a light chain variable region ($V_L$) that comprises a $V_L$ CDR1, a $V_L$ CDR2 and a $V_L$ CDR3 region, wherein the $V_L$ CDR3 region has up to 3 amino acid substitutions as compared to the following sequence: SSYAGSGIYV (SEQ ID NO:12) or ASYAGSGIYV

(SEQ ID NO:13), and wherein the isolated antibody does not have a cysteine at the first position of at least one CDR3 region e.g., at least one of the $V_L$ CDR3 regions. Optionally, the $V_L$ CDR1, $V_L$ CDR2 and $V_L$ CDR3 of the anti-FcRn antibody, collectively, contain up to 10 amino acid substitutions as compared to the following sequences

(a) CDR1: TGTGSDVGSYNLVS (SEQ ID NO:14)

(b) CDR2: GDSQRPS (SEQ ID NO:15)

(c) CDR3: SSYAGSGIYV (SEQ ID NO:12), or ASYAGSGIYV (SEQ ID NO:13).

Any of the anti-FcRn antibodies described above can further comprise a heavy chain variable region ($V_H$) that comprises a $V_H$ CDR1, a $V_H$ CDR2, and a $V_H$ CDR3, wherein the $V_H$ CDR3 has at least 85% (e.g., at least 90% or 95%) homology with LAIGDSY (SEQ ID NO:24). Optionally, the $V_H$ CDR1 and $V_H$ CDR2 of the anti-FcRn antibody have at least 85% (e.g., at least 90% or 95%) homology with EYAMG (SEQ ID NO:22) and SIGSSGGQTKYADSVKG (SEQ ID NO:23), respectively.

In some embodiments, the anti-FcRn antibody comprises a $V_H$ CDR1 having at least 90% homology with EYAMG (SEQ ID NO:22), a $V_H$ CDR2 has at least 90% homology with SIGSSGGQTKYADSVKG (SEQ ID NO:23), and/or a $V_H$ CDR3 has at least 90% homology with LAIGDSY (SEQ ID NO:24). In one example, the anti-FcRn antibody comprises the $V_H$ CDR1 region EYAMG (SEQ ID NO:22), the $V_H$ CDR2 region SIGSSGGQTKYADSVKG (SEQ ID NO:23), and/or the $V_H$ CDR3 region LAIGDSY (SEQ ID NO:24).

In other embodiments, the anti-FcRn antibody disclosed herein comprises a $V_H$ that share at least 85% (e.g., at least 90%, 95%, or 98%) sequence identity to SEQ ID NO:9. In one example, the $V_H$ of the isolated antibody comprises the amino acid sequence of SEQ ID NO:9.

T~~In another aspect,~~ the present disclosure provides an isolated anti-FcRn antibody comprising a heavy chain that comprises a heavy chain variable region ($V_H$) and a heavy chain constant region, wherein the $V_H$ comprises a CDR3 region having at least 85% (e.g., at least 90% or 95%) homology with LAIGDSY (SEQ ID NO:24) and the constant region has a deletion at the position corresponding to the C-terminal lysine residue of SEQ ID NO:17. In some examples, the heavy chain variable of this anti-FcRn antibody further comprises a $V_H$ CDR1 and a $V_H$ CDR2, which have at least 85% (e.g., at least 90% or 95%) homology with EYAMG (SEQ ID NO:22), and SIGSSGGQTKYADSVKG (SEQ ID NO:23), respectively.

In other examples, the heavy chain constant region of the anti-FcRn antibody comprises the amino acid sequence of SEQ ID NO:26.

The above-described anti-FcRn antibody can further comprise a light chain variable region ($V_L$) that comprises a $V_L$ CDR3 at least 85% (e.g., at least 90% or 95%) identical to that of DX-2504 (CSYAGSGIYV; SEQ ID NO:25) and, optionally, a $V_L$ CDR1 at least 85% (e.g., at least 90% or 95%) identical TGTGSDVGSYNLVS (SEQ ID NO:14) and a $V_L$ CDR2 at least 85% (e.g., at least 90% or 95%) identical to GDSQRPS (SEQ ID NO:15). In one example, the anti-FcRn antibody comprises the $V_L$ CDR1 region TGTGSDVGSYNLVS (SEQ ID NO:14), the $V_L$ CDR2 region GDSQRPS (SEQ ID NO:15), and/or the $V_L$ CDR3 region CSYAGSGIYV (SEQ ID NO:25), SSYAGSGIYV (SEQ ID NO:12), or ASYAGSGIYV (SEQ ID NO:13). In another example, the $V_L$ of the anti-FcRn antibody comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, or SEQ ID NO:11.

Any of the anti-FcRn antibodies described above can bind human FcRn with a dissociation constant ($K_D$) of less than 10 nM. The anti-FcRn antibodies provided in the present disclosure can be human or humanized antibodies, or non-immunogenic in a human. For example, they can comprise a human antibody framework region. Alternatively, the anti-FcRn antibodies can be murine antibodies. In other examples, they can be chimeric antibodies.

In some embodiments, the anti-FcRn antibodies provided herein are full-length antibodies (comprising a Fc domain). Alternatively, they can be antigen-binding fragments such as Fab, F(ab)'2, Fv, or ScFv. When desired, the anti-FcRn antibodies are monoclonal antibodies.

Also disclosed herein are (i) a pharmaceutical composition comprising any of the antibodies described herein and a pharmaceutically acceptable carrier, (ii) an isolated nucleic acid comprising a sequence that encodes any of the antibodies provided herein, (iii) a vector comprising any of the nucleic acids comprising a sequence that encodes any of the antibodies provided herein, and (iv) a host cell comprising the vector comprising any of the nucleic acids comprising a sequence that encodes any of the antibodies provided herein.

Any of the anti-FcRn antibodies described herein can be used to detect the presence of an FcRn or modulate the activity of an FcRn, either *in vivo* or *in vitro*.

In one embodiment~~aspect~~, provide herein is a method of detecting an FcRn in a sample, the method comprising: contacting the sample with any of the antibodies provided herein, and

detecting an interaction between the antibody and the FcRn if present.

~~In another aspect~~ the present disclosure provides a method of detecting an FcRn in a subject, the method comprising: administering to the subject any of the antibodies provided herein, which can be conjugated with a detectable molecule such as an imaging label (fluorescent or radioactive), and detecting an interaction between the antibody and the FcRn if present.

~~In yet another aspect,~~ the present disclosure further provides a method of modulating an FcRn activity, the method comprising: contacting an FcRn with any of the antibodies provided herein thereby modulating the activity of the FcRn.

~~In one aspect,~~ the present disclosure also~~invention~~ provides a method of treating an autoimmune disorder or modulating the half life/levels of circulating IgG in a subject, the method comprising: administering to the subject any of the antibodies provided herein in an amount effective to treat the autoimmune disorder or to modulate the half life/levels of circulating IgG in the subject..

Also within the scope of the present disclosure are (a) pharmaceutical compositions for use in modulating the activity of an FcRn, modulating the half life/levels of circulating IgG, and/or treating an autoimmune disorder in a subject in need thereof, wherein the pharmaceutical compositions each comprise one of more of the anti-FcRn antibodies described herein and a pharmaceutically acceptable carrier, (b) the use of any of the anti-FcRn antibodies described herein for any of the just-noted purposes, and (c) the use of any of the anti-FcRn antibodies for the manufacture of a medicament for modulating the activity of FcRn, modulating the half life/levels of circulating IgG, and/or treating an autoimmune disorder in a subject (e.g., a human patient).

These and other aspects and embodiments of the invention are described in greater detail below.

Each of the limitations of the ~~invention~~present disclosure can encompass various embodiments of the ~~invention~~present disclosure. It is, therefore, anticipated that each of the limitations of the ~~invention~~present disclosure involving any one element or combinations of elements can be included in each aspect of the ~~invention~~present disclosure. This ~~invention~~present disclosure is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The ~~invention~~present disclosure is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the

immune deficiency syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, cicatricial pemphigoid, cold agglutinin disease, CREST Syndrome, Crohn's disease, Dego's disease, dermatomyositis, juvenile dermatomyositis, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia, fibromyositis, Grave's disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP). IgA nephropathy, insulin dependent diabetes (Type I), juvenile arthritis, Meniere's disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, pemicious anemia, polyarteritis nodosa, polychondritis, polyglancular syndromes, polymyalgia rheumatic, polymyositis, dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, sarcoidosis, stiff-man syndrome, Takayasu arteritis, ulcerative colitis, uveitis, vasculitis, vitiligo.

~~20. Use of the antibody of claim 1 or 4 in the manufacture of a medicament for treating an autoimmune or inflammatory disease or disorder, wherein the autoimmune or inflammatory disease or disorder is selected from the group consisting of: Multiple Sclerosis, rheumatoid arthritis, inflammatory bowel diseases (IBD), lupus, ankylosing spondylitis, scleroderma, Sjogren's syndrome, Goodpasture's syndrome, Wegener's granulomatosis, polymyalgia rheumatic, temporal arteritis /gian cell arteritis, alopecia areata, anklosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome (ALPS), autoimmune thrombocytopenic purpura (ATP), Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue dermatitis, chronic fatique syndrome immune deficiency syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, cicatricial pemphigoid, cold agglutinin disease, CREST Syndrome, Crohn's disease, Dego's disease, dermatomyositis, juvenile dermatomyositis, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia, fibromyositis, Grave's disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP). IgA nephropathy, insulin dependent diabetes (Type I), juvenile arthritis, Meniere's disease, mixed connective tissue disease,~~

~~myasthenia gravis, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic~~ pemphigus, pemicious anemia, polyarteritis nodosa, polychondritis, polyglancular syndromes, polymyalgia rheumatic, polymyositis, dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, sarcoidosis, stiff-man syndrome, Takayasu arteritis, ulcerative colitis, uveitis, vasculitis, vitiligo.