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

In one aspect, the present disclosure refers to a method of producing an antibody specific to a neonatal Fc receptor (FcRn), the method comprising:

(i) culturing, under conditions suitable for expression of the antibody, a host cell comprising a first nucleic acid encoding a light chain variable region (V_L) of the antibody specific to the FcRn, and a second nucleic acid encoding a heavy chain variable region (V_H) of the antibody specific to the FcRn, wherein each of the first nucleic acid and the second nucleic acid is in operable linkage to a promoter; and

(ii) collecting the antibody specific to the FcRn produced in (i);

wherein:

the V_L comprises a V_L CDR1 that comprises the amino acid sequence of TGTGSDVGSYNLVS (SEQ ID NO:14); a V_L CDR2 that comprises the amino acid sequence of GDSQRPS (SEQ ID NO:15); and a V_L CDR3 that comprises the amino acid sequence of SSYAGSGIYV (SEQ ID NO:12) or ASYAGSGIYV (SEQ ID NO:13); and

the V_H comprises a V_H CDR1 that comprises the amino acid sequence of EYAMG (SEQ ID NO:22); a V_H CDR2 that comprises the amino acid sequence of SIGSSGGQTKYADSVKG (SEQ ID NO:23); and a V_H CDR3 that comprises the amino acid sequence of LAIGDSY (SEQ ID NO:24).

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 example 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 some examples, 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 examples, 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.

Another example 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 CDRI , 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 examples, 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 examples, 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.

In another example, 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 examples, 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 example, 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 example, 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 example, the present disclosure 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 example, the present disclosure 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 examples of the present disclosure are described in greater detail below.

Each of the limitations of the present disclosure can encompass various examples of the present disclosure. It is, therefore, anticipated that each of the limitations of the present disclosure involving any one element or combinations of elements can be included in each example of the present disclosure. This 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 present disclosure is capable of other examples and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the

What is claimed is:

1. A method of producing an antibody specific to a neonatal Fc receptor (FcRn), the method comprising:

(i) culturing, under conditions suitable for expression of the antibody, a host cell comprising a first nucleic acid encoding a light chain variable region (V_L) of the antibody specific to the FcRn, and a second nucleic acid encoding a heavy chain variable region (V_H) of the antibody specific to the FcRn, wherein each of the first nucleic acid and the second nucleic acid is in operable linkage to a promoter; and

(ii) collecting the antibody specific to the FcRn produced in (i);

wherein:

the V_L comprises a V_L CDR1 that comprises the amino acid sequence of TGTGSDVGSYNLVS (SEQ ID NO:14); a V_L CDR2 that comprises the amino acid sequence of GDSQRPS (SEQ ID NO:15); and a V_L CDR3 that comprises the amino acid sequence of SSYAGSGIYV (SEQ ID NO:12) or ASYAGSGIYV (SEQ ID NO:13); and

the V_H comprises a V_H CDR1 that comprises the amino acid sequence of EYAMG (SEQ ID NO:22); a V_H CDR2 that comprises the amino acid sequence of SIGSSGGQTKYADSVKG (SEQ ID NO:23); and a V_H CDR3 that comprises the amino acid sequence of LAIGDSY (SEQ ID NO:24).

2. The method of claim 1, wherein the V_L comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, or SEQ ID NO:11.

3. The method of claim 1, wherein the V_H comprises the amino acid sequence of SEQ ID NO:9.

4. The method of claim 2, wherein the V_H comprises the amino acid sequence of SEQ ID NO:9.

5. The method of claim 1, wherein the second nucleic acid further encodes a heavy chain constant region (C_H), which has a deletion corresponding to the C-terminal lysine residue at the last position of SEQ ID NO:17.

6. The method of claim 1, wherein the first nucleic acid and the second nucleic are on the same expression vector.

7. The method of claim 1, wherein the first nucleic acid and the second nucleic are on two different expression vectors.

8. The method of claim 1, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, a plant cell, or a mammalian cell.

9. The method of claim 8, wherein the host cell is a mammalian cell.

10. The method of claim 9, wherein the mammalian cell is selected from the group consisting of a Chinese Hamster Ovary (CHO) cell, a NS0 myeloma cell, a SP2 cell, a COS cell, and a mammary epithelial cell.

11. The method of claim 9, wherein the host cell lacks an endogenous dihydrofolate reductase ($dhfr^-$).

12. The method of claim 11, wherein the first nucleic acid or second nucleic acid further encodes a DHFR protein.