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# DESCRIPTION

## BACKGROUND OF THE INVENTION

**[0001]** Therapeutic proteins, e.g., therapeutic antibodies, have rapidly become a clinically important drug class for patients with immunological diseases. WO2012/167039 discloses the generation of anti-FcRn antibodies and use thereof for treating various diseases including autoimmune diseases, inflammatory disorders and cancer.

## SUMMARY OF THE INVENTION

**[0002]** The present invention features novel antibodies to human neonatal Fc receptor (FcRn). These anti-FcRn antibodies are useful, e.g., to promote clearance of autoantibodies in a subject, to suppress antigen presentation in a subject, to block an immune response, e.g., block an immune complex-based activation of the immune response in a subject, or to treat immunological diseases (e.g., autoimmune diseases) in a subject.

**[0003]** The subject matter for which protection is sought is as defined in the claims. The embodiments and/or examples of the following description which are not covered by the appended claims, when interpreted according to Article 69 EPC and the Protocol on the Interpretation of Article 69 EPC, are not considered to be part of the present invention.

**[0004]** Any reference as to methods of treatment is considered as a reference to the compounds and compositions of the present invention for use in a method of treatment practised on the human body.

**[0005]** In one aspect, the invention features an isolated antibody that binds to human FcRn, the isolated antibody comprising a polypeptide having the amino acid sequence of SEQ ID NO: 19 and a polypeptide having the amino acid sequence of SEQ ID NO: 24.

**[0006]** In some embodiments, the antibody binds human FcRn with a $K_D$ of less than 200, 150, 100, 50, or 40 pM.

**[0007]** In some embodiments, the antibody binds human FcRn with a $K_D$ that is less than that of an antibody having the light chain variable region and heavy chain variable region of N022, N023, N024, or N026 and further having the same Fc region as that of the antibody to which it is being compared.

**[0008]** The disclosure also provides an isolated antibody containing: (1) a light chain variable region that includes a CDR L1, a CDR L2, and a CDR L3 and (2) a heavy chain variable region that includes a CDR H1, a CDR H2, and a CDR H3, wherein the CDR L1 has the sequence of $X_1$GTGSDVGSYN$X_2$VS (SEQ ID NO: 12), the CDR L2 has the sequence of GD$X_3X_4$RPS (SEQ ID NO: 13), the CDR L3 has the sequence of $X_5$SY$X_6$GSGIYV (SEQ ID NO: 14), the CDR H1 has the sequence of $Z_1$YAMG (SEQ ID NO: 15), the CDR H2 has the sequence of SIG$Z_2$SG$Z_3$QT$Z_4$YADS (SEQ ID NO: 16), and the CDR H3 has the sequence of LA$Z_5Z_6$DSY (SEQ ID NO: 17), wherein $X_1$ is a polar or hydrophobic amino acid, $X_2$ is a hydrophobic amino acid, $X_3$ is a polar amino acid, $X_4$ is a polar or acidic amino acid, $X_5$ is a polar or hydrophobic amino acid, $X_6$ is a hydrophobic amino acid, $Z_1$ is a polar or acidic amino acid, $Z_2$ is a polar or hydrophobic amino acid, $Z_3$ is G, S, or A, $Z_4$ is a basic amino acid, $Z_5$ is a hydrophobic or basic amino acid, and $Z_6$ is G, S, D, Q, or H, and wherein the antibody binds human FcRn with a $K_D$ that is less than or equal to that of antibody having the light chain variable region and heavy chain variable region of N026 and further having the same Fc region as the antibody being compared. In some embodiments, $X_1$ is T, A, S, or I. In other embodiments, $X_2$ is L or I. In some embodiments, $X_3$ is S, N, or T. In still other embodiments, $X_4$ is Q, E, or N, $X_5$ is C, S, I, or Y. In some embodiments, $X_6$ is A or V, $Z_1$ is E, T, D, or N. In further embodiments, $Z_2$ is S or A. In some embodiments, $Z_4$ is K or R. In yet other embodiments, $Z_5$ is I, L, or H.

**[0009]** The disclosure also provides an isolated antibody containing a light chain variable region that includes a CDR L1 having the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), a CDR L2 having the sequence of GDSERPS (SEQ ID NO: 2), and a CDR L3 having the sequence of SSYAGSGIYV (SEQ ID NO: 3), and a heavy chain variable region that includes a CDR H1 having the sequence of $Z_1$YAMG (SEQ ID NO: 15), a CDR H2 having the sequence of SIG$Z_2$SG$Z_3$QTRYADS (SEQ ID NO: 18), and a CDR H3 having the sequence of LAIGDSY (SEQ ID NO: 11), wherein $Z_1$ is T, D, or N, $Z_2$ is S or A, and $Z_3$ is G, S or A.

**[0010]** The isolated antibody of the invention contains a CDR L1 having the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), a CDR L2 having the sequence of GDSERPS (SEQ ID NO: 2), a CDR L3 having the sequence of SSYAGSGIYV (SEQ ID NO: 3), a CDR H1 having the sequence of TYAMG (SEQ ID NO: 4), a CDR H2 having the sequence of SIGASGSQTRYADS (SEQ ID NO: 8), and a CDR H3 having the sequence of LAIGDSY (SEQ ID NO: 11).

**[0011]** The disclosure also provides an isolated antibody containing a CDR L1 having the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), a CDR L2 having the sequence of GDSERPS (SEQ ID NO: 2), a CDR L3 having the sequence of SSYAGSGIYV (SEQ ID NO: 3), a CDR H1 having the sequence of TYAMG (SEQ ID NO: 4), a CDR H2 having the sequence of SIGSSGAQTRYADS (SEQ ID NO: 7), and a CDR H3 having the sequence of LAIGDSY (SEQ ID NO: 11).

**[0012]** The disclosure also provides an isolated antibody containing a CDR L1 having the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), a CDR L2 having the sequence of GDSERPS (SEQ ID NO: 2), a CDR L3 having the sequence of SSYAGSGIYV (SEQ ID NO: 3), a CDR H1 having the sequence of DYAMG (SEQ ID NO: 5), a CDR H2 having the sequence of SIGASGSQTRYADS (SEQ ID NO: 8), and a CDR H3 having the sequence of LAIGDSY (SEQ ID NO: 11).

**[0013]** The disclosure also provides an isolated antibody containing a CDR L1 having the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), a CDR L2 having the sequence of GDSERPS (SEQ ID NO: 2), a CDR L3 having the sequence of SSYAGSGIYV (SEQ ID NO: 3), a CDR H1 having the sequence of NYAMG (SEQ ID NO: 6), a CDR H2 having the sequence of SIGASGAQTRYADS (SEQ ID NO: 9), and a CDR H3 having the sequence of LAIGDSY (SEQ ID NO: 11).

**[0014]** The disclosure also provides an isolated antibody containing a CDR L1 having the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), a CDR L2 having the sequence of GDSERPS (SEQ ID NO: 2), a CDR L3 having the sequence of SSYAGSGIYV (SEQ ID NO: 3), a CDR H1 having the sequence of TYAMG (SEQ ID NO: 4), a CDR H2 having the sequence of SIGASGGQTRYADS (SEQ ID NO: 10), and a CDR H3 having the sequence of LAIGDSY (SEQ ID NO: 11).

**[0015]** The disclosure also provides that the light chain variable region of an isolated antibody has a sequence having at least 90% identity to the sequence of

QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN
TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP
GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC
S (SEQ ID NO: 19).

**[0016]** The disclosure also provides that the heavy chain variable region of an isolated antibody has a sequence having at least 90% identity to the sequence of

EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGSSGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 20).

**[0017]** The disclosure also provides that the heavy chain variable region of an isolated antibody has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 21).

**[0018]** The disclosure also provides that the heavy chain variable region of an isolated antibody has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLEWVSSIGASGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 22).

**[0019]** The disclosure also provides that the heavy chain variable region of an isolated antibody has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGGQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 23).

**[0020]** The disclosure also provides that the heavy chain variable region of an isolated antibody has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24).

**[0021]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN
TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP
GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGSSGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 20)

HEALHNHYTQKSLSLSPG (SEQ ID NO: 20).

**[0022]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 21).

**[0023]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLEWVSSIGASGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 22).

**[0024]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGGQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 23).

**[0025]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK

VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24).

**[0026]** The heavy chain variable region of the isolated antibody of the disclosure may have a sequence having at least 95%, 97%, 99%, or 100% identity to the sequence of any one of SEQ ID NOs: 20-24. The light chain variable region of the isolated antibody of the disclosure may have a sequence having at least 95%, 97%, 99%, or 100% identity to the sequence of SEQ ID NO: 19.

**[0027]** In a particular $K_D$ assay, the $K_D$ of the antibody is less than 200, 150, 100, 50, or 40 pM.

**[0028]** The amino acid positions assigned to complementary determining regions (CDRs) and framework regions (FRs) of any isolated antibody described herein are defined according to EU index of Kabat (Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)).

**[0029]** In yet another aspect, the invention features an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24).

**[0030]** The disclosure also features an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGSSGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 20).

**[0031]** The disclosure also features an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH

VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 21).

**[0032]** The disclosure also features an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLEWVSSIGASGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK

VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 22).

**[0033]** The disclosure also features an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGGQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 23).

**[0034]** In some embodiments of any of the invention, the isolated antibody of the invention is a monoclonal antibody. In some embodiments, the isolated antibody is IgG1. In some embodiments, the isolated antibody includes a λ light chain.

**[0035]** In some embodiments of any of the above aspects, the isolated antibody of the invention is a humanized or fully human antibody.

**[0036]** In some embodiments, the isolated antibody binds to human FcRn with a $K_D$ of 1-100, 5-150, 5-100, 5-75, 5-50, 10-50, or 10-40 pM.

**[0037]** In some embodiments, the isolated antibody of the invention binds rodent, e.g., mouse or rat FcRn. In some embodiments, the isolated antibody of the invention binds rodent, e.g., mouse or rat, FcRn with a $K_D$ of less than 200, 150, 100, 50, or 40 pM.

**[0038]** In another aspect, the invention features a nucleic acid molecule encoding any isolated antibody of the invention.

**[0039]** In yet another aspect, the invention features a vector containing a nucleic acid molecule encoding any antibody of the invention.

**[0040]** In another aspect, the invention features a host cell that expresses any isolated antibody of the invention. The host cell includes a nucleic acid molecule encoding any isolated antibody of the invention or a vector containing a nucleic acid molecule encoding any isolated antibody of the invention, wherein the nucleic acid molecule or vector is expressed by the host cell.

**[0041]** In some embodiments, the host cell is a Chinese hamster ovary (CHO) cell. The host cell may be an Sp2 cell or NS0 cell.

**[0042]** In another aspect, the invention features a method of preparing any isolated antibody of the invention. The method includes: a) providing a host cell that includes a nucleic acid molecule encoding any isolated antibody of the invention or a vector containing a nucleic acid molecule encoding any isolated antibody of the invention, and b) expressing the nucleic acid molecule or vector in the host cell under conditions that allow for the formation of the antibody.

**[0043]** The method may include the step of recovering the antibody from the host cell, e.g., at a concentration of about 1-100, 1-50, 1-25, 2-50, 5-50, or 2-20 mg/ml.

**[0044]** The host cell used in the method may be a CHO cell.

**[0045]** In another aspect, the invention features a pharmaceutical composition including the isolated antibody of the invention and one or more pharmaceutically acceptable carriers or excipients.

**[0046]** In some embodiments, the pharmaceutical composition includes the antibody in a therapeutically effective dose amount.

**[0047]** In another aspect, the invention features an isolated antibody of the invention for use in a method of reducing or treating an immune complex-based activation of an acute immune response which is activated by a medical condition selected from the group consisting of pemphigus vulgaris, lupus nephritis, myasthenia gravis, Guillain-Barré syndrome, antibody-mediated rejection, catastrophic anti-phospholipid antibody syndrome, immune complex-mediated vasculitis, glomerulitis, a channelopathy, neuromyelitis optica, autoimmune hearing loss, idiopathic thrombocytopenia purpura (ITP), autoimmune haemolytic anaemia (AIHA), immune neutropenia, dilated cardiomyopathy, and serum sickness.

**[0048]** In another aspect, the invention features an isolated antibody of the invention for use in a method of reducing or treating an immune complex-based activation of a chronic immune response which is activated by a medical condition selected from the group consisting of chronic inflammatory demyelinating polyneuropathy (CIDP), systemic lupus, a chronic form of a disorder indicated for acute treatment, reactive arthropathies, primary biliary cirrhosis, ulcerative colitis, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

**[0049]** In another aspect, the invention features an isolated antibody of the invention for use in a method of reducing or treating an immune response activated by an autoimmune disease.
In another aspect, the disclosure features a method of increasing IgG catabolism in a subject. In another aspect, the disclosure features a method of reducing autoantibodies in a subject. In yet another aspect, the disclosure features a method of treating or reducing an immune complex-based activation of an immune response in a subject. The methods include administering to the subject any isolated antibody described herein or a pharmaceutical composition including any isolated antibody described herein. In some embodiments, the subject has or the immune response is activated by an autoimmune disease. In particular, the autoimmune disease is selected from the group consisting of alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, Addison's disease, hemolytic anemia, autoimmune hepatitis, hepatitis, Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, limited scleroderma (CREST syndrome), cold agglutinin disease, Crohn's disease, dermatomyositis, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia, fibromyositis, Graves' disease, Hashimoto's thyroiditis, hypothyroidism, inflammatory bowel disease,

autoimmune lymphoproliferative syndrome, idiopathic pulmonary fibrosis, IgA nephropathy, insulin dependent diabetes, juvenile arthritis, lichen planus, lupus, Ménière's Disease, mixed connective tissue disease, multiple sclerosis, pernicious anemia, polyarteritis nodosa, polychondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren's syndrome, stiff-man syndrome, Takayasu arteritis, temporal arteritis, ulcerative colitis, uveitis, vitiligo, and Wegener's granulomatosis.

**Definitions**

**[0050]** The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit FcRn antigen-binding activity.

**[0051]** "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments, diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies.

**[0052]** As used herein, the term "isolated antibody" refers to an antibody which has been separated and/or recovered from a component of its manufacturing host cell environment. Contaminant components of its manufacturing host cell environment are materials which would interfere with research, diagnostic, or therapeutic uses of the antibody. Contaminant components may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In some embodiments, an antibody is purified (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of, for example, a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using, for example, Coomassie blue or silver stain. An isolated antibody includes the antibody *in situ* within recombinant cells. Ordinarily, however, an isolated antibody will be prepared by at least one purification step. A pharmaceutical preparation of an isolated antibody typically has less than 250 ppm (e.g., less than 200ppm, 150ppm. 100 ppm) of host cell proteins (HCP) as determined by an ELISA based HCP assay performed as recommended by an FDA "Guidance for Industry" document.

**[0053]** As used herein, the term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., individual antibodies in the population have the same primary sequence except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific and directed against a single antigenic site (i.e., an epitope on human FcRn). In contrast to polyclonal antibody preparations which typically include different antibodies directed against different epitopes, each monoclonal antibody is directed against a single epitope on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogenous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

**[0054]** As used herein, the terms "variable region" and "variable domain" refer to the portions of the light and heavy chains of an antibody that include amino acid sequences of complementary determining regions (CDRs, e.g., CDR L1, CDR L2, CDR L3, CDR H1, CDR H2, and CDR H3) and framework regions (FRs). According to the methods used in this invention, the amino acid positions assigned to CDRs and FRs are defined according to Kabat (Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a CDR (defined further herein) or FR (defined further herein) of the variable region. For example, a heavy chain variable region may include a single inserted residue (i.e., residue 52a according to Kabat) after residue 52 of CDR H2 and inserted residues (i.e., residues 82a, 82b, 82c, etc. according to Kabat) after residue 82 of heavy chain FR. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the

antibody with a "standard" Kabat numbered sequence.

**[0055]** As used herein, the terms "complementary determining regions" and "CDRs" refer to the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops. A CDR is also known as a hypervariable region. The light chain and heavy chain variable regions each has three CDRs. The light chain variable region contains CDR L1, CDR L2, and CDR L3. The heavy chain variable region contains CDR H1, CDR H2, and CDR H3. Each CDR may include amino acid residues from a complementarity determining region as defined by Kabat (i.e. about residues 24-34 (CDR L1), 50-56 (CDR L2) and 89-97 (CDR L3) in the light chain variable region and about residues 31-35 (CDR H1), 50-65 (CDR H2) and 95-102 (CDR H3) in the heavy chain variable region.

**[0056]** As used herein, the term "FcRn" refers a neonatal Fc receptor that binds to the Fc region of an IgG antibody, e.g., an IgG1 antibody. An exemplary FcRn is human FcRn having UniProt ID No. P55899. Human FcRn is believed to be responsible for maintaining the half-life of IgG by binding and trafficking constitutively internalized IgG back to the cell surface for the recycling of IgG.

**[0057]** As used herein, the terms "affinity" and "binding affinity" refer to the strength of the binding interaction between two molecules. Generally, binding affinity refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule and its binding partner, such as an isolated antibody and its target (e.g., an isolated anti-FcRn antibody of the invention and a human FcRn). Unless indicated otherwise, binding affinity refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair. The binding affinity between two molecules is commonly described by the dissociation constant ($K_D$) or the affinity constant ($K_A$). Two molecules that have low binding affinity for each other generally bind slowly, tend to dissociate easily, and exhibit a large $K_D$. Two molecules that have high affinity for each other generally bind readily, tend to remain bound longer, and exhibit a small $K_D$. One method for determining the $K_D$ of an antibody to human FcRn is described in Example 2 ("the SPR method"). Using this method the $K_D$ of N022, N023, N024, N026, and N027 was 31, 31.4, 35.5, 36.5, and 19.3 pM, respectively.

**[0058]** As used herein, the term "inhibit IgG binding to FcRn" refers to the ability of an anti-FcRn antibody of the invention to block or inhibit the binding of IgG (e.g., IgG1) to human FcRn. In some embodiments, an anti-FcRn antibody of the invention binds FcRn, for example, at the site on human FcRn to which IgG binds. Thus, the anti-FcRn antibody of the invention is able to inhibit the binding of IgG (e.g., a subject's autoantibodies) to FcRn. In some embodiments, the molecule (e.g., an anti-FcRn antibody of the invention) substantially or completely inhibits binding to IgG. In some embodiments, the binding of IgG is reduced by 10%, 20%, 30%, 50%, 70%, 80%, 90%, 95%, or even 100%.

**[0059]** As used herein, the term "hydrophobic amino acid" refers to an amino acid having relatively low-water solubility. Hydrophobic amino acids include, but are not limited to, leucine, isoleucine, alanine, phenylalanine, valine, and proline. Particularly preferred hydrophobic amino acids in the present invention are alanine, leucine, isoleucine, and valine.

**[0060]** As used herein, the term "polar amino acid" refers to an amino acid having a chemical polarity in its side chain induced by atoms with different electronegativity. The polarity of a polar amino acid is dependent on the electronegativity between atoms in the side chain of the amino acid and the asymmetry of the structure of the side chain. Polar amino acids include, but are not limited to, serine, threonine, cysteine, methionine, tyrosine, tryptophan, asparagine, and glutamine. Particularly preferred polar amino acids in the present invention are serine, threonine, asparagine, glutamine, cysteine, and tyrosine.

**[0061]** As used herein, the term "acidic amino acid" refers to an amino acid whose side chain contains a carboxylic acid group having a pKa between 3.5 and 4.5. Acidic amino acids include, but are not limited to, aspartic acid and glutamic acid.

**[0062]** As used herein, the term "basic amino acid" refers to an amino acid whose side chain contains an amino

group having a pKa between 9.5 and 13. Basic amino acids include, but are not limited to, histidine, lysine, and arginine.

**[0063]** As used herein, the term "percent (%) identity" refers to the percentage of amino acid (or nucleic acid) residues of a candidate sequence, e.g., an anti-FcRn antibody of the invention, that are identical to the amino acid (or nucleic acid) residues of a reference sequence, e.g., a wild-type anti-FcRn antibody, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity (i.e., gaps can be introduced in one or both of the candidate and reference sequences for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). Alignment for purposes of determining percent identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, ALIGN, or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. In some embodiments, the percent amino acid (or nucleic acid) sequence identity of a given candidate sequence to, with, or against a given reference sequence (which can alternatively be phrased as a given candidate sequence that has or includes a certain percent amino acid (or nucleic acid) sequence identity to, with, or against a given reference sequence) is calculated as follows:
100 x (fraction of A/B)
where A is the number of amino acid (or nucleic acid) residues scored as identical in the alignment of the candidate sequence and the reference sequence, and where B is the total number of amino acid (or nucleic acid) residues in the reference sequence. In some embodiments where the length of the candidate sequence does not equal to the length of the reference sequence, the percent amino acid (or nucleic acid) sequence identity of the candidate sequence to the reference sequence would not equal to the percent amino acid (or nucleic acid) sequence identity of the reference sequence to the candidate sequence.

**[0064]** In particular embodiments, a reference sequence aligned for comparison with a candidate sequence may show that the candidate sequence exhibits from 50% to 100% identity across the full length of the candidate sequence or a selected portion of contiguous amino acid (or nucleic acid) residues of the candidate sequence. The length of the candidate sequence aligned for comparison purpose is at least 30%, e.g., at least 40%, e.g., at least 50%, 60%, 70%, 80%, 90%, or 100% of the length of the reference sequence. When a position in the candidate sequence is occupied by the same amino acid (or nucleic acid) residue as the corresponding position in the reference sequence, then the molecules are identical at that position.

**[0065]** As used herein, the term "host cell" refers to a vehicle that includes the necessary cellular components, e.g., organelles, needed to express proteins from their corresponding nucleic acids. The nucleic acids are typically included in nucleic acid vectors that can be introduced into the host cell by conventional techniques known in the art (e.g., transformation, transfection, electroporation, calcium phosphate precipitation, direct microinjection, etc.). A host cell may be a prokaryotic cell, e.g., a bacterial cell, or a eukaryotic cell, e.g., a mammalian cell (e.g., a CHO cell). As described herein, a host cell is used to express one or more polypeptides encoding anti-FcRn antibodies of the invention.

**[0066]** As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid molecule to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a phage vector. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "recombinant vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids.

**[0067]** As used herein, the term "subject" refers to a mammal, e.g., preferably a human. Mammals include, but are not limited to, humans and domestic and farm animals, such as monkeys (e.g., a cynomolgus monkey), mice, dogs,

cats, horses, and cows, etc.

**[0068]** As used herein, the term "pharmaceutical composition" refers to a medicinal or pharmaceutical formulation that contains an active ingredient as well as one or more excipients and diluents to enable the active ingredient suitable for the method of administration. The pharmaceutical composition of the present invention includes pharmaceutically acceptable components that are compatible with the anti-FcRn antibody. The pharmaceutical composition may be in aqueous form for intravenous or subcutaneous administration or in tablet or capsule form for oral administration.

**[0069]** As used herein, the term "pharmaceutically acceptable carrier" refers to an excipient or diluent in a pharmaceutical composition. The pharmaceutically acceptable carrier must be compatible with the other ingredients of the formulation and not deleterious to the recipient. In the present invention, the pharmaceutically acceptable carrier must provide adequate pharmaceutical stability to the Fc construct. The nature of the carrier differs with the mode of administration. For example, for intravenous administration, an aqueous solution carrier is generally used; for oral administration, a solid carrier is preferred.

**[0070]** As used herein, the term "therapeutically effective amount" refers to an amount, e.g., pharmaceutical dose, effective in inducing a desired biological effect in a subject or patient or in treating a patient having a condition or disorder described herein. It is also to be understood herein that a "therapeutically effective amount" may be interpreted as an amount giving a desired therapeutic effect, either taken in one dose or in any dosage or route, taken alone or in combination with other therapeutic agents.

**DESCRIPTION OF THE DRAWINGS**

**[0071]**

**FIG. 1** includes two graphs and a table that show IgG competitive binding of antibodies N022-N024, N026, and N027 to human or cynomolgus monkey FcRn at pH 6.0.

**FIG. 2** includes graphs that show the effects of antibodies N023, N024, N026, and N027 on IgG catabolism in mice.

**FIG. 3** includes graphs that show the dose-dependent effects of antibody N027 on IgG levels and target occupancy in mice.

**FIG. 4** includes graphs that show the selective induction of IgG catabolism and target occupancy in cynomolgus monkeys following administration of different doses of antibody N027.

**FIG. 5** includes a graph that shows the biodistribution of N027 in mice.

**FIG. 6** includes an experimental timeline and a graph that shows the efficacy of N027 in a mouse collagen antibody-induced arthritis model.

**FIG. 7** includes an experimental timeline and two graphs that show the efficacy of N027 in a mouse chronic idiopathic thrombocytopenia purpura (ITP) model.

**DETAILED DESCRIPTION OF THE INVENTION**

**[0072]** The present invention features isolated antibodies that bind to human neonatal Fc receptor (FcRn) with high affinity. The present invention features anti-FcRn antibodies, methods and compositions for preparing anti-FcRn antibodies, and uses thereof for blocking FcRn activity, reducing immune complex-based activation of an immune response, and treating immunological diseases.

**I. Anti-FcRn antibodies**

**[0073]** In general, the invention features isolated antibodies that bind to the human FcRn with high affinity. An anti-FcRn antibody of the invention refers to an antibody that can bind to human FcRn and inhibit IgG (e.g., IgG autoantibodies) binding to FcRn. In some embodiments, the antibody is a monoclonal antibody. In other embodiments, the antibody is a polyclonal antibody. In some embodiments, the antibody is selected from the group consisting of a chimeric antibody, an affinity matured antibody, a humanized antibody, and a human antibody. In certain embodiments, the antibody is an antibody fragment, e.g., a Fab, Fab', Fab'-SH, $F(ab')_2$, or scFv.

**[0074]** In some embodiments, the antibody is a chimeric antibody. For example, an antibody contains antigen binding sequences from a non-human donor grafted to a heterologous non-human, human, or humanized sequence (e.g., framework and/or constant domain sequences). In one embodiment, the non-human donor is a mouse. In another embodiment, an antigen binding sequence is synthetic, e.g., obtained by mutagenesis (e.g., phage display screening, etc.). In a further embodiment, a chimeric antibody has non-human (e.g., mouse) variable regions and human constant regions. In one example, a mouse light chain variable region is fused to a human κ light chain. In another example, a mouse heavy chain variable region is fused to a human IgG1 constant region.

**[0075]** In one aspect, the disclosure features an isolated antibody capable of binding to human FcRn. The isolated antibody contains: (1) a light chain variable region that includes a CDR L1, a CDR L2, and a CDR L3 and (2) a heavy chain variable region that includes a CDR H1, a CDR H2, and a CDR H3, wherein the CDR L1 has a sequence having at least 92% identity to the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), the CDR L2 has a sequence having at least 85% identity to the sequence of GDSERPS (SEQ ID NO: 2), the CDR L3 has a sequence having at least 90% identity to the sequence of SSYAGSGIYV (SEQ ID NO: 3), the CDR H1 has a sequence having at least 80% identity to the sequence of TYAMG (SEQ ID NO: 4), DYAMG (SEQ ID NO: 5), or NYAMG (SEQ ID NO: 6), the CDR H2 has a sequence having at least 92% identity to the sequence of SIGSSGAQTRYADS (SEQ ID NO: 7), SIGASGSQTRYADS (SEQ ID NO: 8), SIGASGAQTRYADS (SEQ ID NO: 9), or SIGASGGQTRYADS (SEQ ID NO: 10), and the CDR H3 has a sequence having at least 85% identity to the sequence of LAIGDSY (SEQ ID NO: 11). In some embodiments, the antibody binds human FcRn with a $K_D$ of less than 200, 150, 100, 50, or 40 pM. In some embodiments, the antibody binds human FcRn with a $K_D$ that is less than or equal to that of an antibody having the light chain variable region and heavy chain variable region of N022, N023, N024, N026, or N027, and further having the same Fc region as the antibody being compared.

**[0076]** In some embodiments, an isolated antibody of the disclosure has a CDR L1 that has the sequence of $X_1$GTGSDVGSYN$X_2$VS (SEQ ID NO: 12), a CDR L2 that has the sequence of GD$X_3X_4$RPS (SEQ ID NO: 13), a CDR L3 that has the sequence of $X_5$SY$X_6$GSGIYV (SEQ ID NO: 14), a CDR H1 that has the sequence of $Z_1$YAMG (SEQ ID NO: 15), a CDR H2 that has the sequence of SIG$Z_2$SG$Z_3$QT$Z_4$YADS (SEQ ID NO: 16), and a CDR H3 that has the sequence of LA$Z_5Z_6$DSY (SEQ ID NO: 17), where $X_1$ is a polar or hydrophobic amino acid (e.g., preferably T, A, S, or I), $X_2$ is a hydrophobic amino acid (e.g., preferably L or I), $X_3$ is a polar amino acid (e.g., preferably S, N, or T), $X_4$ is a polar or acidic amino acid (e.g., preferably Q, E, or N), $X_5$ is a polar or hydrophobic amino acid (e.g., preferably C, S, I, or Y), $X_6$ is a hydrophobic amino acid (e.g., preferably A or V), $Z_1$ is a polar or acidic amino acid (e.g., preferably E, T, D, or N), $Z_2$ is a polar or hydrophobic amino acid (e.g., preferably S or A), $Z_3$ is G, S, or A, $Z_4$ is a basic amino acid (e.g., preferably K or R), $Z_5$ is a hydrophobic or basic amino acid (e.g., preferably I, L, or H), and $Z_6$ is G, S, D, Q, or H, and where the antibody binds human FcRn with a $K_D$ of less than 200, 150, 100, 50, or 40 pM.

**[0077]** In other embodiments, an isolated antibody of the disclosure has a CDR L1 that has the sequence of TGTGSDVGSYNLVS (SEQ ID NO: 1), a CDR L2 that has the sequence of GDSERPS (SEQ ID NO: 2), a CDR L3 that has the sequence of SSYAGSGIYV (SEQ ID NO: 3), a CDR H1 that has the sequence of $Z_1$YAMG (SEQ ID NO: 15), a CDR H2 that has the sequence of SIG$Z_2$SG$Z_3$QTRYADS (SEQ ID NO: 18), and a CDR H3 that has the sequence of LAIGDSY (SEQ ID NO: 11), where $Z_1$ is T, D, or N, $Z_2$ is S or A, and $Z_3$ is G, S or A.

**[0078]** Table 1 shows the amino acid sequences of the light and heavy chain complementary determining regions (CDRs) of some exemplary anti-FcRn antibodies of the disclosure and invention.

Table 1

| Anti-FcRn antibody | CDR L1 | CDR L2 | CDR L3 | CDR H1 | CDR H2 | CDR H3 |
|---|---|---|---|---|---|---|
| N022 | TGTGSDVGSYNLVS (SEQ ID NO: 1) | GDSERPS (SEQ ID NO: 2) | SSYAGSGIYV (SEQ ID NO: 3) | TYAMG (SEQ ID NO: 4) | SIGSSGAQTRYADS (SEQ ID NO: 7) | LAIGDSY (SEQ ID NO: 11) |
| N023 | TGTGSDVGSYNLVS (SEQ ID NO: 1) | GDSERPS (SEQ ID NO: 2) | SSYAGSGIYV (SEQ ID NO: 3) | DYAMG (SEQ ID NO: 5) | SIGASGSQTRYADS (SEQ ID NO: 8) | LAIGDSY (SEQ ID NO: 11) |
| N024 | TGTGSDVGSYNLVS (SEQ ID NO: 1) | GDSERPS (SEQ ID NO: 2) | SSYAGSGIYV (SEQ ID NO: 3) | NYAMG (SEQ ID NO: 6) | SIGASGAQTRYADS (SEQ ID NO: 9) | LAIGDSY (SEQ ID NO: 11) |
| N026 | TGTGSDVGSYNLVS (SEQ ID NO: 1) | GDSERPS (SEQ ID NO: 2) | SSYAGSGIYV (SEQ ID NO: 3) | TYAMG (SEQ ID NO: 4) | SIGASGGQTRYADS (SEQ ID NO: 10) | LAIGDSY (SEQ ID NO: 11) |
| N027 | TGTGSDVGSYNLVS (SEQ ID NO: 1) | GDSERPS (SEQ ID NO: 2) | SSYAGSGIYV (SEQ ID NO: 3) | TYAMG (SEQ ID NO: 4) | SIGASGSQTRYADS (SEQ ID NO: 8) | LAIGDSY (SEQ ID NO: 11) |

**[0079]** Table 2 shows the SEQ ID NOs of the light and heavy chain variable regions of these exemplary anti-FcRn antibodies of the disclosure and invention.

Table 2

| Anti-FcRn antibody | Light Chain Variable Region | Heavy Chain Variable Region |
|---|---|---|
| N022 | SEQ ID NO: 19 | SEQ ID NO: 20 |
| N023 | | SEQ ID NO: 21 |
| N024 | | SEQ ID NO: 22 |
| N026 | | SEQ ID NO: 23 |
| N027 | | SEQ ID NO: 24 |

**[0080]** In some embodiments, the light chain variable region of an isolated antibody of the disclosure has a sequence having at least 90% identity to the sequence of

QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN
TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP
GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC
S (SEQ ID NO: 19).

**[0081]** In some embodiments, the heavy chain variable region of an isolated antibody of the disclosure has a sequence having at least 90% identity to the sequence of

EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGSSGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH

NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 20).

**[0082]** In some embodiments, the heavy chain variable region of an isolated antibody of the disclosure has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 21).

**[0083]** In some embodiments, the heavy chain variable region of an isolated antibody of the disclosure has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLEWVSSIGASGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE

MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 22).

**[0084]** In other embodiments, the heavy chain variable region of an isolated antibody of the disclosure has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGGQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 23).

**[0085]** In yet other embodiments, the heavy chain variable region of an isolated antibody of the disclosure has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24).

**[0086]** The disclosure features an isolated antibody including a light chain variable region and a heavy chain variable region, where the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN
TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP
GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH

NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24).

**[0087]** The disclosure also provides an isolated antibody including a light chain variable region and a heavy chain variable region, where the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGSSGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 20).

**[0088]** The disclosure also provides an isolated antibody including a light chain variable region and a heavy chain variable region, where the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 21).

**[0089]** The disclosure also provides an isolated antibody including a light chain variable region and a heavy chain variable region, where the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLEWVSSIGASGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 22).

**[0090]** The disclosure also provides an isolated antibody including a light chain variable region and a heavy chain variable region, where the light chain variable region has a sequence having at least 90% identity to the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has a sequence having at least 90% identity to the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGGQTRYADSVKGRFTI

SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 23).

**[0091]** Furthermore, in any of the anti-FcRn antibodies described herein, the heavy chain variable region of the antibody has a sequence having at least 95%, 97%, 99%, or 100% identity to the sequence of any one of SEQ ID NOs: 20-24. In any of the anti-FcRn antibodies described herein, the light chain variable region has a sequence having at least 95%, 97%, 99%, or 100% identity to the sequence of SEQ ID NO: 19.

**[0092]** The antibodies of the disclosure may further contain amino acid substitutions, additions, and/or deletions outside of the CDRs (i.e., in framework regions (FRs)). In some embodiments, the antibodies of the invention may further include any one or more of the following amino acid substitutions: A23V, S30R, L80V, A84T, E85D, A93V, relative to the sequence of any one of SEQ ID NOs: 20-24, and Q38H, V58I, and G99D, relative to the sequence of SEQ ID NO: 19.

**[0093]** In some embodiments, the antibodies of the disclosure may include amino acid substitutions, additions, and/or deletions in the constant regions (e.g., Fc region) of the antibody that, e.g., lead to decreased effector function, e.g., decreased complement-dependent cytolysis (CDC), antibody-dependent cell-mediated cytolysis (ADCC), and/or antibody-dependent cell-mediated phagocytosis (ADCP), and/or decreased B-cell killing. The constant regions are not involved directly in binding an antibody to its target, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity. In some embodiments, the antibodies of the invention are characterized by decreased binding (i.e., absence of binding) to human complement factor C1q and/or human Fc receptor on natural killer (NK) cells. In other embodiments, the antibodies of the invention are characterized by decreased binding (i.e., absence of binding) to human FcγRI, FcγRIIA, and/or FcγRIIIA. To alter or reduce an antibody-dependent effector function, such as CDC, ADCC, ADCP, and/or B-cell killing, antibodies of the invention may be of the IgG class and contain one or more amino acid substitutions E233, L234, G236, D265, D270, N297, E318, K320, K322, A327, A330, P331, and/or P329 (numbering according to the EU index of Kabat (Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991))). In some embodiments, the antibodies contain the mutations L234A/L235A or D265A/N297A. The resulting effectorless antibody shows very little binding to complement or Fc receptors (i.e., complement C1q binding), indicating low CDC potential.

**[0094]** In other embodiments, the antibodies of the invention may include those having specific amino acid changes that improve stability of the antibody.

**[0095]** Moreover, in other embodiments, to minimize potential immunogenicity, some antibodies of the invention or disclosure, e.g., N024, N026, and N027, may undergo an allotype change from G1m17.1 to G1m17 by substituting amino acids D355 and L357 (relative to the sequence of any one of SEQ ID NOs: 20-24) to glutamic acid and methionine, respectively.

**[0096]** The invention features an isolated antibody that comprises a polypeptide having the amino acid sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and a polypeptide having the amino acid sequence of

EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24).

MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24).

**[0097]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGSSGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 20).

**[0098]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMGWVRQAPGKGLEWVSSIGASGSQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG (SEQ ID NO: 21).

**[0099]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMGWVRQAPGKGLEWVSSIGASGAQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 22).

**[0100]** The disclosure also provides an isolated antibody containing a light chain variable region and a heavy chain variable region, wherein the light chain variable region has the sequence of QSALTQPASVSGSPGQSITISCTGTGSDVGSYNLVSWYQQHPGKAPKLMIYGDSERPSGVSNRFSGSKSGN TASLTISGLQAEDEADYYCSSYAGSGIYVFGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTEC S (SEQ ID NO: 19); and the heavy chain variable region has the sequence of
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMGWVRQAPGKGLEWVSSIGASGGQTRYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARLAIGDSYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK

VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPG (SEQ ID NO: 23).

**[0101]** In any of the anti-FcRn antibodies described herein, in some embodiments, the antibody binds mouse or rat FcRn with a $K_D$ of less than 200, 150, 100, 50, or 40 pM.

**[0102]** In any of the anti-FcRn antibodies described herein, in some embodiments, the antibody binds to human FcRn with an affinity of between 1-100, 5-150, 5-100, 5-75, 5-50, 10-50, or 10-40 pM.

**[0103]** The anti-FcRn antibodies of the disclosure may be of immunoglobulin antibody isotype IgG, IgE, IgM, IgA, or IgD. Preferably, the anti-FcRn antibodies are of immunoglobulin antibody isotype IgG. The anti-FcRn antibodies may also be of any immunoglobulin antibody isotype subclasses. For example, the anti-FcRn antibodies may be of IgG subclass IgG1, IgG2, IgG3, or IgG4. Preferably, the anti-FcRn antibodies are of subclass IgG1. In particular, the anti-FcRn antibodies of the disclosure contain an IgG G1m17 or G1 m17.1 allotype heavy chain. In some disclosure, the light chain of the anti-FcRn antibodies may be a κ light chain, a λ light chain, or a κ-λ chimeric light chain. In preferred embodiments, the anti-FcRn antibodies of the invention contain a full-length λ light chain.

**[0104]** In some embodiments, the antibodies of the invention are monoclonal. The antibodies of the invention may also be polyclonal, chimeric, humanized or fully human. In some embodiments, the antibody of the invention may be affinity matured. In other embodiments, the antibody of the invention may be an antibody fragment.

**[0105]** Without being bound by theory, it is believed that the anti-FcRn antibodies of the invention compete with and inhibit the binding of IgG to human FcRn. Epitope mapping by hydrogen-deuterium exchange of the antibodies of the invention indicates that the antibodies bind to an epitope on FcRn located in and/or adjacent to the Fc-FcRn interaction interface, which suggests that the antibodies of the invention block IgG binding to FcRn by direction inhibition. Furthermore, the epitope-mapped binding site is distant from the albumin-binding site of FcRn. Accordingly, serum albumin-binding should not be inhibited and serum albumin levels should not be decreased. Indeed, experimental evidence shows mouse albumin levels remained constant after anti-FcRn antibody administration, indicating that albumin recycling is not disturbed by antibody binding to FcRn.

**III. FcRn inhibition**

**[0106]** FcRn is a type I transmembrane protein that functions as an IgG- and serum albumin-binding, intracellular vesicular trafficking protein. FcRn is expressed in endothelial cells, luminal epithelial cells, hepatocytes, podocytes, granulocytes, monocytes, macrophages, dendritic cells, and NK cells, but not on B or T cells. FcRn maintains the half-life of IgG by binding and trafficking constitutively internalized IgG back to the cell surface. Binding of both Fc and serum albumin by FcRn occurs in the early endosome at pH 6.0, followed by sorting of the FcRn into vesicles, which traffic the FcRn-bound IgG or albumin back to the cell surface where FcRn rapidly releases the IgG or albumin at pH 7.4. This trafficking cycle maintains the half-life of IgG and albumin by recycling both into the circulation and preventing trafficking to the lysosomes for degradation. FcRn also captures internalized IgG Fc in epithelial cells and transports them bidirectionally to the opposing apical or basolateral membranes. This function allows IgG to traffic to the lumen of organs such as the gastrointestinal tract or the transport of IgG or IgG-antigen complexes from the lumen to the vasculature or lymphoid tissues in the stromal layers.

**[0107]** In order to study the contribution of FcRn to IgG homeostasis, mice have been engineered so that parts of the light and heavy chains of FcRn have been "knocked out" so that these proteins are not expressed (Junghans et al., Proc Natl Acad Sci USA 93:5512, 1996). In these mice, the serum half-life and concentrations of IgG were dramatically reduced, suggesting an FcRn-dependent mechanism of IgG homeostasis. Studies in rodent models, such as the one discussed above, suggest that blockage of FcRn can increase IgG catabolism, including that of pathogenic autoantibodies, thereby inhibiting disease (e.g., an autoimmune disease) development. FcRn may also

contribute to antigen presentation through trafficking of immune complexes to antigen degradation and MHC loading compartments.

**[0108]** The present invention provides isolated anti-FcRn antibodies that bind to human FcRn with high affinity. The anti-FcRn antibodies of the invention compete with and effectively inhibit the binding of other anti-FcRn antibodies (e.g., IgG, IgG autoantibodies) to FcRn, thereby increasing the catabolism and decreasing the half-life of other anti-FcRn antibodies (e.g., IgG, IgG autoantibodies). The anti-FcRn antibodies of the invention may be used in a method of treating or reducing immune complex-based activation of an immune response in a subject, such as an immune response caused by autoantibodies in an autoimmune disease.

**IV. Vectors, host cells, and antibody production**

**[0109]** The anti-FcRn antibodies of the invention can be produced from a host cell. A host cell refers to a vehicle that includes the necessary cellular components, e.g., organelles, needed to express the polypeptides and constructs described herein from their corresponding nucleic acids. The nucleic acids may be included in nucleic acid vectors that can be introduced into the host cell by conventional techniques known in the art (e.g., transformation, transfection, electroporation, calcium phosphate precipitation, direct microinjection, infection, etc). The choice of nucleic acid vectors depends in part on the host cells to be used. Generally, preferred host cells are of either prokaryotic (e.g., bacterial) or eukaryotic (e.g., mammalian) origin.

***Nucleic acid vector construction and host cells***

**[0110]** A nucleic acid sequence encoding the amino acid sequence of an anti-FcRn antibody of the invention may be prepared by a variety of methods known in the art. These methods include, but are not limited to, oligonucleotide-mediated (or site-directed) mutagenesis and PCR mutagenesis. A nucleic acid molecule encoding an anti-FcRn antibody of the invention may be obtained using standard techniques, e.g., gene synthesis. Alternatively, a nucleic acid molecule encoding a wild-type anti-FcRn antibody may be mutated to contain specific amino acid substitutions using standard techniques in the art, e.g., QuikChange™ mutagenesis. Nucleic acid molecules can be synthesized using a nucleotide synthesizer or PCR techniques.

**[0111]** Nucleic acid sequences encoding anti-FcRn antibodies of the invention may be inserted into a vector capable of replicating and expressing the nucleic acid molecules in prokaryotic or eukaryotic host cells. Many vectors are available in the art and can be used for the purpose of the invention. Each vector may contain various components that may be adjusted and optimized for compatibility with the particular host cell. For example, the vector components may include, but are not limited to, an origin of replication, a selection marker gene, a promoter, a ribosome binding site, a signal sequence, the nucleic acid sequence encoding protein of interest, and a transcription termination sequence.

**[0112]** In some embodiments, mammalian cells are used as host cells for the invention. Examples of mammalian cell types include, but are not limited to, human embryonic kidney (HEK) (e.g., HEK293, HEK 293F), Chinese hamster ovary (CHO), HeLa, COS, PC3, Vero, MC3T3, NS0, Sp2/0, VERY, BHK, MDCK, W138, BT483, Hs578T, HTB2, BT20, T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7O3O, and HsS78Bst cells. In other embodiments, E. *coli* cells are used as host cells for the invention. Examples of E. *coli* strains include, but are not limited to, *E. coli* 294 (ATCC®31 ,446), *E. coli* λ 1776 (ATCC®31 ,537, *E. coli* BL21 (DE3) (ATCC® BAA-1025), and *E. coli* RV308 (ATCC® 31,608). Different host cells have characteristic and specific mechanisms for the posttranslational processing and modification of protein products. Appropriate cell lines or host systems may be chosen to ensure the correct modification and processing of the anti-FcRn antibody expressed. The above-described expression vectors may be introduced into appropriate host cells using conventional techniques in the art, e.g., transformation, transfection, electroporation, calcium phosphate precipitation, and direct microinjection. Once the vectors are introduced into host cells for protein production, host

cells are cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. Methods for expression of therapeutic proteins are known in the art, see, for example, Paulina Balbas, Argelia Lorence (eds.) Recombinant Gene Expression: Reviews and Protocols (Methods in Molecular Biology), Humana Press; 2nd ed. 2004 (July 20, 2004) and Vladimir Voynov and Justin A. Caravella (eds.) Therapeutic Proteins: Methods and Protocols (Methods in Molecular Biology) Humana Press; 2nd ed. 2012 (June 28, 2012).

***Protein production, recovery, and purification***

**[0113]** Host cells used to produce the anti-FcRn antibodies of the invention may be grown in media known in the art and suitable for culturing of the selected host cells. Examples of suitable media for mammalian host cells include Minimal Essential Medium (MEM), Dulbecco's Modified Eagle's Medium (DMEM), Expi293™ Expression Medium, DMEM with supplemented fetal bovine serum (FBS), and RPMI-1640. Examples of suitable media for bacterial host cells include Luria broth (LB) plus necessary supplements, such as a selection agent, e.g., ampicillin. Host cells are cultured at suitable temperatures, such as from about 20 °C to about 39 °C, e.g., from 25 °C to about 37 °C, preferably 37 °C, and $CO_2$ levels, such as 5 to 10% (preferably 8%). The pH of the medium is generally from about 6.8 to 7.4, e.g., 7.0, depending mainly on the host organism. If an inducible promoter is used in the expression vector of the invention, protein expression is induced under conditions suitable for the activation of the promoter.

**[0114]** Protein recovery typically involves disrupting the host cell, generally by such means as osmotic shock, sonication, or lysis. Once the cells are disrupted, cell debris may be removed by centrifugation or filtration. The proteins may be further purified. An anti-FcRn antibody of the invention may be purified by any method known in the art of protein purification, for example, by protein A affinity, other chromatography (e.g., ion exchange, affinity, and size-exclusion column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins, (see Process Scale Purification of Antibodies, Uwe Gottschalk (ed.) John Wiley & Sons, Inc., 2009). In some instances, an anti-FcRn antibody can be conjugated to marker sequences, such as a peptide to facilitate purification. An example of a marker amino acid sequence is a hexa-histidine peptide (His-tag), which binds to nickel-functionalized agarose affinity column with micromolar affinity. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein.

**[0115]** Alternatively, anti-FcRn antibodies of the invention can be produced by the cells of a subject (e.g., a human), e.g., in the context of therapy, by administrating a vector (e.g., a retroviral vector, adenoviral vector, poxviral vector (e.g., vaccinia viral vector, such as Modified Vaccinia Ankara (MVA)), adeno-associated viral vector, and alphaviral vector) containing a nucleic acid molecule encoding the anti-FcRn antibody of the invention. The vector, once inside a cell of the subject (e.g., by transformation, transfection, electroporation, calcium phosphate precipitation, direct microinjection, infection, etc) will promote expression of the anti-FcRn antibody, which is then secreted from the cell. If treatment of a disease or disorder is the desired outcome, no further action may be required. If collection of the protein is desired, blood may be collected from the subject and the protein purified from the blood by methods known in the art.

**V. Pharmaceutical compositions and preparations**

**[0116]** The invention features pharmaceutical compositions that include one or more anti-FcRn antibodies described herein. In some embodiments, pharmaceutical compositions of the invention contain one or more antibodies of the disclosure or invention, e.g., N022-N024, N026, and N027, as the therapeutic proteins. In other embodiments, pharmaceutical compositions of the invention containing one or more antibodies of the disclosure or invention, e.g., N022-N024, N026, and N027, may be used in combination with other agents (e.g., therapeutic biologics and/or small molecules) or compositions in a therapy. In addition to a therapeutically effective amount of the antibody, the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, which can be formulated by methods known to those skilled in the art.

**[0117]** Acceptable carriers and excipients in the pharmaceutical compositions are nontoxic to recipients at the dosages and concentrations employed. Acceptable carriers and excipients may include buffers, antioxidants, preservatives, polymers, amino acids, and carbohydrates. Pharmaceutical compositions of the invention can be administered parenterally in the form of an injectable formulation. Pharmaceutical compositions for injection (i.e., intravenous injection) can be formulated using a sterile solution or any pharmaceutically acceptable liquid as a vehicle. Pharmaceutically acceptable vehicles include, but are not limited to, sterile water, physiological saline, and cell culture media (e.g., Dulbecco's Modified Eagle Medium (DMEM), α-Modified Eagles Medium (α-MEM), F-12 medium). Formulation methods are known in the art, see e.g., Banga (ed.) Therapeutic Peptides and Proteins: Formulation, Processing and Delivery Systems (2nd ed.) Taylor & Francis Group, CRC Press (2006).

**[0118]** The pharmaceutical composition may be formed in a unit dose form as needed. The amount of active component, e.g., one or more anti-FcRn antibodies of the disclosure or invention (e.g., N022-N024, N026, and N027, preferably N027 and/or N024), included in the pharmaceutical preparations is such that a suitable dose within the designated range is provided (e.g., a dose within the range of 0.01-500 mg/kg of body weight).

**VI. Routes, dosage, and administration**

**[0119]** Pharmaceutical compositions of the invention that contain one or more anti-FcRn antibodies of the disclosure or invention (e.g., N022-N024, N026, and N027, preferably N027 and/or N024) as the therapeutic proteins may be formulated for intravenous administration, parenteral administration, subcutaneous administration, intramuscular administration, intra-arterial administration, intrathecal administration, or intraperitoneal administration. In particular, intravenous administration is preferred. The pharmaceutical composition may also be formulated for, or administered via, oral, nasal, spray, aerosol, rectal, or vaginal administration. For injectable formulations, various effective pharmaceutical carriers are known in the art.

**[0120]** The dosage of the pharmaceutical compositions of the invention depends on factors including the route of administration, the disease to be treated, and physical characteristics, e.g., age, weight, general health, of the subject. Typically, the amount of an anti-FcRn antibody of the invention (i.e. N027) contained within a single dose may be an amount that effectively prevents, delays, or treats the disease without inducing significant toxicity. A pharmaceutical composition of the invention may include a dosage of an anti-FcRn antibody of the invention ranging from 0.01 to 500 mg/kg (e.g., 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg/kg) and, in a more specific embodiment, about 1 to about 100 mg/kg and, in a more specific embodiment, about 1 to about 50 mg/kg. The dosage may be adapted by the physician in accordance with conventional factors such as the extent of the disease and different parameters of the subject.

**[0121]** The pharmaceutical compositions are administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective to result in an improvement or remediation of the symptoms. The pharmaceutical compositions are administered in a variety of dosage forms, e.g., intravenous dosage forms, subcutaneous dosage forms, and oral dosage forms (e.g., ingestible solutions, drug release capsules). Generally, therapeutic proteins are dosed at 1-100 mg/kg, e.g., 1-50 mg/kg. Pharmaceutical compositions of the invention that contain an anti-FcRn antibody of the disclosure or invention (e.g., any one of N022-N024, N026, and N027, preferably N027 or N024) may be administered to a subject in need thereof, for example, one or more times (e.g., 1-10 times or more) daily, weekly, monthly, biannually, annually, or as medically necessary. Dosages may be provided in either a single or multiple dosage regimens. The timing between administrations may decrease as the medical condition improves or increase as the health of the patient declines.

**VII. Indications**

**[0122]** The blockade of human FcRn by anti-FcRn antibodies of the invention may be of therapeutic benefit in

diseases that are driven by IgG autoantibodies. The ability of FcRn blockade to induce overall IgG catabolism and removal of multiple species of autoantibodies without perturbing serum albumin, small circulating metabolites, or lipoproteins offers a method to expand the utility and accessibility of an autoantibody removal strategy to patients with autoantibody-driven autoimmune disease pathology. While the invention is not bound by theory, the dominant mechanism of action of an anti-FcRn antibody of the invention may be to increase the catabolism of pathogenic autoantibodies in circulation and decrease autoantibody and immune complex deposition in affected tissues.

**[0123]** The pharmaceutical compositions of the disclosure or invention containing one or more anti-FcRn antibodies (e.g. N022-N024, N026, and N027, preferably N027 and/or N024) are useful to promote catabolism and clearance of pathogenic antibodies, e.g., IgG and IgG autoantibodies in a subject, to reduce the immune response, e.g., to block immune complex-based activation of the immune response in a subject, and to treat immunological conditions or diseases in a subject. In particular, the pharmaceutical compositions and methods of the invention are useful to reduce or treat an immune complex-based activation of an acute or chronic immune response. The acute immune response may be activated by a medical condition selected from the group consisting of pemphigus vulgaris, lupus nephritis, myasthenia gravis, Guillain-Barré syndrome, antibody-mediated rejection, catastrophic anti-phospholipid antibody syndrome, immune complex-mediated vasculitis, glomerulitis, a channelopathy, neuromyelitis optica, autoimmune hearing loss, idiopathic thrombocytopenia purpura (ITP), autoimmune haemolytic anaemia (AIHA), immune neutropenia, dialated cardiomyopathy, and serum sickness. The chronic immune response may be activated by a medical condition selected from the group consisting of chronic inflammatory demyelinating polyneuropathy (CIDP), systemic lupus, a chronic form of a disorder indicated for acute treatment, reactive arthropathies, primary biliary cirrhosis, ulcerative colitis, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

**[0124]** In some embodiments, the pharmaceutical compositions and methods of the invention are useful to reduce or treat an immune response activated by an autoimmune disease. The autoimmune disease may be selected from the group consisting of alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, Addison's disease, hemolytic anemia, autoimmune hepatitis, hepatitis, Behcets disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, limited scleroderma (CREST syndrome), cold agglutinin disease, Crohn's disease, dermatomyositis, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia, fibromyositis, Graves' disease, Hashimoto's thyroiditis, hypothyroidism, inflammatory bowel disease, autoimmune lymphoproliferative syndrome, idiopathic pulmonary fibrosis, IgA nephropathy, insulin dependent diabetes, juvenile arthritis, lichen planus, lupus, Ménière's Disease, mixed connective tissue disease, multiple sclerosis, pernicious anemia, polyarteritis nodosa, polychondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren's syndrome, stiff-man syndrome, Takayasu arteritis, temporal arteritis, ulcerative colitis, uveitis, vitiligo, and Wegener's granulomatosis.

**[0125]** In particular, the pharmaceutical compositions and methods of the invention are useful to reduce or treat an immune response activated by systemic lupus erythematosus, antiphospholipid syndrome, pemphigus vulgaris/bullous pemphigoid, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, myasthenia gravis, or neuromyelitis optica.

**EXAMPLES**

**Example 1 - Antibody production**

**[0126]** IgG heavy and light chain nucleic acid molecules were cloned in vector pCDNA 3.3 using osteonectin secretion signals. HEK 293F cells were grown in Expi293 media at 37 °C with 8% $CO_2$. Cells were transfected at a density of $3\times10^6$/ml with 1 mg total DNA per liter. Enhancers were added on days 2 and 3 following manufacturer's

directions and the cells were cultured until day 5 or 6 before cell viability dropped to below 50% to 60%. The cells were then spun out by centrifugation and the spent media was sterile filtered and stored at 4 °C until antibody purification. Antibodies were purified by a two-column procedure: POROS Protein A chromatography followed by POROS HS-50 cation exchange chromatography. The former separated most of the host cell proteins from the expressed antibodies while the latter removed the heavy chain dimers, light chain dimers, and half antibodies, as well as higher molecular weight species. The fractions from the HS-50 cation exchange column were pooled based on an SDS-PAGE gel analysis to maximize purity of the full length antibodies. The collected fractions were put over a Sephadex G50 buffer exchange column equilibrated in PBS at pH 7.2. The peak fractions were pooled and concentrated to greater than 10 mg/ml using 30 kDa spin concentrators and frozen at -30 °C in 2 mg and 5 mg aliquots. The final protein samples were checked for purity by SDS-PAGE.

**Example 2 - Binding affinities**

**[0127]** Through affinity maturation, we identified more than 100 anti-FcRn antibodies having binding affinities to human FcRn with a $K_D$ in the sub-micromolar range. Five antibodies (N022-N024, N026, and N027) were selected for further characterization. Surface Plasmon Resonance (SPR) was used to determine the on- and off-rates ($k_a$ and $k_d$, respectively) for each of these five antibodies. Briefly, a Bio-Rad GLC sensor chip was inserted into the ProteOn XPR 36 and air initialized. After initialization the running buffer was switched to freshly prepared buffer, either HBSP+ (0.01 M HEPES, 0.15 M NaCl, 0.05% P20, pH 7.4) or Sodium Phosphate Buffer (0.02 M Sodium Phosphate, 0.15 M NaCl, 0.05% P20, pH 6.0) as appropriate, which was used for the remainder of the assay and for all dilutions. The chip was preconditioned using one injection each of 0.5% SDS, 50mM NaOH and 10mM HCl at 30 µl/min for 60 seconds (s). A mouse anti-Human Fc mAb from GE Healthcare (BR100839) was diluted to 10 µg/ml in 10 mM acetate buffer pH 5.0 and approximately 5,700 response units (RU) was immobilized using standard amine coupling chemistry in the horizontal orientation onto a GLC sensor chip. The anti-hFcRn mAbs to be tested were captured onto the surface in the vertical orientation, with the goal of immobilizing approximately 200 response units (RU) per interaction spot. The rhFcRn was diluted in a five-point three-fold dilution series starting at 1.25 µg/ml, leaving one lane as buffer-only for a double reference. The analyte was flowed across the sensor surface in the horizontal orientation at 100 µl/min for 240 s with a 3,600 s dissociation time. Regeneration was accomplished by injecting 3M $MgCl_2$ at 100 µl/min for 30 s in both the horizontal and vertical directions. These procedures were repeated for all ligands.

**[0128]** Data analysis was conducted using the ProteOn Manager software. Each interaction step was adjusted for the Y and X direction using the Auto Process tool, followed by interspot channel referencing to remove non-specific interactions and blank lane double referencing to remove assay drift. The data was fit using the Langmuir 1:1 kinetic model with a grouped Rmax. The $k_a$, $k_d$ and $K_D$ values obtained from ProteOn Manager in a single run were averaged and their percent CV was calculated in Microsoft Excel when the N was three or greater. Table 3 shows that five anti-FcRn antibodies of the invention, N022, N022, N024, N026, and N027, all bind with high affinity to human FcRn at pH 7.4. The equilibrium dissociation constant, $K_D$, of the anti-FcRn antibodies of the invention ranged from 19.4 pM (N027) to 36.5 pM (N026) for binding to human FcRn at pH 7.4. Table 3 also shows the rapid on-rates and slow off-rates of the five anti-FcRn antibodies. At pH 7.4, the on-rates were in the range of 0.93-1.42 × $10^6$ 1/Ms for binding to human FcRn. The off-rates were in the range of 2.31-4.44 × $10^6$ 1/s.

Table 3

| | $k_a$ (1/Ms) | $k_d$ (1/s) | $K_D$ (M) | $R_{max}$ | Chi2 | $K_D$ (pM) |
|---|---|---|---|---|---|---|
| **N022** | 1.42E+06 | 4.42E-05 | 3.10E-11 | 146.93 | 7.65 | 31 |
| **N023** | 9.27E+05 | 2.91E-05 | 3.14E-11 | 193.43 | 5.26 | 31.4 |
| **N024** | 1.13E+06 | 4.03E-05 | 3.55E-11 | 181.17 | 6.12 | 35.5 |
| **N026** | 1.22E+06 | 4.44E-05 | 3.65E-11 | 163.9 | 5.68 | 36.5 |
| **N027** | 1.19E+06 | 2.31E-05 | 1.94E-11 | 211.33 | 7.81 | 19.4 |

**Example 3 - IgG competition**

**[0129]** The ability of anti-FcRn antibodies of the invention to compete with IgG for binding to human or cynomolgus monkey FcRn was evaluated on human embryonic kidney (HEK) 293 cells ectopically expressing cell surface, glycophosphatidylinositol (GPI)-linked FcRn. Human and cynomolgus monkey FcRn alpha amino acid sequences exhibit 97.5% sequence identity. Nine amino acid residues of 355 are different between human and cynomolgus monkey FcRn alpha, but none are in the epitope-mapped binding region. The level of cell-bound IgG was determined using 66 nM of fluorescent probe-labeled, non-specific IgG. The binding of IgG to cell surface FcRn was done at pH 6.0, which allows the Fc portion of IgG to interact with FcRn. As shown in FIG. 1, the amount of cell-bound IgG significantly decreased as the concentration of the anti-FcRn antibody (N022-N024, N026, or N027) increased. The binding of IgG was inhibited in a concentration- and saturation-dependent manner by each of the five exemplary anti-FcRn antibodies of the invention, demonstrating the ability of the anti-FcRn antibodies, N022-N024, N026, and N027, to effectively compete with and inhibit binding of IgG to FcRn at pH 6.0. The EC50 values of the antibodies ranged between 2 and 6 nM.

**Example 4 - Effect of anti-FcRn antibodies on IgG catabolism in mice**

**[0130]** To measure the effect of the anti-FcRn antibodies of the invention on IgG catabolism *in vivo,* human FcRn transgenic mouse strain FcRn-/-hFcRn (32) Tg mice, which lacks mouse FcRn but expresses human FcRn in a tissue distribution similar to the endogenous mouse and human FcRn, was used. FcRn-/-hFcRn (32) Tg mice injected with 500 mg/kg human IgG on day 0 were administered a single dose of an anti-FcRn antibody at 10 mg/kg on days 1 and 4. As shown in FIG. 2, the catabolism of IgG was increased by the administration of anti-FcRn antibodies as seen by lower levels of IgG measured over time in anti-FcRn antibody-treated mice. The activities of N024 ($K_D$ = 35.5 pM), N026 ($K_D$ = 36.5 pM), and N027 ($K_D$ = 19.4 pM) appeared to be to be similar at 10 mg/kg.

**Example 5 - *In vitro* and *in vivo* functional characterizations of anti-FcRn antibodies**

***In vitro***

**[0131]** Cellular binding affinities of the antibodies of the invention were measured on human embryonic kidney (HEK) 293 cells ectopically expressing cell surface, glycophosphatidylinositol (GPI)-linked human or cynomolgus monkey FcRn. FcRn is a type I transmembrane protein with the IgG and albumin binding domains oriented to the luminal side of endosomal membranes or to the cell surface when transported to the plasma membrane. The binding of anti-FcRn antibodies to cell surface, membrane-associated FcRn on HEK293 cells at pH 7.4 mimics binding in a physiologically-relevant environment and at the pH where only the Fab domain and not the Fc domain of the antibodies interact with FcRn. The FcRn extracellular domain was displayed on the cell surface at high density through a C-terminal engineered GPI linkage. The anti-FcRn antibodies of the invention were labeled with a fluorescent probe. The antibodies were allowed to bind for 30 minutes on ice. Cells were then washed at 4 °C and bound antibodies were detected using a fluorophore-labeled secondary antibody, e.g., a goat anti-human IgG $F(ab)_2$. The binding to human FcRn was concentration dependent and antibodies of the invention displayed EC50 values ranging from 4 to 7 nM.

**[0132]** Cellular binding affinities of the antibodies of the invention were also measured on endogenously expressed human FcRn. Monocytes express the highest levels of FcRn and show the highest percent positivity for FcRn expression in mouse and human blood. Monocytic cell line THP-1 was used to evaluate binding of anti-FcRn antibodies to endogenous human FcRn at pH 7.4. Since endogenous FcRn is primarily in intracellular endosomal vesicles in THP-1 cells, the cells were first permeablized with a mild detergent and fixed prior to incubation for 30 minutes at 4 °C with anti-FcRn antibodies in the presence of bovine serum to block non-specific Fc receptor

binding. This assay was able to distinguish antibodies with better binding to endogenous human FcRn. The binding of anti-FcRn antibodies to THP-1 cells is concentration dependent. All antibodies of the invention, e.g., N022-N024, N026, and N027, showed better binding affinities than IgG1. Antibody N027 displayed the highest binding affinity with an EC50 value of 3.0 nM.

**[0133]** The ability of anti-FcRn antibodies of the invention to compete with IgG for binding to human or cynomolgus monkey FcRn was evaluated on human embryonic kidney (HEK) 293 cells ectopically expressing cell surface, GPI-linked FcRn. The level of cell-bound IgG was determined using fluorescent probe-labeled, non-specific IgG. The binding of IgG to cell surface FcRn was done at pH 6.0, which allows the Fc portion of IgG to interact with FcRn. As shown in Example 3 and FIG. 1, the amount of cell-bound IgG significantly decreased as the concentration of the anti-FcRn antibody increased. The binding of IgG was inhibited in a concentration- and saturation-dependent manner by each of the five exemplary anti-FcRn antibodies of the invention, e.g., N022-N024, N026, and N027, demonstrating the ability of the anti-FcRn antibodies to effectively compete with and inhibit binding of IgG to FcRn at pH 6.0. The EC50 values of the antibodies ranged from 2 to 6 nM.

**[0134]** Epitope mapping by hydrogen-deuterium exchange of the antibodies of the invention indicated that the antibodies bind to an epitope on human FcRn located in and/or adjacent to the Fc-FcRn interaction interface, which suggests that the antibodies of the invention block IgG binding to FcRn by direction inhibition. Furthermore, the epitope-mapped binding site is distant from the albumin-binding site of FcRn, thus, serum albumin-binding should not be inhibited and serum albumin levels should not be decreased. An enzyme-linked immunosorbent assay (ELISA) was used to confirm that the antibodies of the invention do not inhibit serum albumin binding to FcRn. Soluble His-tagged extracellular domain of human FcRn was bound to the plate surface and pre-incubated with increasing concentrations of anti-FcRn antibody at pH 6.0. Horseradish peroxidase (HRP)-conjugated human serum albumin was allowed to bind to the soluble, His-tagged FcRn. None of the antibodies inhibited albumin binding to FcRn. Furthermore, *in vivo* experimental evidence also showed that mouse albumin levels remained constant after anti-FcRn antibody administration, indicating that albumin recycling was not disturbed by antibody binding to FcRn.

***In vivo***

**[0135]** To test the *in vivo* effect of anti-FcRn antibodies of the invention on IgG catabolism, human FcRn transgenic mouse strain FcRn-/-hFcRn (32) Tg mice, which lack mouse FcRn but express human FcRn in a tissue distribution similar to that of the endogenous mouse and human FcRn, were used. FcRn-/-hFcRn (32) Tg mice injected with human IgG on day 0 were administered a single dose of an anti-FcRn antibody at 10 mg/kg on days 1 and 4. As shown in Example 3 and FIG. 2, the catabolism of IgG was increased by the administration of anti-FcRn antibodies as seen by lower levels of IgG measured over time in anti-FcRn antibody-treated mice. The activities of N024 ($K_D$ = 35.5 pM), N026 ($K_D$ = 36.5 pM), and N027 ($K_D$ = 19.4 pM) appeared to be to be similar at 10 mg/kg.

**Example 6 - Effect of anti-FcRn antibodies on IgG levels and target occupancy in mice**

**[0136]** N027 was dosed intravenously (i.v.) 24 hrs after administration of 500 mg/kg IVIg (tracer) to Tg32 human FcRn (hFCGRT) transgenic, mouse FcRn (mFCGRT) knockout mice. Circulating human IgG was detected by ELISA on each day. Target occupancy was measured on each day in monocytes from lysed whole blood by fluorescence-activated cell sorting (FACS), after incubation of cells with immunophenotyping cell surface markers followed by fixation and permeabilization. Unoccupied FcRn was measured by staining with Dy650-labeled N027 (n = 4 males per group). As shown in FIG. 3, IgG level and the percentage of unoccupied FcRn were decreased by the administration of N027 in a dose-dependent manner.

**Example 7 - Selective induction of IgG catabolism and target occupancy in cynomolgus monkeys**

**[0137]** N027 was dosed i.v. at t = 0 in cynomolgus monkeys. Circulating endogenous IgG and albumin was detected by ELISA. Target occupancy was measured in monocytes from lysed whole blood by FACS, after incubation of cells with immunophenotyping cell surface markers followed by fixation and permeabilization. Unoccupied FcRn was measured by staining with Dy650-labeled N027. (n = 3 males per group). As shown in FIG. 4, IgG level and the percentage of unoccupied FcRn were decreased by the administration of N027 in a dose-dependent manner, while plasma albumin level stayed unchanged.

**Example 8 - Biodistribution of N027 in mice**

**[0138]** N027 or isotype human IgG1 control antibody labeled with fluorophore (VT680) was administered i.v. to Tg32 human FcRn transgenic, mouse FcRn knockout mice at 30 mg/kg. Levels of labeled antibody were measured in individual organs by quantitative ex vivo optical imaging. FIG. 5 shows the biodistribution of N027 in various organs in mice.

**Example 9 - Efficacy of N027 in mouse collagen antibody-induced arthritis**

**[0139]** Collagen antibody-induced arthritis was induced in Tg32 human FcRn transgenic, mouse FcRn knockout mice by intraperitoneal (i.p.) injection of ArthritoMab™ cocktail (MD Biosciences) on day 1 and inflammatory disease activity induced with 100 µg LPS i.p. on day 4. N027 was dosed therapeutically i.v. at 5 mg/kg (arrow), on day 6 post disease induction and randomization. IVIG at 1 g/kg (positive control group) or vehicle-PBS (negative control) were dosed on day 6 after randomization (n = 5 per group). As shown in FIG. 6, N027 potently inhibits collagen antibody-induced arthritis in human transgenic FcRn mice when dosed therapeutically.

**Example 10 - Efficacy of N027 in mouse chronic idiopathic thrombocytopenia purpura (ITP)**

**[0140]** Thrombocytopenia was induced in Tg32 human FcRn (hFCGRT) transgenic, mouse FcRn (mFCGRT) knockout mice by continuous infusion of anti-platelet antibody (anti-CD41, MWReg30) subcutaneous (s.c.) miniosmotic pump. Circulating platelet levels were decreased to 300 × 109/L or less by 72 hrs (Day 3) after pump implantation. N027 was dosed therapeutically i.v. 72 hrs (day 3) and 120 hrs (Day 5) post-pump implantation (A, n = 4 per group; B, n = 7 per group). FIG. 7 shows the effects of N027 on platelet levels in mice having thrombocytopenia.

# REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

**Patent documents cited in the description**


- WO2012167039A [0001]

**Non-patent literature cited in the description**


- **KABAT**Sequences of Proteins of Immunological InterestPublic Health Service, National Institutes of Health19910000 [0028] [0054] [0093]
- **JUNGHANS et al.**Proc Natl Acad Sci USA, 1996, vol. 93, 5512- [0107]
- Recombinant Gene Expression: Reviews and Protocols (Methods in Molecular Biology)Humana Press20040720 [0112]
- Therapeutic Proteins: Methods and Protocols (Methods in Molecular Biology)Humana Press20120628 [0112]
- Process Scale Purification of Antibodies,John Wiley & Sons, Inc.20090000 [0114]
- Therapeutic Peptides and Proteins: Formulation, Processing and Delivery SystemsTaylor & Francis Group, CRC Press20060000 [0117]

## Patentkrav

**1**. Et isoleret antistof, der binder til humant FcRn, det isolerede antistof omfatter et polypeptid med aminosyresekvensen SEQ ID NO: 19 og et polypeptid med aminosyresekvensen SEQ ID NO: 24.

**2.** Farmaceutisk sammensætning omfattende det isolerede antistof ifølge krav 1 og en eller flere farmaceutisk acceptable bærere eller excipienser.

**3.** Isoleret antistof ifølge krav 1 til anvendelse i en fremgangsmåde til at reducere eller behandle en immunkompleks-baseret aktivering af en akut immunrespons, som aktiveres af en medicinsk tilstand udvalgt fra gruppen bestående af pemfigus vulgaris, lupus nefritis, myasthenia gravis, Guillain-Barre syndrom, antistofmedieret afstødning, katastrofalt antiphospholipid antistof syndrom, immunkompleks medieret vaskulitis, glomerulitis, en kanalopati, neuromyelitis optica, autoimmunt høretab, idiopatisk trombocytopeni (ITP), autoimmun hæmalytisk anæmi (AIHA), immunneutropeni, dilat kardiomyopati og serumsyge.

**4.** Isoleret antistof til anvendelse ifølge krav 3, hvor tilstanden er myasthenia gravis.

**5.** Isoleret antistof til anvendelse ifølge krav 3, hvor tilstanden er lupus nephritis.

**6.** Isoleret antistof til anvendelse ifølge krav 3, hvor tilstanden er AIHA.

**7.** Isoleret antistof ifølge krav 1 til anvendelse i en fremgangsmåde til at reducere eller behandle en immunkompleks-baseret aktivering af en kronisk immunrespons, som aktiveres af en medicinsk tilstand udvalgt fra gruppen bestående af kronisk inflammatorisk demyeliniserende polyneuropati (CIDP), systemisk lupus, reaktive arthropatier, primær biliær cirrose, ulcerøs colitis og antineutrofil cytoplasmatisk antistof (ANCA)-associeret vaskulitis.

**8.** Isoleret antistof til anvendelse ifølge krav 7, hvor tilstanden er CIDP.

**9.** Isoleret antistof ifølge krav 1 til anvendelse i en fremgangsmåde til at reducere eller behandle et immunrespons aktiveret af en autoimmun sygdom.

**10.** Isoleret antistof til anvendelse ifølge krav 9, hvor nævnte autoimmune sygdom er udvalgt fra gruppen bestående af alopecia areata, ankyloserende spondylitis, anti-tifosfolipid syndrom, Addisons sygdom, hæmolytisk anæmi, autoimmun hepatitis, hepatitis, Behcets sygdom, bulløs pemfigoid, kardiomyopati, cøliaki sprue-dermatitis, kronisk træthed immun dysfunktionssyndrom, kronisk inflammatorisk demyeliniserende polyneuropati, Churg-Strauss syndrom,

cicatricial pemfigoid, begrænset sklerodermi (CREST syndrom), kold agglutinin sygdom, discus-agglutinin, essentiel blandet kryoglobulinæmi, fibromyalgi, fibromyositis, Graves' sygdom, Hashimotos thyroiditis, hypothyroidisme, inflammatorisk tarmsygdom, autoimmunt lymfoproliferativt syndrom, idiopatisk lungefibrose, IgA nefropati, nefropati, IgA, nefropati, Insulin-afhængig diabetes, juvenil artritis, lichen planus, lupus, Menieres sygdom, blandet bindevævssygdom, multipel sklerose, perniciøs anæmi, polyarteritis nodosa, polychondritis, polyglandulære syndromer, polymyalgia rheumatica, polymyositis, primær agammaglobulinæmi, primær biliær cirrose, psoriasis, Raynauds sygdom, Reiters syndrom, reumatisk feber, reumatoid artitis, sarkoidose, skleroderma, Sjogrens syndrom, stiff-person syndrom, Takayasu arteritis, temporal arteritis, ulcerøs colitis, uveitis, vitiligo og Wegeners granulomatose.

**11.** Isoleret antistof til anvendelse ifølge krav 10, hvor nævnte autoimmune sygdom er hæmolytisk anæmi.

**12.** Isoleret antistof til anvendelse ifølge krav 10, hvor nævnte autoimmune sygdom er rheumatoid arthritis.

**13.** Nukleinsyremolekyle, der koder for det isolerede antistof ifølge krav 1.

**14.** Vektor indeholdende nukleinsyren ifølge krav 13.

**15.** Værtscelle, der udtrykker det isolerede antistof ifølge krav 1, hvor værtscellen omfatter nukleinsyremolekylet ifølge krav 13 eller vektoren ifølge krav 14, hvor nukleinsyremolekylet eller vektoren er udtrykt i værtscellen.

**16.** Værtscelle ifølge krav 15, hvor værtscellen er en kinesisk hamster-ovariecelle (CHO).

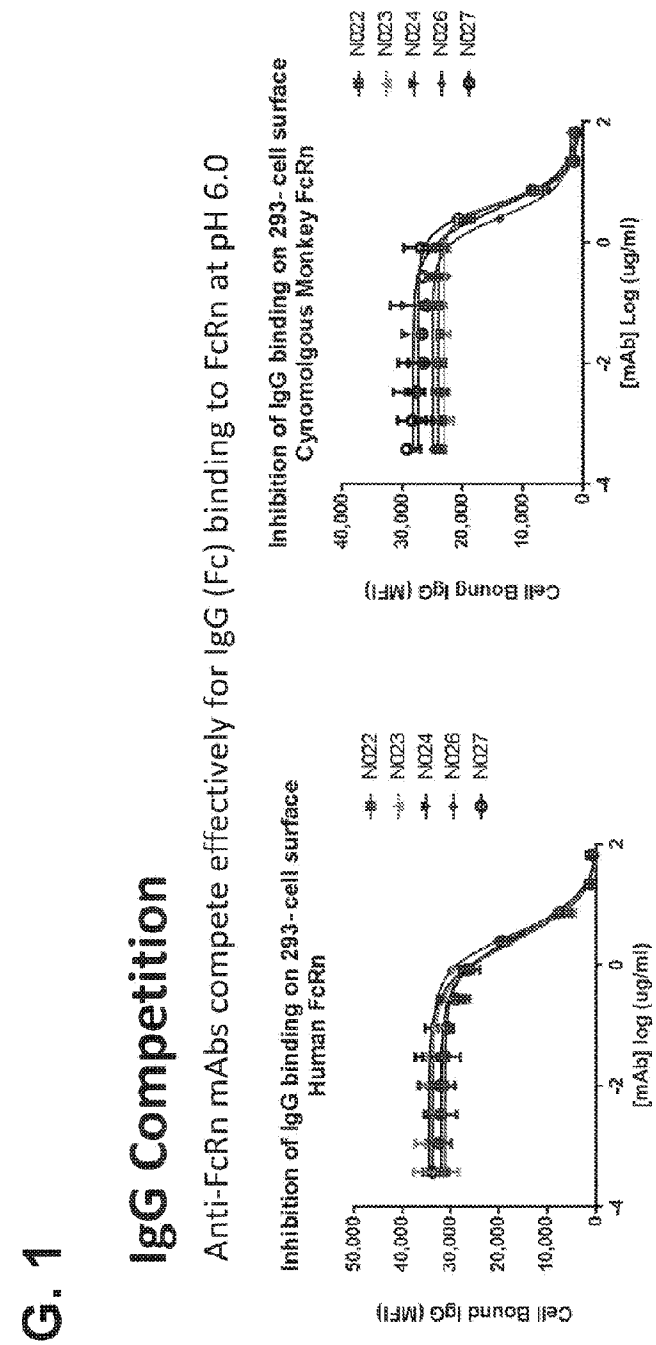
**17.** Fremgangsmåde til fremstilling af det isolerede antistof ifølge krav 1, fremgangsmåden omfatter:

a) tilvejebringelse af en værtscelle omfattende et nukleinsyremolekyle ifølge krav 13 eller en vektor ifølge krav 14; og

b) at udtrykke nukleinsyremolekylet eller vektoren i værtscellen under betingelser, der tillader dannelsen af antistoffet.

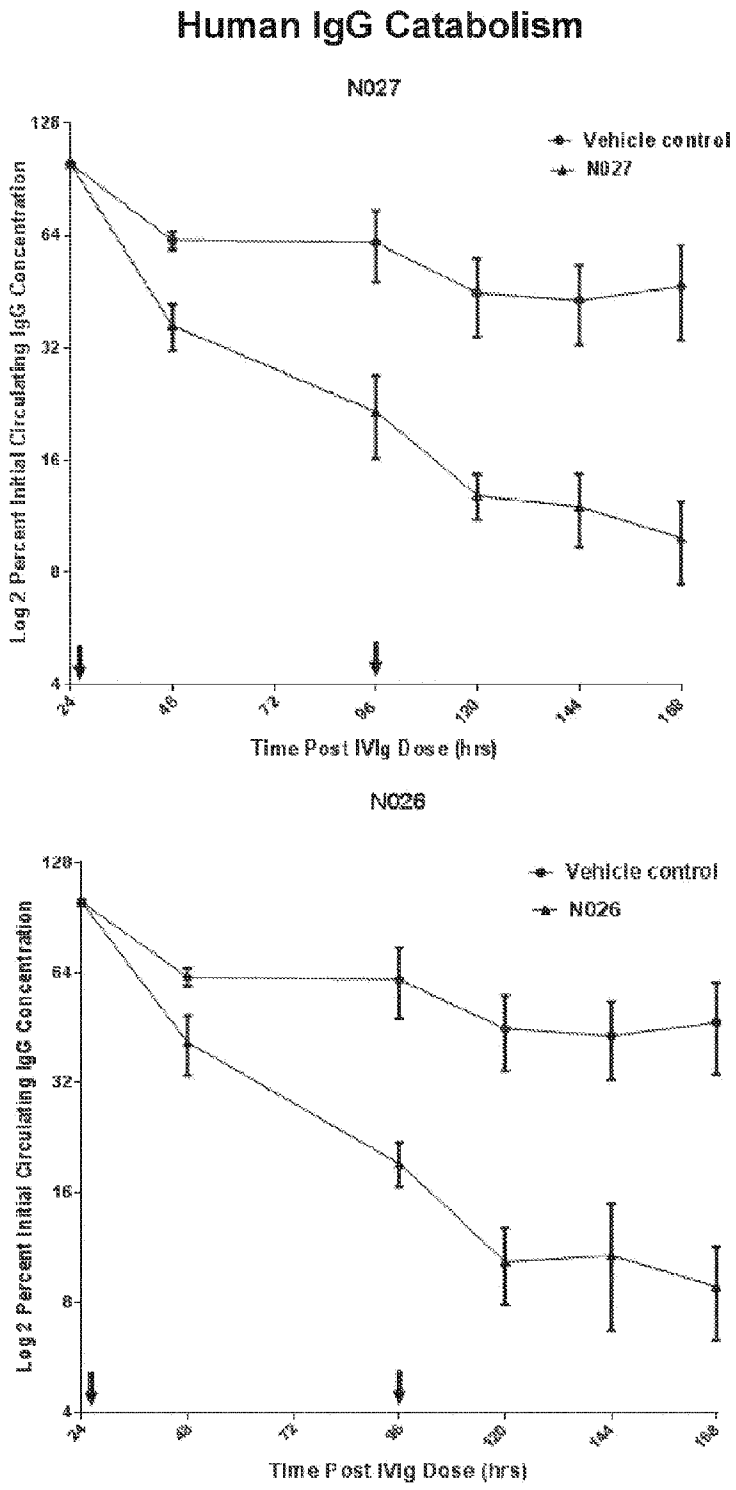
# DRAWINGS

FIG. 1




| EC50 (nM) | N022 | N023 | N024 | N026 | N027 |
|---|---|---|---|---|---|
| Human FcRn | 2.93 | 2.48 | 2.48 | 3.24 | 3.25 |
| Cynomolgus FcRn | 4.80 | 5.16 | 3.51 | 2.68 | 4.46 |

FIG. 2


Human IgG Catabolism
N027
Vehicle control
N027
Log 2 Percent Initial Circulating IgG Concentration
128
64
32
16
8
4
24
48
72
96
120
144
168
Time Post IVIg Dose (hrs)
N026
Vehicle control
N026
Log 2 Percent Initial Circulating IgG Concentration
128
64
32
16
8
4
24
48
72
96
120
144
168
Time Post IVIg Dose (hrs)

# FIG. 2 Cont. Human IgG Catabolism

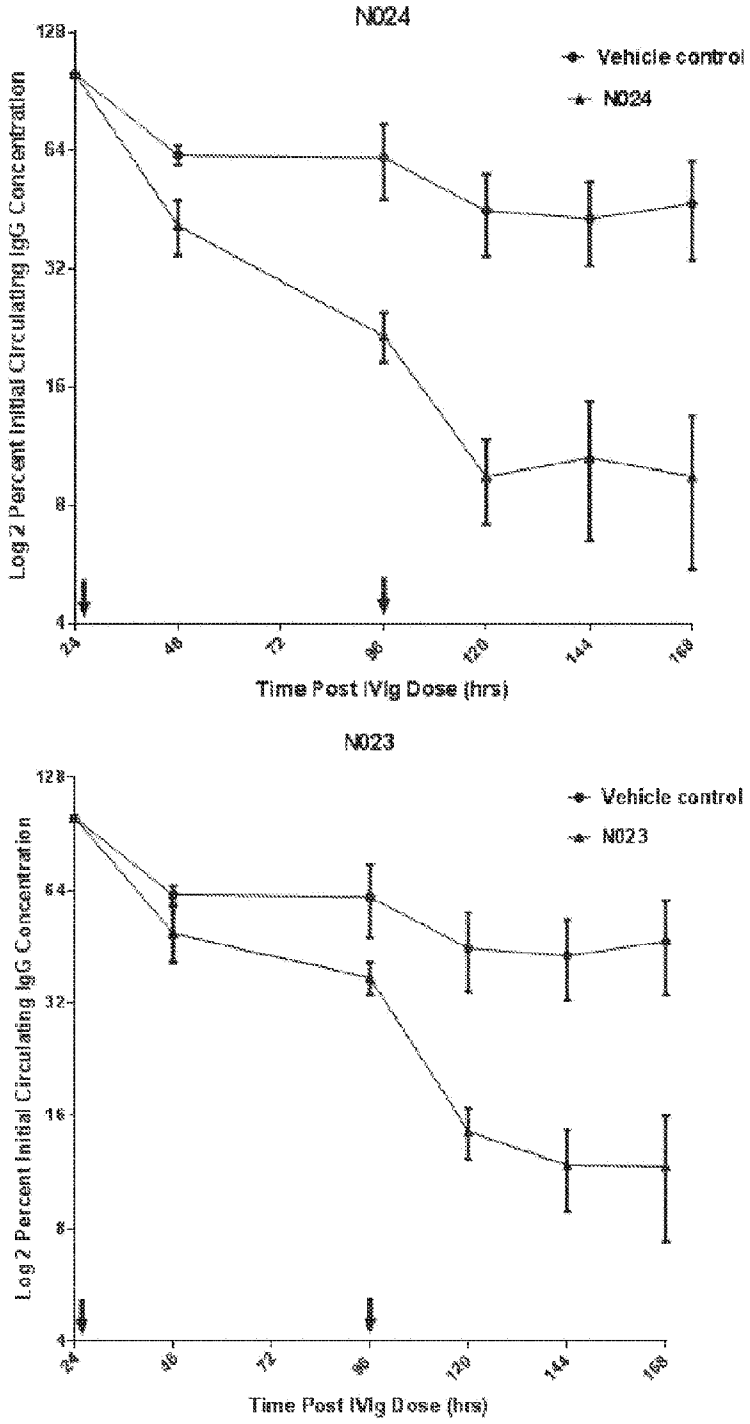


FIG. 3

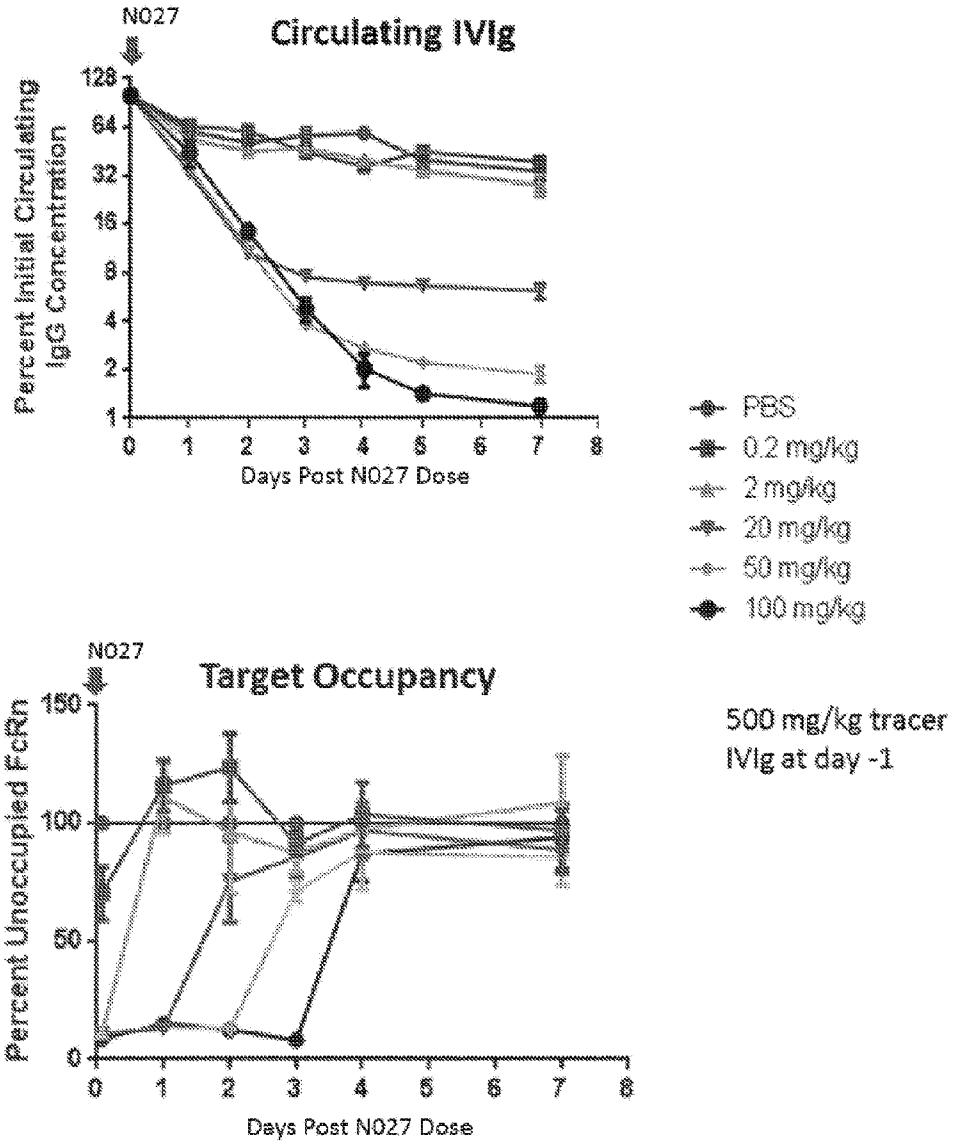

N027
Circulating IVIg
Percent Initial Circulating IgG Concentration
128
64
32
16
8
4
2
1
0 1 2 3 4 5 6 7 8
Days Post N027 Dose
PBS
0.2 mg/kg
2 mg/kg
20 mg/kg
50 mg/kg
100 mg/kg
N027
Target Occupancy
Percent Unoccupied FcRn
150
100
50
0
0 1 2 3 4 5 6 7 8
Days Post N027 Dose
500 mg/kg tracer
IVIg at day -1

FIG. 4

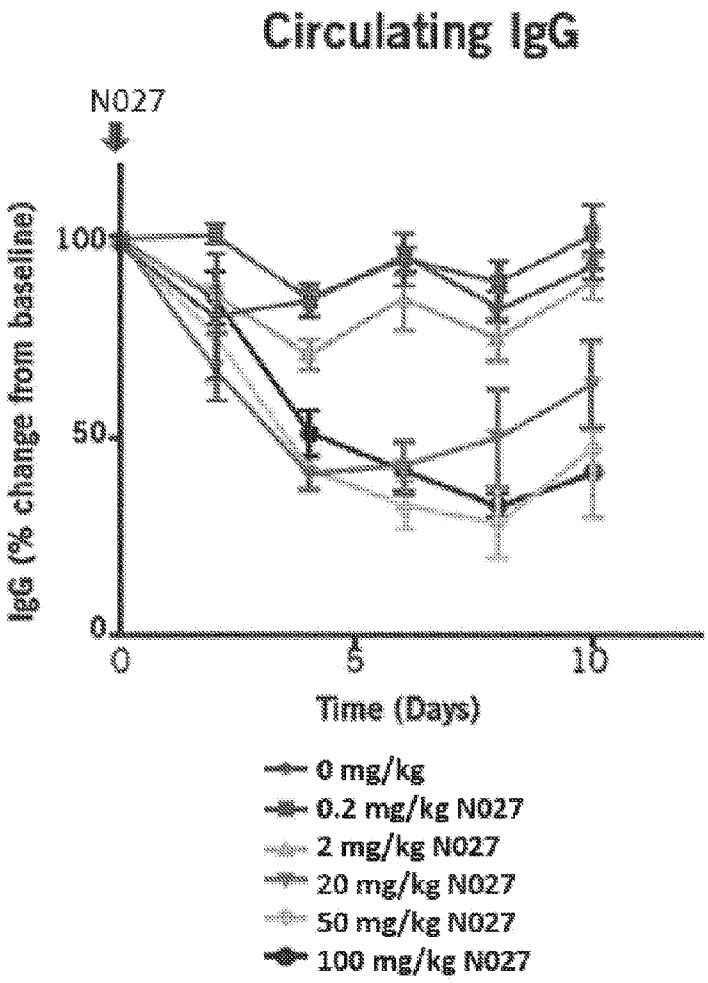

Circulating IgG
N027
IgG (% change from baseline)
100
50
0
0
5
10
Time (Days)
0 mg/kg
0.2 mg/kg N027
2 mg/kg N027
20 mg/kg N027
50 mg/kg N027
100 mg/kg N027

FIG. 4 Cont.

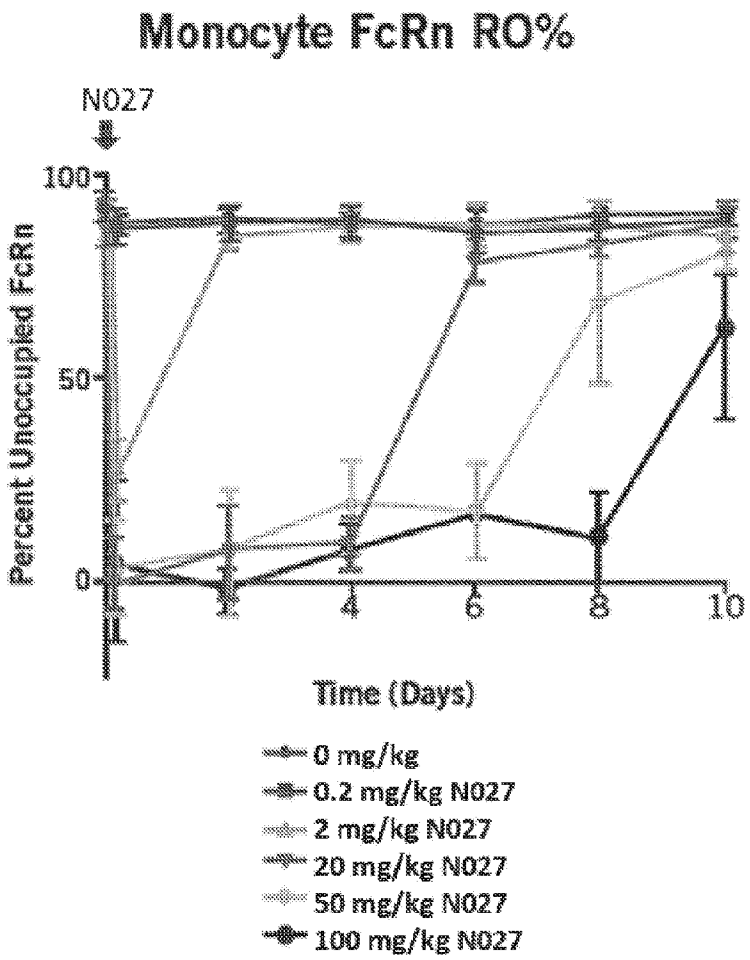

Monocyte FcRn RO%
N027
100
50
0
Percent Unoccupied FcRn
2
4
6
8
10
Time (Days)
0 mg/kg
0.2 mg/kg N027
2 mg/kg N027
20 mg/kg N027
50 mg/kg N027
100 mg/kg N027

FIG. 4 Cont.

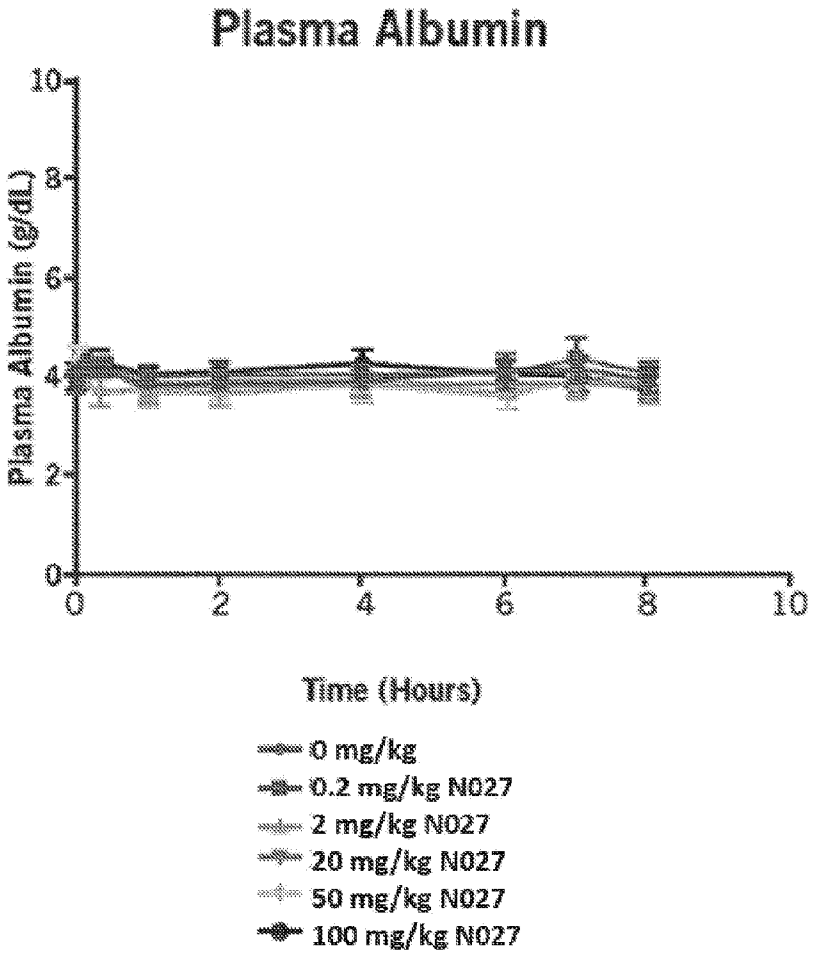

Plasma Albumin
Plasma Albumin (g/dL)
10
8
6
4
2
0
0
2
4
6
8
10
Time (Hours)
0 mg/kg
0.2 mg/kg N027
2 mg/kg N027
20 mg/kg N027
50 mg/kg N027
100 mg/kg N027

FIG. 5

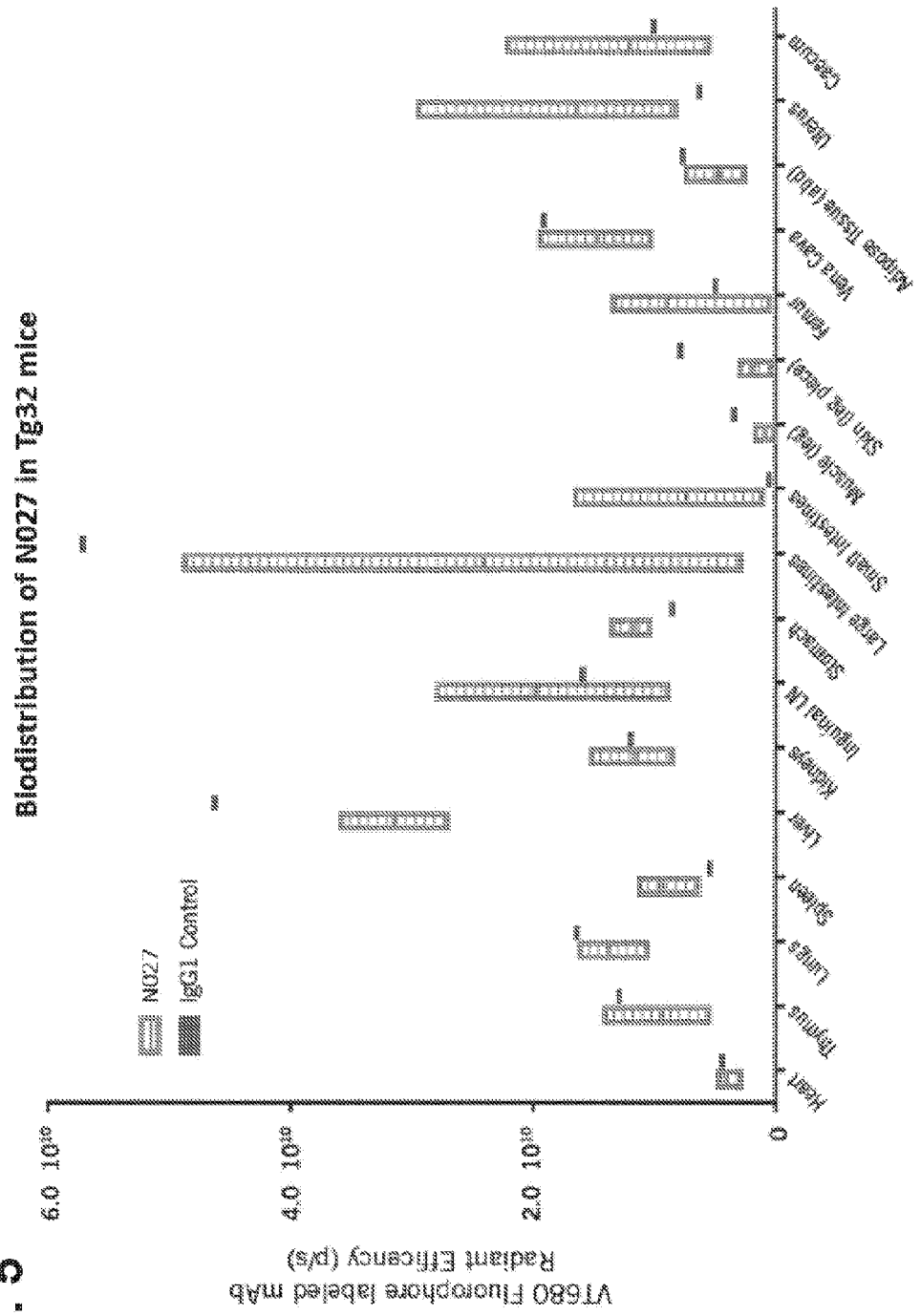

Biodistribution of N027 in Tg32 mice
VT680 Fluorophore labeled mAb
Radiant Efficency (p/s)
6.0 10^6
4.0 10^6
2.0 10^6
0
N027
IgG1 Control
Heart
Thymus
Lungs
Spleen
Liver
Kidneys
Lymph Un
Stomach
Large Intestines
Small Intestines
Muscle (leg)
Skin (low perf)
Femur
Vena Cava
Adipose Tissue (abd)
Ureters
Caecum

FIG. 6

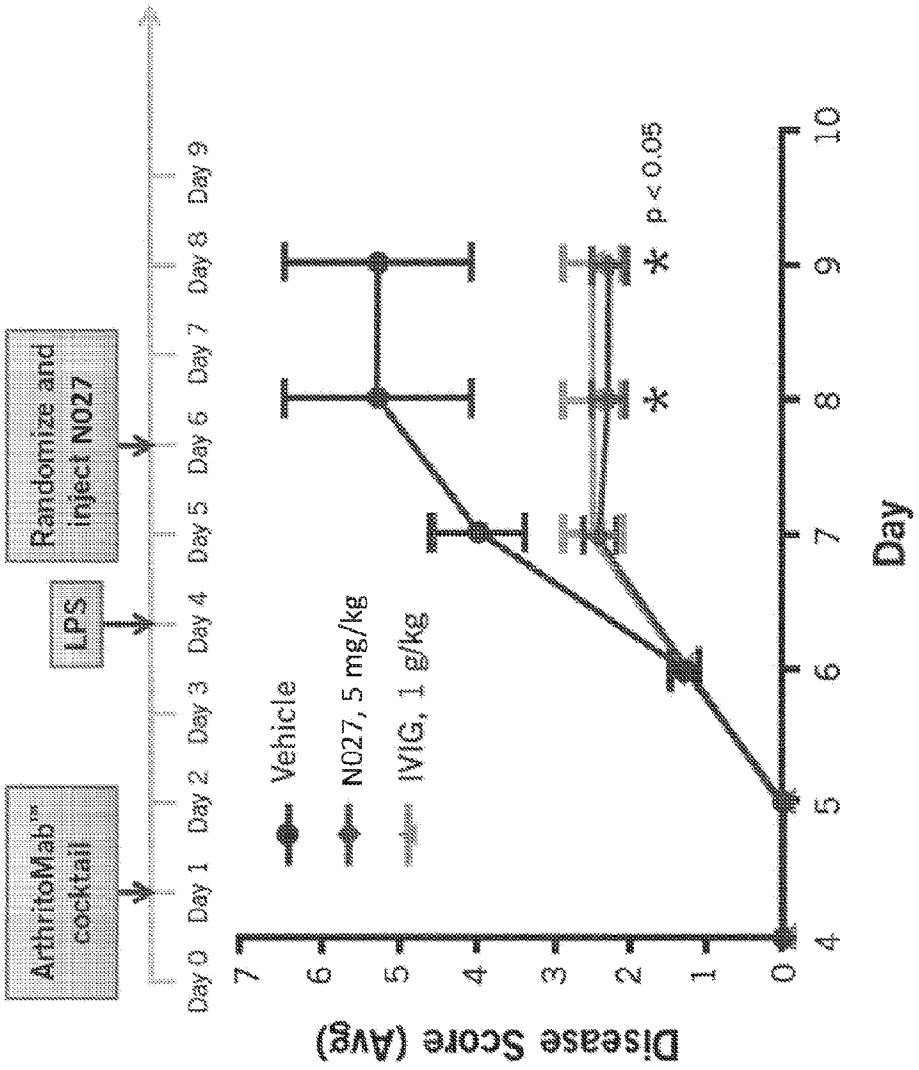
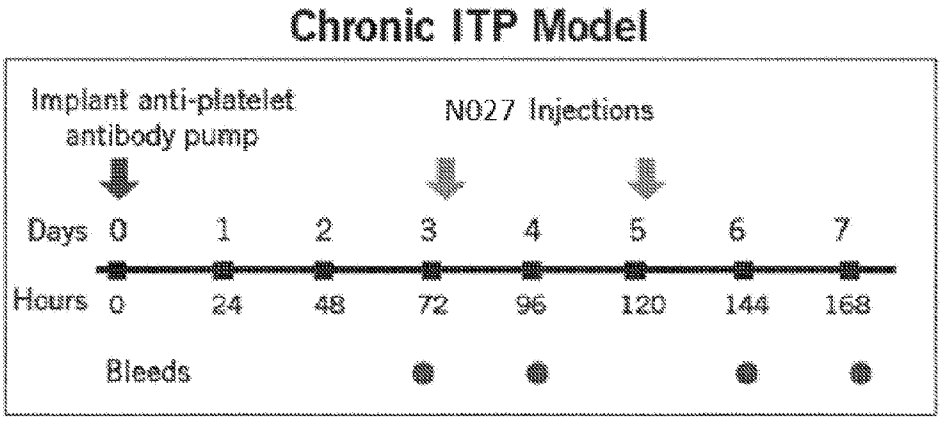

ArthritoMab™ cocktail
LPS
Randomize and inject N027
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Vehicle
N027, 5 mg/kg
IVIG, 1 g/kg
p < 0.05
*
*
Disease Score (Avg)
Day
0
1
2
3
4
5
6
7
4
5
6
7
8
9
10

FIG. 7


Chronic ITP Model
Implant anti-platelet antibody pump
N027 Injections
Days 0 1 2 3 4 5 6 7
Hours 0 24 48 72 96 120 144 168
Bleeds

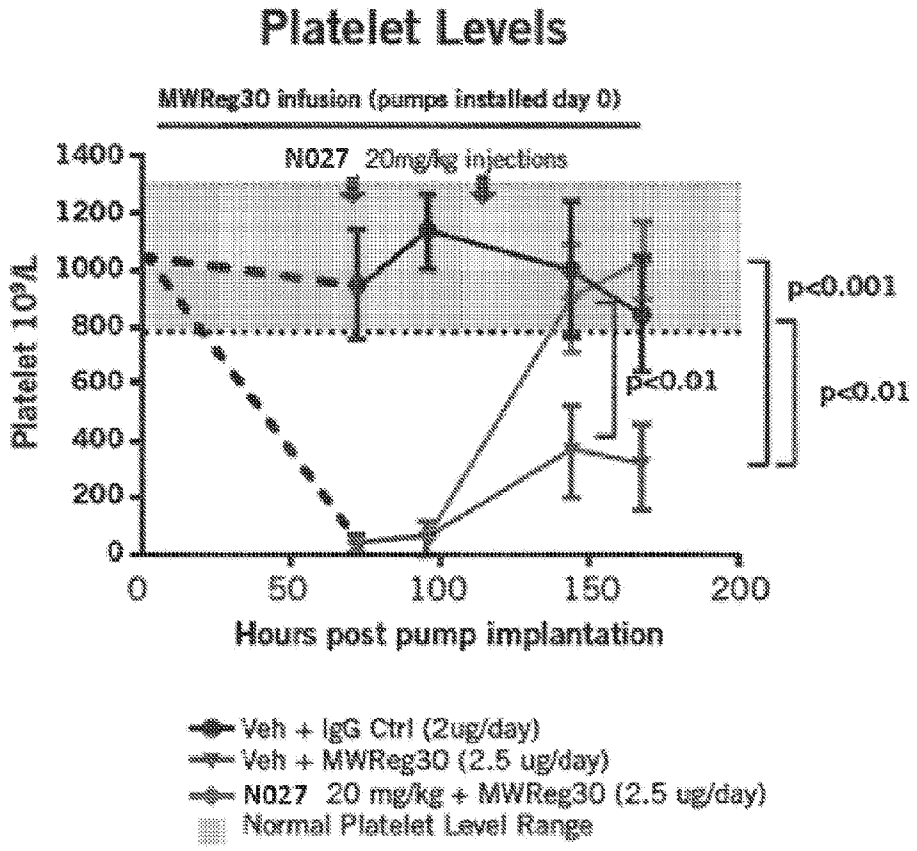
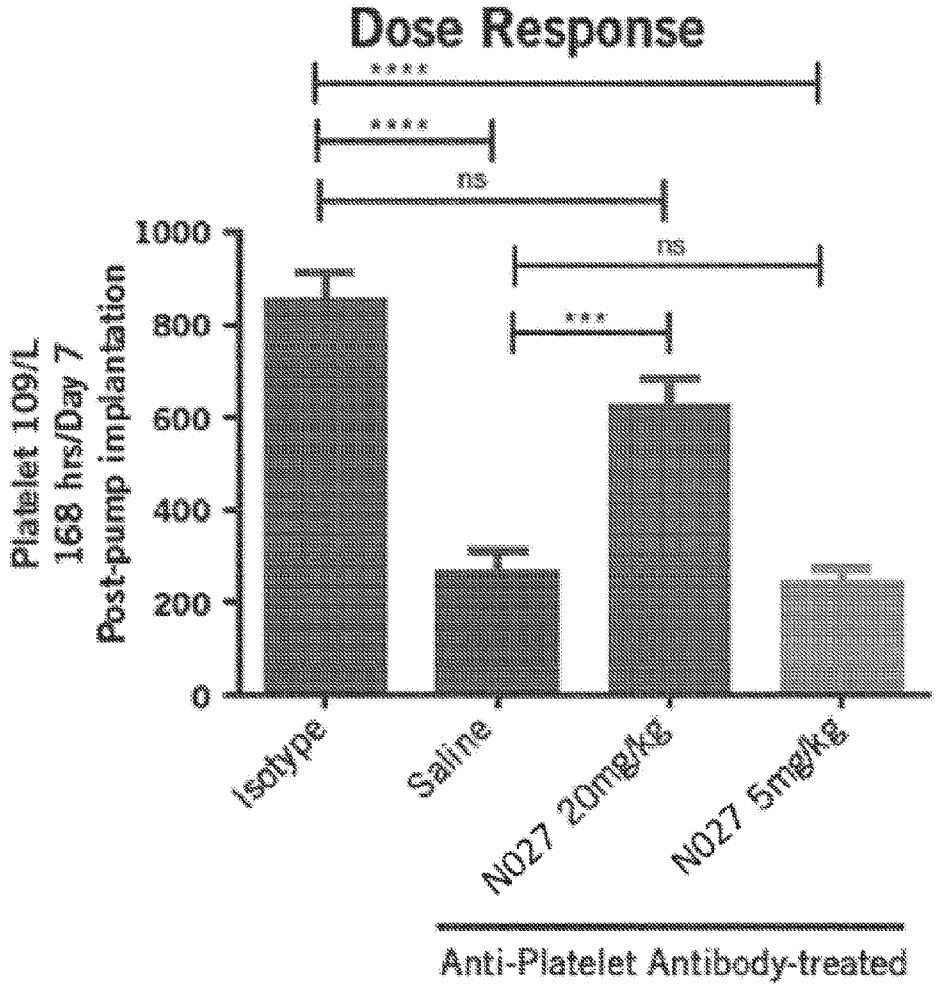

Platelet Levels
MWReg30 infusion (pumps installed day 0)
N027 20mg/kg injections
Platelet 10³/L
1400
1200
1000
800
600
400
200
0
0 50 100 150 200
Hours post pump implantation
p<0.001
p<0.01
p<0.01
Veh + IgG Ctrl (2ug/day)
Veh + MWReg30 (2.5 ug/day)
N027 20 mg/kg + MWReg30 (2.5 ug/day)
Normal Platelet Level Range

FIG. 7 Cont.


Dose Response
****
****
ns
ns
***
Platelet 10^9/L
168 hrs/Day 7
Post-pump implantation
1000
800
600
400
200
0
Isotype
Saline
N027 20mg/kg
N027 5mg/kg
Anti-Platelet Antibody-treated