WHAT IS CLAIMED IS:

1. Use of (a) an agent that reduces the interaction of immunoglobulin G (IgG) with the neonatal Fc receptor (FcRn), wherein the agent is an anti-FcRn antibody, wherein the anti-FcRn antibody is selected from efgartigimod or M281; and (b) a recombinant viral vector comprising a therapeutic heterologous polynucleotide in the manufacture of a medicament for a combinatorial therapy to enhance the efficacy of gene therapy treatment in a subject, wherein (a) the agent; and (b) the recombinant viral vector are to be administered to said subject.
2. Use of (a) an agent that reduces the interaction of immunoglobulin G (IgG) with neonatal Fc receptor (FcRn), wherein the agent is selected from the group consisting of an anti-FcRn antibody, an FcRn binding affibody, an antibody that enhances IgG degradation (ABDEG), an FcRn binding peptide (FcBP), and an FcRn binding small molecule; (b) a recombinant viral vector comprising a therapeutic heterologous polynucleotide; and (c) a protease, wherein the protease is IdeS or a modified variant thereof set forth in any of SEQ ID NOs: 3-18, 23, or 48 in the manufacture of a medicament for combinatorial therapy to enhance the efficacy of gene therapy treatment in a subject, wherein (a) the agent; (b) the recombinant viral vector; and (c) the protease are to be administered to said subject in the combinatorial therapy.
3. The use of claim 1 or 2, wherein
   (a) said subject is in need of treatment for a disease caused by a loss of function or activity of a protein, and said heterologous polynucleotide encodes a polypeptide or peptide that provides or supplements a function or activity of said protein, or
   (b) said subject is in need of treatment for a disease caused by a gain of function, activity or expression of a protein, and said heterologous polynucleotide is transcribed into a nucleic acid that inhibits, decreases or reduces expression of said gain of function, activity or expression of said protein.
4. The use of any of claims 1 – 3, wherein FcRn-mediated IgG recycling is to be reduced in said subject.
5. The use of any of claims 1 – 4, wherein IgG clearance is to be enhanced in said subject.
6. The use of any of claims 1 – 5, wherein:
   (i) (a) the agent is to be administered before (b) the recombinant viral vector;
   (ii) (b) the recombinant viral vector is to be administered before (a) the agent;

(iii) (a) the agent and (b) the recombinant viral vector are to be administered at about the same time; or

(iv) (a) the agent is to be administered two or more times before or after (b) the recombinant viral vector.

7. The use of claim 1 or any of claims 3 - 6, wherein an amount of a protease is to be further administered to said subject.

8. The use of claim 7, wherein said protease is effective to degrade or digest and/or inhibit or reduce effector function of antibodies that bind to said recombinant viral vector and/or said polypeptide or peptide encoded by said heterologous polynucleotide and/or said heterologous polynucleotide.

9. The use of claim 7, wherein:

(i) said protease is to be further administered before, after or at about the same time as (a) the agent;

(ii) said protease is to be further administered before, after or at about the same time as (b) the recombinant viral vector;

(iii) said protease is to be further administered two or more times before, after or at about the same time as (a) the agent; or

(iv) said protease is to be further administered two or more times before, after or at about the same time as (b) the recombinant viral vector.

10. The use of any of claims 7 – 9, wherein:

(i) said protease comprises a cysteine protease or a thiol protease;

(ii) said protease comprises a protease from *Streptococcus pyogenes*, *Streptococcus equi* or *Mycoplasma canis*; or

(iii) said protease comprises IdeS or a modified variant thereof set forth in any of SEQ ID NOs: 3 – 18, 23 or 48.

11. The use of any of claims 1 – 10, wherein said viral vector comprises a lentiviral vector, an adenoviral vector or an adeno-associated virus (AAV) vector.

12. The use of claim 11, wherein said AAV vector comprises capsid proteins to which the antibodies or IgG bind.

13. The use of claim 11, wherein said AAV vector comprises VP1, VP2 and/or VP3 capsid proteins to which the antibodies or IgG bind.

14. The use of any of claims 11 – 13, wherein said AAV vector comprises VP1, VP2 and/or VP3 capsid protein selected from the group consisting of AAV1, AAV2,

AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV3B, AAV-2i8, Rh10, Rh74, SEQ ID NO:1 and SEQ ID NO:2 VP1, VP2 and/or VP3 capsid proteins.

15. The use of any of claims 1 – 14, wherein said subject has antibodies or IgG that bind to said viral vector.

16. The use of any of claims 1 – 14, wherein antibodies or IgG that bind to said viral vector are absent from said subject.

17. The use of any of claims 1 – 16, wherein said subject has antibodies or IgG that bind to said polypeptide or peptide encoded by said heterologous polynucleotide.

18. The use of any of claims 7 – 17, wherein said antibodies comprise IgG, IgM, IgA, IgD and/or IgE.

19. The use of any of claims 1 – 18, wherein a biological sample from said subject is to be analyzed for the presence, amount or an effector function of viral vector binding antibodies or IgG present in said sample before (a) the agent has been administered, after (a) the agent but before (b) the recombinant viral vector has been administered and/or after (a) the agent and (b) the recombinant viral vector have been administered.

20. The use of any of claims 1 – 19, wherein said use leads to a reduction of 20-50%, 50-75%, 75-90%, 90-95% or 95% or more of said viral vector binding antibodies or IgG.

21. The use of claim 19, wherein said viral vector binding antibodies or IgG present in said biological sample or blood product from said subject is less than 1:100,000, and this ratio indicates that, when the ratio is 1:100,000, 1 part of said biological sample or blood product diluted in 100,000 parts of buffer results in 50% viral vector neutralization.

22. The use of any of claims 1 – 21, wherein the presence or quantity of the amount of antibodies or IgG that bind to a polypeptide or peptide encoded by said heterologous polynucleotide is to be determined, after (a) the agent but before (b) the recombinant viral vector has been administered and/or after (a) the agent and (b) the recombinant viral vector have been administered.

23. The use of any of claims 1 – 21, wherein the presence or quantity of the amount of antibodies or IgG that bind to said heterologous polynucleotide or nucleic acid is to be determined after (a) the agent has been administered but before (b) the recombinant viral vector and/or after (a) the agent and (b) the recombinant viral vector have been administered.

24. The use of any of claims 1 – 23, wherein said subject has a lung disease (*e.g.*, cystic fibrosis), a bleeding disorder (*e.g.*, hemophilia A or hemophilia B with or without inhibitors), thalassemia, a blood disorder (*e.g.*, anemia), Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), epilepsy, a lysosomal storage disease (*e.g.*, aspartylglucosaminuria), Batten disease, late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), cystinosis, Fabry disease, Gaucher disease types I, II, and III, glycogen storage disease II (Pompe disease), GM2-gangliosidosis type I (Tay Sachs disease), GM2-gangliosidosis type II (Sandhoff disease), mucolipidosis types I (sialidosis type I and II), II (I-cell disease), III (pseudo-Hurler disease) and IV, mucopolysaccharide storage diseases (Hurler disease and variants, Hunter, Sanfilippo Types A,B,C,D, Morquio Types A and B, Maroteaux-Lamy and Sly diseases), Niemann-Pick disease types A/B, C1 and C2, and Schindler disease types I and II), hereditary angioedema (HAE), a copper or iron accumulation disorder (*e.g.*, Wilson's or Menkes disease), lysosomal acid lipase deficiency, a neurological or neurodegenerative disorder, cancer, type 1 or type 2 diabetes, adenosine deaminase deficiency, a metabolic defect (*e.g.*, glycogen storage diseases), a disease of solid organs (*e.g.*, brain, liver, kidney, heart), or an infectious viral (*e.g.*, hepatitis B and C, HIV, etc.), bacterial or fungal disease.

25. The use of any of claims 1 – 23, wherein said subject has hemophilia A, hemophilia A with inhibitory antibodies, hemophilia B, hemophilia B with inhibitory antibodies, a deficiency in any coagulation Factor: VII, VIII, IX, X, XI, V, XII, II, von Willebrand factor, or a combined FV/FVIII deficiency, thalassemia, vitamin K epoxide reductase C1 deficiency or gamma-carboxylase deficiency.

26. The use of any of claims 1 – 23, wherein said subject has anemia, bleeding associated with trauma, injury, thrombosis, thrombocytopenia, stroke, coagulopathy, disseminated intravascular coagulation (DIC); over-anticoagulation associated with heparin, low molecular weight heparin, pentasaccharide, warfarin, small molecule antithrombotics (*i.e.*, FXa inhibitors), a platelet disorder, Bernard Soulier syndrome, Glanzmann thrombasthenia, or storage pool deficiency.

27. The use of any of claims 1 – 23, wherein said heterologous polynucleotide encodes a protein selected from the group consisting of insulin, glucagon, growth hormone (GH), parathyroid hormone (PTH), growth hormone releasing factor (GRF), follicle stimulating hormone (FSH), luteinizing hormone (LH), human chorionic

gonadotropin (hCG), vascular endothelial growth factor (VEGF), angiopoietins, angiostatin, granulocyte colony stimulating factor (GCSF), erythropoietin (EPO), connective tissue growth factor (CTGF), basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), epidermal growth factor (EGF), transforming growth factor α (TGFα), platelet-derived growth factor (PDGF), insulin growth factors I and II (IGF-I and IGF-II), TGFβ, activins, inhibins, bone morphogenic protein (BMP), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins NT-3 and NT4/5, ciliary neurotrophic factor (CNTF), glial cell line derived neurotrophic factor (GDNF), neurturin, agrin, netrin-1 and netrin-2, hepatocyte growth factor (HGF), ephrins, noggin, sonic hedgehog and tyrosine hydroxylase.

28. The use of any of claims 1 – 23, wherein said heterologous polynucleotide encodes a protein selected from the group consisting of thrombopoietin (TPO), interleukins (IL1 through IL-36), monocyte chemoattractant protein, leukemia inhibitory factor, granulocyte-macrophage colony stimulating factor, Fas ligand, tumor necrosis factors α and β, interferons α, β, and γ, stem cell factor, flk-2/flt3 ligand, IgG, IgM, IgA, IgD and IgE, chimeric immunoglobulins, humanized antibodies, single chain antibodies, T cell receptors, chimeric T cell receptors, single chain T cell receptors, class I and class II MHC molecules.

29. The use of any of claims 1 – 23, wherein said heterologous polynucleotide encodes CFTR (cystic fibrosis transmembrane regulator protein), a blood coagulation (clotting) factor (Factor XIII, Factor IX, Factor VIII, Factor X, Factor VII, Factor VIIa, protein C, etc.) a gain of function blood coagulation factor, an antibody, retinal pigment epithelium-specific 65 kDa protein (RPE65), erythropoietin, LDL receptor, lipoprotein lipase, ornithine transcarbamylase, β-globin, α-globin, spectrin, α-antitrypsin, adenosine deaminase (ADA), a metal transporter (ATP7A or ATP7), sulfamidase, an enzyme involved in lysosomal storage disease (ARSA), hypoxanthine guanine phosphoribosyl transferase, β-25 glucocerebrosidase, sphingomyelinase, lysosomal hexosaminidase, branched-chain keto acid dehydrogenase, a hormone, a growth factor, insulin-like growth factor 1 or 2, platelet derived growth factor, epidermal growth factor, nerve growth factor, neurotrophic factor -3 and -4, brain-derived neurotrophic factor, glial derived growth factor, transforming growth factor α and β, a cytokine, α-interferon, β-interferon, interferon-γ, interleukin-2, interleukin-4, interleukin 12, granulocyte-macrophage colony stimulating factor, lymphotoxin, a

suicide gene product, herpes simplex virus thymidine kinase, cytosine deaminase, diphtheria toxin, cytochrome P450, deoxycytidine kinase, tumor necrosis factor, a drug resistance protein, a tumor suppressor protein (*e.g.*, p53, Rb, Wt-1, NF1, Von Hippel–Lindau (VHL), adenomatous polyposis coli (APC)), a peptide with immunomodulatory properties, a tolerogenic or immunogenic peptide or protein Tregitope or hCDR1, insulin, glucokinase, guanylate cyclase 2D (LCA-GUCY2D), Rab escort protein 1 (Choroideremia), LCA 5 (LCA-Lebercilin), ornithine ketoacid aminotransferase (Gyrate Atrophy), Retinoschisin 1 (X-linked Retinoschisis), USH1C (Usher's Syndrome 1C), X-linked retinitis pigmentosa GTPase (XLRP), MERTK (AR forms of RP: retinitis pigmentosa), DFNB1 (Connexin 26 deafness), ACHM 2, 3 and 4 (Achromatopsia), PKD-1 or PKD-2 (Polycystic kidney disease), TPP1, CLN2, a sulfatase, N-acetylglucosamine-1-phosphate transferase, cathepsin A, GM2-AP, NPC1, VPC2, a sphingolipid activator protein, one or more zinc finger nuclease for genome editing, and one or more donor sequence used as repair templates for genome editing.

30. The use of any of claims 1 – 23, wherein said heterologous polynucleotide encodes an inhibitory nucleic acid.

31. The use of claim 30, wherein said inhibitory nucleic acid is selected from the group consisting of a siRNA, an antisense molecule, miRNA, RNAi, a ribozyme and a shRNA.

32. The use of claim 30, wherein said inhibitory nucleic acid binds to a gene, a transcript of a gene, or a transcript of a gene associated with a polynucleotide repeat disease selected from the group consisting of a huntingtin (HTT) gene, a gene associated with dentatorubropallidoluysian atrophy (atrophin 1, ATN1), androgen receptor on the X chromosome in spinobulbar muscular atrophy, human Ataxin-1, -2, -3, and -7, $Ca_v2.1$ P/Q voltage-dependent calcium channel (CACNA1A), TATA-binding protein, Ataxin 8 opposite strand (ATXN8OS), Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B beta isoform in spinocerebellar ataxia (type 1, 2, 3, 6, 7, 8, 12 17), *FMR1* (fragile X mental retardation 1) in fragile X syndrome, *FMR1* (fragile X mental retardation 1) in fragile X-associated tremor/ataxia syndrome, *FMR1* (fragile X mental retardation 2) or AF4/FMR2 family member 2 in fragile XE mental retardation; Myotonin-protein kinase (MT-PK) in myotonic dystrophy; Frataxin in Friedreich's ataxia; a mutant of superoxide dismutase 1 (SOD1) gene in amyotrophic lateral sclerosis; a gene involved in pathogenesis of Parkinson's disease and/or

Alzheimer's disease; apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9), hypercholesterolemia; HIV Tat, human immunodeficiency virus transactivator of transcription gene, in HIV infection; HIV TAR, HIV TAR, human immunodeficiency virus transactivator response element gene, in HIV infection; C-C chemokine receptor (CCR5) in HIV infection; Rous sarcoma virus (RSV) nucleocapsid protein in RSV infection, liver-specific microRNA (miR-122) in hepatitis C virus infection; p53, acute kidney injury or delayed graft function kidney transplant or kidney injury acute renal failure; protein kinase N3 (PKN3) in advance recurrent or metastatic solid malignancies; LMP2, LMP2 also known as proteasome subunit beta-type 9 (PSMB 9), metastatic melanoma; LMP7,also known as proteasome subunit beta-type 8 (PSMB 8), metastatic melanoma; MECL1 also known as proteasome subunit beta-type 10 (PSMB 10), metastatic melanoma; vascular endothelial growth factor (VEGF) in solid tumors; kinesin spindle protein in solid tumors, apoptosis suppressor B-cell CLL/lymphoma (BCL-2) in chronic myeloid leukemia; ribonucleotide reductase M2 (RRM2) in solid tumors; Furin in solid tumors; polo-like kinase 1 (PLK1) in liver tumors, diacylglycerol acyltransferase 1 (DGAT1) in hepatitis C infection, beta-catenin in familial adenomatous polyposis; beta2 adrenergic receptor, glaucoma; RTP801/Redd1 also known as DNA damage-inducible transcript 4 protein, in diabetic macular edema (DME) or age-related macular degeneration; vascular endothelial growth factor receptor I (VEGFR1) in age-related macular degeneration or choroidal neovascularization, caspase 2 in non-arteritic ischaemic optic neuropathy; Keratin 6A N17K mutant protein in pachyonychia congenital; influenza A virus genome/gene sequences in influenza infection; severe acute respiratory syndrome (SARS) coronavirus genome/gene sequences in SARS infection; respiratory syncytial virus genome/gene sequences in respiratory syncytial virus infection; Ebola filovirus genome/gene sequence in Ebola infection; hepatitis B and C virus genome/gene sequences in hepatitis B and C infection; herpes simplex virus (HSV) genome/gene sequences in HSV infection, coxsackievirus B3 genome/gene sequences in coxsackievirus B3 infection; silencing of a pathogenic allele of a gene (allele-specific silencing) like torsin A (TOR1A) in primary dystonia, pan-class I and HLA-allele specific in transplant; and mutant rhodopsin gene (RHO) in autosomal dominantly inherited retinitis pigmentosa (adRP).

33. The use of any of claims 1 – 32, wherein said polypeptide encoded by said heterologous polynucleotide comprises a gene editing nuclease.

34. The use of any of claims 1 – 33, wherein (a) the agent and/or (b) the recombinant viral vector are to be administered two or more times.

35. The use of any of claims 1 – 34, wherein said subject is a human.

36. A package having disposed therein:

(a) a recombinant viral vector comprising a heterologous polynucleotide that encodes a polypeptide or peptide;

(b) an agent that reduces interaction of IgG with FcRn, wherein the agent is an anti-FcRn antibody, wherein the anti-FcRn antibody is selected from efgartigimod or M281;

(c) a protease, wherein the protease is IdeS or a modified variant thereof set forth in any of SEQ ID Nos:3-18, 23, or 48 that degrades or digests antibodies; and

(d) a label with instructions for the use according to any of claims 1 – 35, wherein (a), (b) and (c) are in separate or the same container.

37. A package having disposed therein:

(a) a recombinant viral vector comprising a heterologous polynucleotide that is transcribed into a nucleic acid that inhibits, decreases or reduces expression of a protein;

(b) an agent that reduces interaction of IgG with FcRn, wherein the agent is an anti-FcRn antibody, wherein the anti-FcRn antibody is selected from efgartigimod or M281;

(c) a protease , wherein the protease is IdeS or a modified variant thereof set forth in any of SEQ ID Nos: 3-18, 23, or 48 that degrades or digests antibodies; and

(d) a label with instructions for the use according to any of claims 1 – 35, wherein (a), (b) and (c) are in separate or the same container.

38. The use of claim 2, wherein the anti-FcRn antibody comprises any one of SEQ ID NOs:51-56.

39. The use of claim 2, wherein the anti-FcRN antibody comprises any one or both of SEQ ID NO:49 and SEQ ID NO:50.

40. The use of claim 2, wherein the anti-FcRn antibody comprises efgartigimod.