

CLAIMS

1. An FcRn-antagonist for use in reducing the serum levels of an Fc-containing agent in a subject, wherein the FcRn-antagonist consists of a variant IgG1 Fc region, or FcRn-binding fragment thereof, wherein the Fc domains of the Fc region or FcRn-binding fragment thereof comprise the amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436 respectively, and wherein the Fc region binds to FcRn with increased affinity and reduced pH dependence relative to a wild-type IgG1 Fc region, wherein the Fc-containing agent has not been administered to the subject, and wherein the Fc-containing agent is an antibody.
2. An FcRn-antagonist for use in reducing the serum levels of pathogenic IgG antibodies in a subject, wherein the FcRn-antagonist consists of a variant IgG1 Fc region, or FcRn-binding fragment thereof, wherein the Fc domains of the Fc region or FcRn-binding fragment thereof comprise the amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436 respectively, and wherein the Fc region binds to FcRn with increased affinity and reduced pH dependence relative to a wild-type IgG1 Fc region.
3. Use of an FcRn-antagonist in the manufacture of a medicament for reducing the serum levels of an Fc-containing agent in a subject, wherein the FcRn-antagonist consists of a variant IgG1 Fc region, or FcRn-binding fragment thereof, wherein the Fc domains of the Fc region or FcRn-binding fragment thereof comprise the amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436 respectively, wherein the Fc region binds to FcRn with increased affinity and reduced pH dependence relative to a wild-type IgG1 Fc region, wherein the Fc-containing agent has not been administered to the subject, and wherein the Fc-containing agent is an antibody.
4. Use of an FcRn-antagonist in the manufacture of a medicament for reducing the serum levels of pathogenic IgG antibodies in a subject, wherein the FcRn-

antagonist consists of a variant IgG1 Fc region, or FcRn-binding fragment thereof, wherein the Fc domains of the Fc region or FcRn-binding fragment thereof comprise the amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436 respectively, and wherein the Fc region binds to FcRn with increased affinity and reduced pH dependence relative to a wild-type IgG1 Fc region.

5. The use of claim 3 or 4, wherein the amino acid sequence of at least one of the Fc domains of the variant Fc region is selected from an amino acid sequence set forth in SEQ ID NO: 1, 2, and 3.
6. The use of any one of claims 3-5, wherein the amino acid sequence of both of the Fc domains of the variant Fc region are independently selected from an amino acid sequence set forth in SEQ ID NO: 1, 2, and 3.
7. The use of any one of claims 3-6, wherein the amino acid sequence of the Fc domains of the variant Fc region consists of the amino acid sequence set forth in SEQ ID NO:1.
8. The use of any one of claims 3-6, wherein the amino acid sequence of the Fc domains of the variant Fc region consists of the amino acid sequence set forth in SEQ ID NO:2.
9. The use of any one of claims 3-6, wherein the amino acid sequence of the Fc domains of the variant Fc region consists of the amino acid sequence set forth in SEQ ID NO:3.
10. The use of any one of claims 3-9, wherein the variant Fc region is linked to a half-life extender, or linked to a binding molecule that specifically binds to a half-life extender present in a subject.
11. The use of claim 10, wherein the half-life extender is polyethylene glycol or human serum albumin.

12. The use of any one of claims 3-9, wherein the variant Fc region is linked to a binding molecule that specifically binds to a half-life extender present in a subject.
13. The use of claim 12, wherein the half-life extender is a binding molecule that specifically binds to human serum albumin.
14. The use of any one of claims 3-13, wherein the subject has an antibody-mediated disorder.
15. The use of claim 14, wherein the antibody-mediated disorder is an autoimmune disease.
16. The use of claim 15, wherein the autoimmune disease is selected from the group consisting of allogenic islet graft rejection, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, Alzheimer's disease, antineutrophil cytoplasmic autoantibodies (ANCA), autoimmune diseases of the adrenal gland, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune myocarditis, autoimmune neutropenia, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, autoimmune urticaria, Behcet's disease, bullous pemphigoid, cardiomyopathy, Castleman syndrome, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, dermatomyositis, dilated cardiomyopathy, discoid lupus, epidermolysis bullosa acquisita, essential mixed cryoglobulinemia, factor VIII deficiency, fibromyalgia-fibromyositis, glomerulonephritis, Graves' disease, Guillain-Barré syndrome, Goodpasture's syndrome, graft-versus-host disease (GVHD), Hashimoto's thyroiditis, hemophilia A, idiopathic membranous neuropathy, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP), IgA neuropathy, IgM polyneuropathies, immune mediated thrombocytopenia, juvenile arthritis,

Kawasaki's disease, lichen planus, lichen sclerosus, lupus erythematosus, Ménière's disease, mixed connective tissue disease, mucous membrane pemphigoid, multiple sclerosis, type 1 diabetes mellitus, multifocal motor neuropathy (MMN), myasthenia gravis, paraneoplastic bullous pemphigoid, pemphigoid gestationis, pemphigus vulgaris, pemphigus foliaceus, pernicious anemia, polyarteritis nodosa, polychondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, psoriatic arthritis, relapsing polychondritis, Raynaud's phenomenon, Reiter's syndrome, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren's syndrome, solid organ transplant rejection, stiff-man syndrome, systemic lupus erythematosus, Takayasu's arteritis, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), temporal arteritis/giant cell arteritis, thrombotic thrombocytopenia purpura, ulcerative colitis, uveitis, dermatitis herpetiformis vasculitis, anti-neutrophil cytoplasmic antibody-associated vasculitides, vitiligo, and Wegener's granulomatosis.

17. The use of claim 14, wherein the antibody-mediated disorder is treatable using intravenous immunoglobulin (IVIG), plasmapheresis and/or immunoadsorption.
18. The use of claim 15, wherein the autoimmune disease is an autoimmune channelopathy.
19. The use of claim 18, wherein the channelopathy is selected from the group consisting of autoimmune limbic encephalitis, epilepsy, neuromyelitis optica, Lambert-Eaton myasthenic syndrome, myasthenia gravis, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis, Morvan syndrome, neuromyotonia, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), and glycine receptor antibody-associated disorder.

20. The use of claim 14, wherein the antibody-mediated disorder is hyperglobulinemia.
21. The use of any one of claims 14-20, wherein the FcRn-antagonist is for administration to the subject simultaneously or sequentially with an additional therapeutic agent.
22. The use of claim 21, wherein the additional therapeutic agent is an anti-inflammatory agent or a leucocyte depleting agent.
23. The use of claim 22, wherein the leucocyte depleting agent is a B-cell depleting agent.
24. The use of claim 23, wherein the B-cell depleting agent is an antibody.
25. The use of claim 24, wherein the antibody specifically binds to CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD53, CD70, CD72, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, or CD86.
26. The use of claim 21, wherein the additional therapeutic agent is rituximab, daclizumab, basiliximab, muromonab-CD3, infliximab, adalimumab, omalizumab, efalizumab, natalizumab, tocilizumab, eculizumab, golimumab, canakinumab, ustekinumab, belimumab, or a combination thereof.
27. An FcRn-antagonist which consists of a variant Fc region of IgG2, IgG3 or IgG4, or FcRn-binding fragment thereof, wherein the Fc domains of the Fc region or FcRn-binding fragment thereof comprise the amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436 respectively, and wherein the Fc region binds to FcRn with increased affinity and reduced pH dependence relative to the native Fc region.
28. A pharmaceutical composition comprising the FcRn-antagonist of claim 27 and a pharmaceutically acceptable carrier or excipient.

29. An FcRn-antagonist or pharmaceutical composition according to claim 27 or 28 for use in reducing the serum levels of an Fc-containing agent in a subject.
30. An FcRn-antagonist or pharmaceutical composition according to claim 27 or 28 for use in treating an antibody-mediated disorder in a subject.
31. Use of the FcRn-antagonist or pharmaceutical composition according to claim 27 or 28 in the manufacture of a medicament for reducing the serum levels of an Fc-containing agent in a subject.
32. Use of the FcRn-antagonist or pharmaceutical composition according to claim 27 or 28 in the manufacture of a medicament for treating an antibody-mediated disorder in a subject.
33. A nucleic acid molecule or molecules encoding the FcRn-antagonist of any one of claims 1, 2, 27, 29, and 30.
34. An expression vector comprising the nucleic acid molecule or molecules of claim 33.
35. A host cell comprising the nucleic acid molecule or molecules of claim 33 or the expression vector of claim 34.
36. A method of producing an FcRn-antagonist, comprising culturing the host cell of claim 35 under conditions such that an FcRn-antagonist is expressed.