

~~We claim:~~CLAIMS

- ~~1. An isolated FeRn antagonist comprising a variant Fc region, or FeRn binding fragment thereof, 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, 2, or 3, and wherein the FeRn antagonist does not comprise an antibody variable region or a CH1 domain.~~
- ~~2. The FeRn antagonist of claims 1, wherein the variant Fc region has an increased affinity for an Fc gamma receptor relative to the affinity of a wild type IgG1 Fc region for the Fc gamma receptor.~~
- ~~3. An isolated FeRn antagonist comprising a variant Fc region, or FeRn binding fragment thereof, wherein the Fc domains of the Fc region 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 has an increased affinity for an Fc gamma receptor relative to a the affinity of a wild-type IgG1 Fc region for the Fc gamma receptor.~~
- ~~4. The FeRn antagonist of claim 3, wherein the Fc region is an IgG Fc region.~~
- ~~5. The FeRn antagonist of claim 3, wherein the Fc region is an IgG1 Fc region.~~
- ~~6. The FeRn antagonist of claim 3, wherein the Fc region is chimeric Fc region.~~
- ~~7. The FeRn antagonist of claim 3, wherein the amino acid sequence of the Fc domains of the variant Fc region comprises the amino acid sequence set forth in SEQ ID NO:1, 2, or 3.~~
- ~~8. The FeRn antagonist of claim 3, 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, 2, or 3.~~
- ~~9. The FeRn antagonist of claim 3, which consists of a variant Fc region, 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, 2, or 3.~~

10. The FeRn antagonist of any one of claims 2-9, wherein the FeRn antagonist does not comprise an antibody variable region or a CH1 domain.

11. The FeRn antagonist of any one of claims 1-10, wherein the FeRn antagonist does not comprise a free cysteine residue.

12. The FeRn antagonist of any one claims 1-11, wherein the variant Fc region has increased affinity for CD16a.

13. The FeRn antagonist of any one of claims 1-12, wherein the Fc domains of the variant Fc region do not comprise an N-linked glycan at EU position 297.

14. The FeRn antagonist of any one of claims 1-12, wherein the Fc domains of the variant Fc region comprise an Fc domain having an afucosylated N-linked glycan at EU position 297.

15. The FeRn antagonist of any one of claims 1-12, wherein the Fc domains of the variant Fc region comprise an N-linked glycan having a bisecting GlcNac at EU position 297 of the Fc domains.

16. The FeRn antagonist of any one of the preceding claims, wherein the variant Fc region is linked to a half-life extender.

17. The FeRn antagonist of claim 16, wherein the half-life extender is polyethylene glycol or human serum albumin.

18. An FeRn antagonist composition comprising a plurality of FeRn antagonist molecules of claim 14, wherein at least 50% (optionally, at least 60, 70, 80, 90, 95, or 99%) of the molecules comprise a variant Fc region, or FeRn binding fragment thereof, comprising an afucosylated N-linked glycan.

19. An FeRn antagonist composition comprising a plurality of FeRn antagonist molecules of claim 15, wherein at least 50% (optionally, at least 60, 70, 80, 90, 95, or 99%) of the molecules comprise a variant Fc region, or FeRn binding fragment thereof, comprising an N-linked glycan having a bisecting GlcNac.

20. A pharmaceutical composition comprising the FeRn antagonist or FeRn antagonist composition of any one of the preceding claims and a pharmaceutically acceptable carrier or excipient.

21. A method of inhibiting FeRn function in a subject, the method comprising administering to the subject an effective amount of the pharmaceutical composition of claim 20.

22. A method of reducing the serum levels of an Fe-containing agent in subject that has been administered the Fe-containing agent, the method comprising simultaneously or sequentially administering to subject an effective amount of the pharmaceutical composition of claim 20.

23. The method of claim 22, wherein the Fe-containing agent is an antibody or immunoadhesin.

24. The method of claim 22, wherein the Fe-containing agent is a therapeutic or diagnostic agent.

25. The method of claim 22, wherein the Fe-containing agent is an imaging agent.

26. The method of claim 22, wherein the Fe-containing agent is an antibody drug conjugate.

27. A method of treating an antibody-mediated disorder in a subject, the method comprising administering to the subject an effective amount of the pharmaceutical composition of claim 20.

28. The method of claim 27, wherein the antibody-mediated disorder is an autoimmune disease.

29. The method of claim 28, wherein the autoimmune disease is selected from the group consisting of allogeneic 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, Beheet's disease, bullous pemphigoid, cardiomyopathy, Castleman's syndrome, celiac spruce dermatitis, chronic fatigue immune disfunction syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), Churg Strauss syndrome, cicatrical 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, Grave's disease, Guillain-Barre, 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 plantus, lichen sclerosus, lupus erthematosus, Meniere'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 agammaglobulinulinemia, primary biliary cirrhosis, psoriasis, psoriatic arthritis, relapsing polychondritis, Reynauld's phenomenon, Reiter's syndrome, rheumatoid arthritis, sarcoidosis, scleroderma, Sjorgen's syndrome, solid organ transplant rejection, stiff man syndrome, systemic lupus erythematosus, takayasu arteritis, toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS), temporal arteristis/giant cell arteritis, thrombotic thrombocytopenia purpura, ulcerative colitis, uveitis, dermatitis herpetiformis vasculitis, anti neutrophil cytoplasmic antibody associated vasculitides, vitiligo, and Wegner's granulomatosis.~~

30. The method of claim 27, wherein the antibody mediated disorder is treatable using intravenous immunoglobulin (IVIG), plasmapheresis and/or immunoadsorption.

31. The method of claim 27, wherein the autoimmune disease is an autoimmune channelopathy.

- 5 32. ~~The method of claim 31, 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.~~
33. ~~The method of claim 27, wherein the antibody-mediated disorder is hyperglobulinemia.~~
- 10 34. ~~The method of claim 27, wherein the FeRn antagonist is administered to the subject simultaneously or sequentially with an additional therapeutic agent.~~
35. ~~The method of claim 34, wherein the additional therapeutic agent is an anti-inflammatory agent.~~
36. ~~The method of claim 34, wherein the additional therapeutic agent is a leucocyte-depleting agent.~~
- 15 37. ~~The method of claim 36, wherein the leucocyte-depleting agent is a B-cell depleting agent.~~
38. ~~The method of claim 37, wherein the B-cell depleting agent is an antibody.~~
- 20 39. ~~The method of claim 38, 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.~~
40. ~~The method of claim 34, wherein the additional therapeutic agent is rituximab, daclizumab, basiliximab, muronomab-CD3, infliximab, adalimumab, omalizumab, efalizumab, natalizumab, tocilizumab, eculizumab, golimumab, canakinumab, ustekinumab, belimumab, or a combination thereof.~~
- 25 41. ~~A nucleic acid molecule encoding the FeRn-antagonist of any one of claims 1-19.~~

~~42. An expression vector comprising the nucleic acid molecule of claim 41.~~

~~43. A host cell comprising the expression vector of claim 42.~~

~~44. A method of producing an FcRn-antagonist, comprising culturing the host cell of claim 43 under conditions such that an FcRn-antagonist is expressed.~~

5 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
10 436 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.

15 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.

20 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
25 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.

5 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.

10 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.

15 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.

20 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.

25 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.