

CLAIMS

1. A method of treating an IgG-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified Fc domain comprising a combination of the following four amino acid residues:
 - a tyrosine (Y) at amino acid position 252,
 - an aspartic acid (D) or a glutamic acid (E) at amino acid position 256,
 - a tryptophan (W) or a glutamine (Q) at amino acid position 307, and
 - a phenylalanine (F) or a tyrosine (Y) at amino acid position 434;according to Eu numbering, wherein the therapeutically effective amount of the FcRn antagonist increases the clearance of serum IgG in the subject.
2. The method of claim 1, wherein the modified Fc domain comprises a combination of amino acid residues selected from the group consisting of:
 - a) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;
 - b) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;
 - c) a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434;
 - d) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a phenylalanine (F) at amino acid position 434;
 - e) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434; and
 - f) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a phenylalanine (F) at amino acid position 434.
3. The method of claim 1, wherein the modified Fc domain comprises a quadruple amino acid substitution selected from the group consisting of
M252Y/T256D/T307Q/N434Y,

M252Y/T256E/T307W/N434Y,
M252Y/T256E/T307Q/N434Y,
M252Y/T256D/T307Q/N434F,
M252Y/T256D/T307W/N434Y, and
M252Y/T256D/T307W/N434F.

4. A method of treating an IgG-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified Fc domain comprising a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to Eu numbering, wherein the therapeutically effective amount of the FcRn antagonist increases the clearance of serum IgG in the subject.
5. A method of treating an IgG-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified Fc domain comprising a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to Eu numbering, wherein the therapeutically effective amount of the FcRn antagonist increases the clearance of serum IgG in the subject.
6. A method of treating an IgG-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified Fc domain comprising a tyrosine (Y) at amino acid position 252, a glutamic acid (E) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to Eu numbering, wherein the therapeutically effective amount of the FcRn antagonist increases the clearance of serum IgG in the subject.
7. A method of treating an IgG-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified Fc domain comprising a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a glutamine (Q) at amino acid position 307, and a phenylalanine (F) at amino acid position 434, according to Eu numbering, wherein the therapeutically effective amount of the FcRn antagonist increases the clearance of serum IgG in the subject.

8. A method of treating an IgG-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified Fc domain comprising a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434, according to Eu numbering, wherein the therapeutically effective amount of the FcRn antagonist increases the clearance of serum IgG in the subject.
9. A method of treating an IgG-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified Fc domain comprising a combination of the following amino acid residues:
- a) a tyrosine (Y) at amino acid position 252 and a tyrosine (Y) at amino acid position 434,
 - b) a tyrosine (Y) at amino acid position 252, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434,
 - c) a tyrosine (Y) at amino acid position 252, an aspartic acid (D) at amino acid position 256, and a tyrosine (Y) at amino acid position 434, or
 - d) an aspartic acid (D) at amino acid position 256, a tryptophan (W) at amino acid position 307, and a tyrosine (Y) at amino acid position 434,
- according to Eu numbering, wherein the therapeutically effective amount of the FcRn antagonist increases the clearance of serum IgG in the subject.
10. The method of claim 9, wherein the modified Fc domain comprises a combination of amino acid substitutions selected from the group consisting of
- M252Y/N434Y,
 - M252Y/T307W/N434Y,
 - M252Y/T256D/N434Y, and
 - T256D/307W/N434Y.
11. The method of any one of the preceding claims, wherein the IgG-mediated disorder is an autoimmune disease.
12. The method of claim 11, wherein the autoimmune disease is selected from the group consisting of graft versus host disease (GVHD), systemic lupus erythematosus (SLE),

myasthenia gravis, systemic sclerosis (SSc)/scleroderma, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, diabetes, multiple sclerosis, pemphigus vulgaris, atopic dermatitis, psoriasis, asthma, allergy, idiopathic pulmonary fibrosis (IPF), idiopathic thrombocytopenia purpura (ITP), and hidradenitis suppurativa.

13. A method of enhancing diagnostic imaging in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an FcRn antagonist comprising a modified human IgG Fc domain comprising a combination of amino acid substitutions selected from the group consisting of

M252Y/T256D/T307Q/N434Y,

M252Y/T256E/T307W/N434Y,

M252Y/T256E/T307Q/N434Y,

M252Y/T256D/T307Q/N434F,

M252Y/T256D/T307W/N434Y,

M252Y/T256D/T307W/N434F,

M252Y/N434Y,

M252Y/T307W/N434Y,

M252Y/T256D/N434Y, and

T256D/307W/N434Y,

according to Eu numbering.

14. The method of claim 13, further comprising administering to the subject a radiolabeled IgG antibody.

15. The method of claim 14, wherein the FcRn antagonist is administered after the radiolabeled antibody, thereby enhancing contrast for the radiolabeled antibody.

16. A method of reducing exposure of a non-target tissue to a radiolabeled antibody during diagnostic imaging in a subject in need thereof, comprising administering to the subject an effective amount of an FcRn antagonist comprising a modified Fc domain comprising a combination of amino acid substitutions selected from the group consisting of

M252Y/T256D/T307Q/N434Y,

M252Y/T256E/T307W/N434Y,

M252Y/T256E/T307Q/N434Y,

M252Y/T256D/T307Q/N434F,
M252Y/T256D/T307W/N434Y,
M252Y/T256D/T307W/N434F,
M252Y/N434Y,
M252Y/T307W/N434Y,
M252Y/T256D/N434Y, and
T256D/307W/N434Y,

according to Eu numbering.

17. The method of any one of the preceding claims, wherein the modified Fc domain is a modified human IgG Fc domain.
18. The method of claim 17, wherein the modified Fc domain is a modified human IgG1 Fc domain.
19. The method of any one of the preceding claims, wherein the modified Fc domain has enhanced FcRn binding affinity at an acidic pH and at a non-acidic pH compared to a wildtype Fc domain, optionally wherein the acidic pH is about 6.0 and optionally wherein the non-acidic pH is about 7.4.
20. The method of any one of the preceding claims, wherein the modified Fc domain is a modified human IgG Fc domain and has enhanced FcRn binding affinity at an acidic pH and/or a non-acidic pH compared to a human IgG Fc domain of the same subtype comprising amino acid substitutions M252Y/S254T/T256E/H433K/N434F, optionally wherein the acidic pH is about 6.0 and optionally wherein the non-acidic pH is about 7.4.
21. The method of any one of the preceding claims, wherein the modified Fc domain has reduced FcγRIIIa binding affinity compared to a wildtype Fc domain.
22. The method of any one of the preceding claims, wherein the FcRn antagonist comprises the amino acid sequence SEQ ID NO:1, 2, 3, or 4, or an FcRn-binding portion thereof, with the amino acid substitutions.

23. The method of any one of claims 1-22, wherein the FcRn antagonist is a binding polypeptide that binds one or more targets that are not FcRn.
24. The method of any one of claims 1-22, wherein the FcRn antagonist is an antibody or comprises an antigen-binding fragment thereof.
25. The method of claim 24, wherein the FcRn antagonist is a monoclonal antibody.
26. The method of claim 25, wherein the antibody is a chimeric, humanized, or human antibody.
27. The method of any one of claims 1-22, wherein the FcRn antagonist is an Fc fusion protein.
28. The method of claim 27, wherein the Fc fusion protein is an immunoadhesin.
29. The method of any one of claims 1-22, wherein the FcRn antagonist is an Fc fragment.
30. Use of an FcRn antagonist for the manufacture of a medicament to treat a subject in need thereof in the method of any one of claims 1-29.
31. An FcRn antagonist for use to treat a subject in need thereof in the method of any one of claims 1-29.
32. An isolated polypeptide consisting of a modified Fc domain, comprising a combination of amino acid substitutions recited in any one of claims 1-10.
33. The isolated polypeptide of claim 32, wherein the modified Fc domain is a modified human IgG Fc domain.
34. The isolated polypeptide of claim 33, wherein the modified Fc domain comprises the amino acid sequence SEQ ID NO:1, 2, 3, or 4, or an FcRn-binding portion thereof, with the recited substitutions.

35. A pharmaceutical composition comprising the isolated polypeptide of any one of claims 32-34 and a pharmaceutically acceptable carrier.