

CLAIMS

1. Use of an FcRn antagonist for the manufacture of a medicament for increasing the clearance of serum IgG in a subject in need thereof, wherein the FcRn antagonist comprises 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.

2. The use 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 use 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. Use of an FcRn antagonist for the manufacture of a medicament for increasing the clearance of serum IgG in a subject in need thereof, wherein the FcRn antagonist comprises 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.

5. Use of an FcRn antagonist for the manufacture of a medicament for increasing the clearance of serum IgG in a subject in need thereof, wherein the FcRn antagonist comprises 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.
6. Use of an FcRn antagonist for the manufacture of a medicament for increasing the clearance of serum IgG in a subject in need thereof, wherein the FcRn antagonist comprises 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.
7. Use of an FcRn antagonist for the manufacture of a medicament for increasing the clearance of serum IgG in a subject in need thereof, wherein the FcRn antagonist comprises 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.
8. Use of an FcRn antagonist for the manufacture of a medicament for increasing the clearance of serum IgG in a subject in need thereof, wherein the FcRn antagonist comprises 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.

9. Use of an FcRn antagonist for the manufacture of a medicament for increasing the clearance of serum IgG in a subject in need thereof, wherein the FcRn antagonist comprises 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.

10. The use 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/T307W/N434Y.

11. The use of any one of the preceding claims, wherein the subject has an IgG-mediated disorder.

12. The use of any one of the preceding claims, wherein the IgG-mediated disorder is an autoimmune disease.

13. The use of claim 12, 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.

14. Use of an FcRn antagonist for the manufacture of an agent for enhancing diagnostic imaging in a subject in need thereof receiving a radiolabeled IgG imaging agent, wherein the FcRn antagonist comprises 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/T307W/N434Y,
according to Eu numbering.

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

16. Use of an FcRn antagonist for the manufacture of a medicament for reducing exposure of a non-target tissue to a radiolabeled IgG antibody during diagnostic imaging in a subject in need thereof in a method comprising administering to the subject an effective amount of the FcRn antagonist, wherein the FcRn antagonist comprises 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/T307W/N434Y,

according to Eu numbering.

17. The use of any one of the preceding claims, wherein the modified Fc domain is a modified human IgG Fc domain.

18. The use of claim 17, wherein the modified Fc domain is a modified human IgG1 Fc domain.

19. The use 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 use 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 use 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 use of any one of the preceding claims, wherein the FcRn antagonist comprises the amino acid sequence SEQ ID NO:1, 2, 3, or 4, with the amino acid substitutions.
23. The use 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 use of any one of claims 1-22, wherein the FcRn antagonist is an antibody or comprises an antigen-binding fragment thereof.
25. The use of claim 24, wherein the FcRn antagonist is a monoclonal antibody.
26. The use of claim 25, wherein the antibody is a chimeric, humanized, or human antibody.
27. The use of any one of claims 1-22, wherein the FcRn antagonist is an Fc fusion protein.
28. The use of claim 27, wherein the Fc fusion protein is an immunoadhesin.
29. The use of any one of claims 1-22, wherein the FcRn antagonist is an Fc fragment.
30. An isolated polypeptide consisting of a modified Fc domain, comprising a combination of amino acid substitutions recited in any one of claims 1-10.

31. The isolated polypeptide of claim 30, wherein the modified Fc domain is a modified human IgG Fc domain.
32. The isolated polypeptide of claim 31, wherein the modified Fc domain comprises the amino acid sequence SEQ ID NO:1, 2, 3, or 4, with the recited substitutions.
33. A pharmaceutical composition comprising the isolated polypeptide of any one of claims 30-32 and a pharmaceutically acceptable carrier.