[CLAIMS]

[Claim 1] An antigen-binding molecule comprising a modified FcRn-binding domain, wherein the modified FcRn-binding domain comprises an amino acid substitution at one or more positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436, wherein the numbers indicate the position of the substitution according to the EU numbering,

wherein the antigen-binding molecule has improved pharmacokinetics compared to a control antibody comprising an intact FcRn-binding domain,

wherein binding activity of the modified FcRn-binding domain of the antigen-binding molecule for a pre-existing anti-drug antibody (ADA) is not significantly increased as compared to a binding affinity of the intact FcRn-binding domain of the control antibody,

wherein the FcRn-binding domain further comprises an amino acid substitution at one or more positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440.

[Claim 2] The antigen-binding molecule according to claim 1, wherein the modified FcRn-binding domain comprises an amino acid substitution of an amino acid at one or more position combinations selected from the group consisting of

a) EU252, EU254 and EU256;
b) EU252, EU434 and EU436;
c) EU250, EU252, EU307, EU308, EU311, EU434 and EU436;
d) EU428 and EU434; and
e) EU424,

and wherein the FcRn-binding domain further comprises an amino acid substitution of an amino acid at one or more position combinations selected from the group consisting of

a) EU387;
b) EU422;
c) EU424;
d) EU426;
e) EU436;
f) EU438;
g) EU440;
h) EU422 and EU424; and
i) EU438 and EU440.

[Claim 3] The antigen-binding molecule according to claim 1 or 2, wherein the modified FcRn-binding domain comprises

at position EU250 a valine,
at position EU252 a tyrosine,
at position EU254 a threonine,
at position EU307 a glutamine,
at position EU308 a proline,
at position EU311 an alanine or a histidine,
at position EU428 an isoleucine,
at position EU434 a tyrosine, or a tryptophan, and/or
at position EU436 an isoleucine, a leucine, a valine, a threonine, or a phenylalanine.

[Claim 4] The antigen-binding molecule according to any one of claims 1 to 3, wherein the ratio of high molecular weight species is less than 2%.

[Claim 5] The antigen-binding molecule according to any one of claims 1 to 4, wherein antigen-binding molecule comprises an antigen-binding domain having
a) a lower binding activity for the antigen at pH 5.5-6.5 than at pH 7-8 or
b) a "calcium concentration-dependent binding" activity for the antigen.

[Claim 6] The antigen-binding molecule according to any one of claims 1 to 3, wherein the binding activity of said binding molecule for the FcRn at pH 7 is 50-150nM, Tm is higher than 63.0 degrees C, and Epibase score is less than 250.

[Claim 7] The antigen-binding molecule according to any one of claims 1 to 3, and wherein the binding activity of said binding molecule for FcRn at pH 7 is 15-50nM, Tm is higher than 60 degrees C, and Epibase score is less than 500.

[Claim 8] The antigen-binding molecule according to any one of claims 1 to 3, and wherein the binding activity of said the binding molecule for FcRn at pH 7 is stronger than 15nM, Tm is higher than 57.5 degrees C, and Epibase score is less than 500.

[Claim 9] The antigen-binding molecule according to claim 1, wherein the FcRn-binding domain comprises one or more amino acid substitutions selected from the group consisting of
at position EU387 an arginine;
at position EU422 a glutamic acid, an arginine, or a serine, an aspartic acid, a lysine, a threonine or a glutamine;
at position EU424 a glutamic acid or an arginine, a lysine, or an asparagine;
at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
at position EU436 a threonine;

at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 10] The antigen-binding molecule according to any one of claim 1 to 9, wherein the modified FcRn-binding domain comprises three or more substitutions, wherein the three or more substitutions are one of the combinations set forth in Tables 12 to 13.

[Claim 11] The antigen-binding molecule according to any one of claims 1 to 10, wherein the modified FcRn-binding domain comprises three or more substitutions, wherein the three or more substitutions are one of the combinations set forth in Tables 14 to 15.

[Claim 12] The antigen-binding molecule according to any one of claims 1 to 11, wherein the FcRn-binding domain comprises:
a) at position EU252 a tyrosine, at position EU387 an arginine, at position EU434 a tyrosine, and at position EU436 a valine; or
b) at position EU252 a tyrosine, at position EU422 a glutamic acid, at position EU434 a tyrosine, and at position EU436 a valine; or
c) at position EU252 a tyrosine, at position EU422 an arginine, at position EU434 a tyrosine, and at position EU436 a valine; or
d) at position EU252 a tyrosine, at position EU422 a serine, at position EU434 a tyrosine, and at position EU436 a valine; or
e) at position EU252 a tyrosine, at position EU424 a glutamic acid, at position EU434 a tyrosine, and at position EU436 a valine; or
f) at position EU252 a tyrosine, at position EU424 an arginine, at position EU434 a tyrosine, and at position EU436 a valine; or
g) at position EU252 a tyrosine, at position EU434 a tyrosine , at position EU436 a valine, and at position EU438 a glutamic acid; or
h) at position EU252 a tyrosine, at position EU434 a tyrosine, at position EU436 a valine, and at position EU438 an arginine; or
i) at position EU252 a tyrosine, at position EU434 a tyrosine, at position EU436 a valine, and at position EU438 a serine; or
j) at position EU252 a tyrosine, at position EU434 a tyrosine, at position EU436 a valine, and at position EU440 a glutamic acid.

[Claim 13] The antigen-binding molecule according to any one of claims 1 to 12, wherein the antigen-binding molecule is an antibody.

[Claim 14] Use of the antigen-binding molecule according to any one of claims 1 to 13 in the manufacture of a medicament for treating an autoimmune disease, a transplant rejection (graft-vs.-host disease) or an allergic disease; wherein the medicament improves antigen-binding molecule-mediated antigen uptake into cells.

[Claim 15] Use of the antigen-binding molecule according to any one of claims 1 to 13 in the manufacture of a medicament for treating an autoimmune disease, a

transplant rejection (graft-vs.-host disease) or an allergic disease; wherein the medicament reduces the plasma concentration of a specific antigen, wherein the antigen-binding molecule comprises an antigen-binding domain which can bind said antigen.

[Claim16] A method for improving the pharmacokinetics of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of
a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecules at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and
b) introducing further amino acid substitution into an FcRn-binding domain of said antigen-binding molecules at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440.

[Claim 17] A method for delaying the elimination of an antigen-binding molecule in a subject without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and

b) introducing further amino acid substitution into an FcRn-binding domain of said antigen-binding molecules at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440.

[Claim 18] A method of prolonging the plasma retention time of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and

b) introducing further amino acid substitution into an FcRn-binding domain of said antigen-binding molecules at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440.

[Claim 19] A method for increasing the plasma antigen-elimination rate of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and

b) introducing further amino acid substitution into an FcRn-binding domain of said antigen-binding molecules at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440.

[Claim 20] A method for increasing the ability of an antigen-binding molecule to eliminate plasma antigen without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and

b) introducing further amino acid substitution into an FcRn-binding domain of said antigen-binding molecules at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440.

[Claim 21] The method according to any one of claims 16 to 20, wherein further an amino acid substitution at position EU256 into the FcRn-binding domain is introduced.

[Claim 22] A method for producing antigen-binding molecules according to any one of claims 1 to 13, which comprises the steps of
(a) selecting a parent FcRn-binding domain and altering the parent FcRn by introducing an amino acid substitution at one or more positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436;
(b) selecting an antigen-binding domain of an antigen-binding molecule and altering at least one amino acid in the antigen-binding domain in order to get a pH-dependent antigen-binding domain or a calcium-ion dependent antigen-binding domain;
(c) obtaining a gene encoding an antigen-binding molecule in which the human FcRn-binding domain and the antigen-binding domain prepared in (a) and (b) are linked and
(d) producing an antigen-binding molecule using the gene prepared in (c).

[Claim 23] The method according to claim 22, wherein in step a) further an amino acid substitution at position EU256 into the FcRn-binding domain is introduced.

[Claim 24] The method according to any one of claims 22 to 23, wherein the method further comprises a step of introducing in the FcRn-binding domain an amino acid substitution at one or more positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440.

[Claim 25] An antigen-binding molecule comprising a modified FcRn-binding domain, wherein the modified FcRn-binding domain comprises an amino acid substitution at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438 and EU440, wherein the binding affinity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA) at a neutral pH is not significantly increased as compared to the binding affinity of antigen-binding molecule comprising an intact FcRn-binding domain,

wherein the antigen-binding molecule further has an increased binding affinity for an FcRn in the neutral or acidic pH ranges.

[Claim 26] The antigen-binding molecule according to claim 25, wherein the modified FcRn-binding domain comprises an amino acid substitution of an amino acid at one or more position combinations selected from the group consisting of

a) EU387;
b) EU422;
c) EU424;
d) EU426;
e) EU436;
f) EU438;
g) EU440;
h) EU422 and EU424; and
i) EU438 and EU440.

[Claim 27] The antigen-binding molecule according to claims 25 or 26, wherein the amino acid substituting one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU433, EU436, EU438 and EU440 is selected from the group consisting of
a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, aspartic acid, lysine, threonine, or glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or asparagines;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;

e) at position EU433 an aspartic acid
f) at position EU436 a threonine
g) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
h) at position EU440 a glutamic acid, an aspartic acid, or a glutamine.

[Claim 28] The antigen-binding molecule according to any one of claims 25 to 27, wherein the modified FcRn-binding domain further comprises an amino acid substitution at one or more positions of the FcRn-binding domain selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU309, EU311, EU428, EU434, and EU436, wherein said substitutions confer an increase in FcRn-binding activity in the neutral pH or acidic pH range.

[Claim 29] The antigen-binding molecule according to any one of claims 25 to 28, wherein the modified FcRn-binding domain comprises amino acid substitutions at the FcRn-binding domain positions
i) a) EU438/EU440 or b) EU424; and
ii) a) EU434, b) EU252/EU254/EU256; c) EU428/EU434; or d) EU250/EU428.

[Claim 30] The antigen-binding molecule according to claim 29, wherein the modified FcRn-binding domain comprises amino acid substitutions
i) a) EU438R/EU440E or b) EU424N; and
ii) a) M434H; b) M252Y/S254T/T256E; c) M428L/N434S; or d) T250Q and M428L (EU numbering).

[Claim 31] The antigen-binding molecule according to claim 30, wherein the modified FcRn-binding domain comprises three or more amino acid substitutions wherein the three or more substitutions are one of the combinations set forth in Tables 13 and 15.

[Claim 32] The antigen-binding molecule according to any one of claims 25 to 27 wherein the modified FcRn-binding domain comprises substitutions
a) at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU438, EU440, EU433, or at two or more positions wherein the two positions are one of the combinations of the group consisting of EU422/EU424, and EU438/EU440; and
b) two or more positions wherein the two positions are one of the combinations set forth in Table 9.

[Claim 33] The antigen-binding molecule according to claim 32, wherein the modified FcRn-binding domain comprises three or more the amino acid substitutions wherein the three or more the amino acid substitutions are one of the combinations set forth in Tables 12 or 14.

[Claim 34] The antigen-binding molecule of any one of claims 25 to 33 wherein said antigen-binding molecule comprises a pH-dependent antigen-binding domain or a calcium ion-dependent antigen-binding domain.

CLAIMS

[Claim 1] An antigen-binding molecule comprising a modified FcRn-binding domain, wherein the modified FcRn-binding domain comprises an amino acid substitution at one or more positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436, wherein the numbers indicate the position of the substitution according to the EU numbering,

wherein the antigen-binding molecule has improved pharmacokinetics compared to a control antibody comprising an intact FcRn-binding domain,

wherein binding activity of the modified FcRn-binding domain of the antigen-binding molecule for a pre-existing anti-drug antibody (ADA) is not significantly increased as compared to a binding affinity of the intact FcRn-binding domain of the control antibody,

wherein the FcRn-binding domain further comprises one or more amino acid substitutions selected from the group consisting of

a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, alysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
e) at position EU436 a threonine;
f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
g) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 2] The antigen-binding molecule according to claim 1, wherein the modified FcRn-binding domain comprises an amino acid substitution of an amino acid at one or more position combinations selected from the group consisting of

a) EU252, EU254 and EU256;
b) EU252, EU434 and EU436;
c) EU250, EU252, EU307, EU308, EU311, EU434 and EU436;
d) EU428 and EU434; and
e) EU424,

and wherein the FcRn-binding domain further comprises one or more amino acid substitutions selected from the group consisting of

f) at position EU387 an arginine;
g) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine or a glutamine;
h) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
i) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
j) at position EU436 a threonine;
k) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
l) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 3] The antigen-binding molecule according to claim 1, wherein the modified FcRn-binding domain comprises an amino acid substitution of an amino acid at one or more position combinations selected from the group consisting of

a) EU252, EU254 and EU256;
b) EU252, EU434 and EU436;
c) EU250, EU252, EU307, EU308, EU311, EU434 and EU436;
d) EU428 and EU434; and
e) EU424,
and wherein the FcRn-binding domain further comprises amino acid substitution combinations selected from the group consisting of
f) at position EU387 an arginine;
g) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
h) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
i) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
j) at position EU436 a threonine;
k) at position EU438 a glutamic acid, an arginine, a serine, or a lysine;
l) at position EU440 a glutamic acid, aspartic acid or a glutamine;
m) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine or a glutamine and
at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine; and
n) at position EU438 a glutamic acid, an arginine, a serine, or a lysine and
at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 4] The antigen-binding molecule according to any one of claims 1 to 3, wherein the modified FcRn-binding domain comprises
at position EU250 a valine,
at position EU252 a tyrosine,
at position EU254 a threonine,
at position EU307 a glutamine,
at position EU308 a proline,
at position EU311 an alanine or a histidine,
at position EU428 an isoleucine,
at position EU434 a tyrosine, or a tryptophan, and/or
at position EU436 an isoleucine, a leucine, a valine, a threonine, or a phenylalanine.

[Claim 5] The antigen-binding molecule according to any one of claims 1 to 4, wherein the ratio of high molecular weight species is less than 2%.

[Claim 6] The antigen-binding molecule according to any one of claims 1 to 5, wherein antigen-binding molecule comprises an antigen-binding domain having
a) a lower binding activity for the antigen at pH 5.5-6.5 than at pH 7-8 or
b) a "calcium concentration-dependent binding" activity for the antigen.

[Claim 7] The antigen-binding molecule according to any one of claims 1 to 4, wherein the binding activity of said binding molecule for the FcRn at pH 7 is 50-150nM, Tm is higher than 63.0 degrees C, and Epibase score is less than 250.

[Claim 8] The antigen-binding molecule according to any one of claims 1 to 4, and wherein the binding activity of said binding molecule for FcRn at pH 7 is 15-50nM, Tm is higher than 60 degrees C, and Epibase score is less than 500.

[Claim 9] The antigen-binding molecule according to any one of claims 1 to 4, and wherein the binding activity of said the binding molecule for FcRn at pH 7 is stronger than 15nM, Tm is higher than 57.5 degrees C, and Epibase score is less than 500.

[Claim 10] The antigen-binding molecule according to any one of claim 1 to 9, wherein the modified FcRn-binding domain comprises three or more substitutions, wherein the three or more substitutions are one of the combinations set forth in Tables 12 to 13.

[Claim 11] The antigen-binding molecule according to any one of claims 1 to 10, wherein the modified FcRn-binding domain comprises three or more substitutions, wherein the three or more substitutions are one of the combinations set forth in Tables 14 to 15.

[Claim 12] The antigen-binding molecule according to any one of claims 1 to 11, wherein the FcRn-binding domain comprises:

a) at position EU252 a tyrosine, at position EU387 an arginine, at position EU434 a tyrosine, and at position EU436 a valine; or
b) at position EU252 a tyrosine, at position EU422 a glutamic acid, at position EU434 a tyrosine, and at position EU436 a valine; or
c) at position EU252 a tyrosine, at position EU422 an arginine, at position EU434 a tyrosine, and at position EU436 a valine; or
d) at position EU252 a tyrosine, at position EU422 a serine, at position EU434 a tyrosine, and at position EU436 a valine; or
e) at position EU252 a tyrosine, at position EU424 a glutamic acid, at position EU434 a tyrosine, and at position EU436 a valine; or
f) at position EU252 a tyrosine, at position EU424 an arginine, at position EU434 a tyrosine, and at position EU436 a valine; or
g) at position EU252 a tyrosine, at position EU434 a tyrosine , at position EU436 a valine, and at position EU438 a glutamic acid; or
h) at position EU252 a tyrosine, at position EU434 a tyrosine, at position EU436 a valine, and at position EU438 an arginine; or
i) at position EU252 a tyrosine, at position EU434 a tyrosine, at position EU436 a valine, and at position EU438 a serine; or
j) at position EU252 a tyrosine, at position EU434 a tyrosine, at position EU436 a valine, and at position EU440 a glutamic acid.

[Claim 13] The antigen-binding molecule according to any one of claims 1 to 12, wherein the antigen-binding molecule is an antibody.

[Claim 14] Use of the antigen-binding molecule according to any one of claims 1 to 13 in the manufacture of a medicament for treating an autoimmune disease, a transplant rejection (graft-vs.-host disease) or an allergic disease; wherein the medicament improves antigen-binding molecule-mediated antigen uptake into cells.

[Claim 15] Use of the antigen-binding molecule according to any one of claims 1 to 13 in the manufacture of a medicament for treating an autoimmune disease, a transplant rejection (graft-vs.-host disease) or an allergic disease; wherein the medicament reduces the plasma concentration of a specific antigen, wherein the antigen-binding molecule comprises an antigen-binding domain which can bind said antigen.

[Claim16] A method for improving the pharmacokinetics of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecules at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and

b) introducing further one or more amino acid substitutions into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of

i) at position EU387 an arginine;
ii) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
iii) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
iv) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
v) at position EU436 a threonine;
vi) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
vii) at position EU440 a glutamic acid, aspartic acid or a glutamine;.

[Claim 17] A method for delaying the elimination of an antigen-binding molecule in a subject without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and

b) introducing further one or more amino acid substitution into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of

i) at position EU387 an arginine;
ii) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
iii) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
iv) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
v) at position EU436 a threonine;
vi) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
vii) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 18] A method of prolonging the plasma retention time of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and
b) introducing further one or more amino acid substitution into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of
   i) at position EU387 an arginine;
   ii) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
   iii) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
   iv) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
   v) at position EU436 a threonine;
   vi) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
   vii) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 19] A method for increasing the plasma antigen-elimination rate of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and
b) introducing further one or more amino acid substitution into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of
   i) at position EU387 an arginine;
   ii) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
   iii) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
   iv) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
   v) at position EU436 a threonine;
   vi) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
   vii) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 20] A method for increasing the ability of an antigen-binding molecule to eliminate plasma antigen without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising the steps of

a) introducing an amino acid substitution into an FcRn-binding domain of said antigen-binding molecule at one or more of the positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and
b) introducing further one or more amino acid substitution into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of
   i) at position EU387 an arginine;
   ii) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a

lysine, a threonine, or a glutamine;
iii) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
iv) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
v) at position EU436 a threonine;
vi) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
vii) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 21] The method according to any one of claims 16 to 20, wherein further an amino acid substitution at position EU256 into the FcRn-binding domain is introduced.

[Claim 22] A method for producing antigen-binding molecules according to any one of claims 1 to 13, which comprises the steps of
(a) selecting a parent FcRn-binding domain and altering the parent FcRn by
i) introducing an amino acid substitution at one or more positions selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU311, EU428, EU434, and EU436; and
ii) introducing further one or more amino acid substitution selected from the group consisting of
[1] at position EU387 an arginine;
[2] at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
[3] at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
[4] at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
[5] at position EU436 a threonine;
[6] at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
[7] at position EU440 a glutamic acid, aspartic acid or a glutamine.
(b) selecting an antigen-binding domain of an antigen-binding molecule and altering at least one amino acid in the antigen-binding domain in order to get a pH-dependent antigen-binding domain or a calcium-ion dependent antigen-binding domain;
(c) obtaining a gene encoding an antigen-binding molecule in which the human FcRn-binding domain and the antigen-binding domain prepared in (a) and (b) are linked and
(d) producing an antigen-binding molecule using the gene prepared in (c).

[Claim 23] The method according to claim 22, wherein in step a) further an amino acid substitution at position EU256 into the FcRn-binding domain is introduced.

[Claim 24] An antigen-binding molecule comprising a modified FcRn-binding domain, wherein the modified FcRn-binding domain comprises one or more amino acid substitutions selected from the group consisting of
a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, alysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;

e) at position EU436 a threonine;
f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
g) at position EU440 a glutamic acid, aspartic acid or a glutamine.

wherein the binding affinity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA) at a neutral pH is not significantly increased as compared to the binding affinity of antigen-binding molecule comprising an intact FcRn-binding domain,

wherein the antigen-binding molecule further has an increased binding affinity for an FcRn in the neutral or acidic pH ranges.

[Claim 25] The antigen-binding molecule according to claim 24, wherein the one or more amino acid substitutions are selected from the group consisting of
a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
e) at position EU436 a threonine;
f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine;
g) at position EU440 a glutamic acid, aspartic acid or a glutamine;
h) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine or a glutamine and
at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine; and
i) at position EU438 a glutamic acid, an arginine, a serine, or a lysine and
at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 26] The antigen-binding molecule according to claim 24 or 25, wherein the modified FcRn-binding domain further comprises an amino acid substitution at one or more positions of the FcRn-binding domain selected from the group consisting of EU250, EU252, EU254, EU307, EU308, EU309, EU311, EU428, EU434, and EU436, wherein said substitutions confer an increase in FcRn-binding activity in the neutral pH or acidic pH range.

[Claim 27] The antigen-binding molecule according to any one of claims 24 to 26, wherein the modified FcRn-binding domain comprises amino acid substitutions at the FcRn-binding domain positions
i) a) EU438/EU440 or b) EU424; and
ii) a) EU434, b) EU252/EU254/EU256; c) EU428/EU434; or d) EU250/EU428.

[Claim 28] The antigen-binding molecule according to claim 27, wherein the modified FcRn-binding domain comprises amino acid substitutions
i) a) EU438R/EU440E or b) EU424N; and
ii) a) M434H; b) M252Y/S254T/T256E; c) M428L/N434S; or d) T250Q and M428L (EU numbering).

[Claim 29] The antigen-binding molecule according to claim 28, wherein the modified FcRn-binding domain comprises three or more amino acid substitutions wherein

the three or more substitutions are one of the combinations set forth in Tables 13 and 15.

[Claim 30] The antigen-binding molecule according to claim 24 or 25 wherein the modified FcRn-binding domain comprises substitutions
a) at one or more of the positions selected from the group consisting of EU387, EU422, EU424, EU426, EU436, EU438, EU440, or at two or more positions wherein the two positions are one of the combinations of the group consisting of EU422/EU424, and EU438/EU440; and
b) two or more positions wherein the two positions are one of the combinations set forth in Table 9.

[Claim 31] The antigen-binding molecule according to claim 30, wherein the modified FcRn-binding domain comprises three or more the amino acid substitutions wherein the three or more the amino acid substitutions are one of the combinations set forth in Tables 12 or 14.

[Claim 32] The antigen-binding molecule of any one of claims 24 to 31 wherein said antigen-binding molecule comprises a pH-dependent antigen-binding domain or a calcium ion-dependent antigen-binding domain.

[Claim 33] The antigen-binding molecule according to any one of claims 24 to 32, wherein the antigen-binding molecule is an antibody.

[Claim 34] Use of the antigen-binding molecule according to any one of claims 24 to 33 in the manufacture of a medicament for treating an autoimmune disease, a transplant rejection (graft-vs.-host disease) or an allergic disease; wherein the medicament improves antigen-binding molecule-mediated antigen uptake into cells.

[Claim 35] Use of the antigen-binding molecule according to any one of claims 24 to 33 in the manufacture of a medicament for treating an autoimmune disease, a transplant rejection (graft-vs.-host disease) or an allergic disease; wherein the medicament reduces the plasma concentration of a specific antigen, wherein the antigen-binding molecule comprises an antigen-binding domain which can bind said antigen.

[Claim 36] A method for improving the pharmacokinetics of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising introducing one or more amino acid substitutions into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of
a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, alysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
e) at position EU436 a threonine;

f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
g) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 37] A method for delaying the elimination of an antigen-binding molecule in a subject without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising introducing one or more amino acid substitutions into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of
a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, alysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
e) at position EU436 a threonine;
f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
g) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 38] A method of prolonging the plasma retention time of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising introducing one or more amino acid substitutions into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of
a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, alysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
e) at position EU436 a threonine;
f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
g) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 39] A method for increasing the plasma antigen-elimination rate of an antigen-binding molecule without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising introducing one or more amino acid substitutions into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of
a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, alysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
e) at position EU436 a threonine;
f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
g) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 40] A method for increasing the ability of an antigen-binding molecule to eliminate

plasma antigen without significantly increasing the binding activity of said antigen-binding molecule for a pre-existing anti-drug antibody (ADA), comprising introducing one or more amino acid substitutions into an FcRn-binding domain of said antigen-binding molecules selected from the group consisting of

a) at position EU387 an arginine;
b) at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, alysine, a threonine, or a glutamine;
c) at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
d) at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
e) at position EU436 a threonine;
f) at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
g) at position EU440 a glutamic acid, aspartic acid or a glutamine.

[Claim 41] The method according to any one of claims 36 to 40, wherein further an amino acid substitution at position EU256 into the FcRn-binding domain is introduced.

[Claim 42] A method for producing antigen-binding molecules according to any one of claims 24 to 33, which comprises the steps of

(a) selecting a parent FcRn-binding domain and altering the parent FcRn by introducing one or more amino acid substitution selected from the group consisting of
  [1] at position EU387 an arginine;
  [2] at position EU422 a glutamic acid, an arginine, a serine, an aspartic acid, a lysine, a threonine, or a glutamine;
  [3] at position EU424 a glutamic acid, an arginine, a lysine, or an asparagine;
  [4] at position EU426 an aspartic acid, a glutamine, an alanine, or a tyrosine;
  [5] at position EU436 a threonine;
  [6] at position EU438 a glutamic acid, an arginine, a serine, or a lysine; and
  [7] at position EU440 a glutamic acid, aspartic acid or a glutamine.

(b) selecting an antigen-binding domain of an antigen-binding molecule and altering at least one amino acid in the antigen-binding domain in order to get a pH-dependent antigen-binding domain or a calcium-ion dependent antigen-binding domain;
(c) obtaining a gene encoding an antigen-binding molecule in which the human FcRn-binding domain and the antigen-binding domain prepared in (a) and (b) are linked and
(d) producing an antigen-binding molecule using the gene prepared in (c).

[Claim 43] The method according to claim 42, wherein in step a) further an amino acid substitution at position EU256 into the FcRn-binding domain is introduced.