

Non Patent Literature

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Summary

[0031] In one nonexclusive example, a non-limited objective of examples of Disclosure A is to provide molecules with improved pharmacokinetic properties over antibodies, such as ion concentration-dependent antigen binding properties that improve antibody half-life and/or antigen clearance from the plasma. In one aspect, the present disclosure refers to an antibody comprising an antigen-binding domain whose antigen-binding activity changes according to hydrogen ion concentration (pH) conditions, wherein (i) a modified light chain comprising an amino acid sequence in which amino acid residues at positions 18, 24, 45, 79, and 107, according to Kabat numbering, in the amino acid sequence of SEQ ID NO: 32 are substituted with Arg (R), Arg (R), Lys (K), Gln (Q), and Lys (K), respectively, and (ii) a modified heavy chain comprising an amino acid sequence in which amino acid residues at positions 16, 43, 64, and 105, according to Kabat numbering, in the amino acid sequence of SEQ ID NO: 24, 26, 28 or 30 are substituted with Gln (Q), Arg (R), Lys (K), and Gln (Q), respectively.

[0032] In one nonexclusive example, a non-limited objective of examples of Disclosure B is to provide, safe and more favorable Fc region variants that have increased half-life and decreased binding to pre-existing anti-drug antibodies (ADAs).

[0033] In one nonexclusive example, a non-limited objective of examples of Disclosure C is to provide anti-IL-8 antibodies that have pH-dependent binding affinity towards IL-8. An additional example relates to anti-IL-8 antibodies that have an effect of rapidly eliminating IL-8 compared to a reference antibody when administered to an individual. In another example, Disclosure C relates to anti-IL-8 antibodies that can

and

(d) collecting the modified antibody from the host cell culture.

In further examples, the method optionally further comprises any one or more of:

(e) selecting an antibody which can promote elimination of an antigen from plasma;

(f) selecting an antibody with enhanced binding activity to an extracellular matrix;

(g) selecting an antibody with enhanced FcγR-binding activity under a neutral pH condition (e.g., pH 7.4);

(h) selecting an antibody with enhanced FcγRIIb-binding activity under a neutral pH condition (e.g., pH 7.4);

(i) selecting an antibody with maintained or enhanced FcγRIIb-binding activity and decreased binding activity to one or more activating FcγR, preferably selected from the group consisting of FcγRIa, FcγRIb, FcγRIc, FcγRIIIa, FcγRIIIb and FcγRIIa;

(j) selecting an antibody with enhanced FcRn-binding activity under a neutral pH condition (e.g., pH 7.4);

(k) selecting an antibody with an increased isoelectric point (pI);

(l) confirming the isoelectric point (pI) of the collected antibody, and then selecting an antibody with an increased isoelectric point (pI); and

(m) selecting an antibody whose antigen-binding activity is changed or increased according to ion concentration conditions;

as compared to the antibody before the modification.

[0040a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as described herein. In yet another aspect, the present disclosure refers to a nucleic acid encoding the antibody as described herein. In a still further aspect, the present disclosure refers to a vector comprising the nucleic acid as described herein. In another aspect, the present disclosure refers to a host cell comprising the vector as described herein. In yet a further aspect, the present disclosure refers to a method for producing an antibody comprising an antigen-binding domain whose antigen-binding activity changes according to hydrogen ion concentration (pH) conditions, wherein the method comprises culturing the host cell as described herein and collecting the antibody from the cell culture.

[0041] Another example of Disclosure A relates to, for example, without limitation:

[D1] a method for producing a modified antibody, whose half-life in plasma is prolonged or reduced, as compared to that before the modification of the antibody, wherein the method comprises:

(a) modifying a nucleic acid encoding the antibody before the modification to change the charge of at least one amino acid residue at a position selected from the group consisting of position 196, 253, 254, 256, 258, 278, 280, 281, 282, 285, 286, 307, 309, 311, 315, 327, 330, 342, 343, 345, 356, 358, 359, 361, 362, 373, 382, 384, 385, 386, 387, 389, 399, 400, 401, 402, 413, 415, 418, 419, 421, 424, 430, 433, 434, and 443, according to EU numbering;

(b) culturing a host cell to express the nucleic acid; and

(c) collecting the antibody from the host cell culture; or

[D2] a method for prolonging or reducing the half-life of an antibody in plasma wherein the method comprises modifying at least one amino acid residue at a position selected from the group consisting of position 196, 253, 254, 256, 258, 278, 280, 281, 282, 285, 286, 307, 309, 311, 315, 327, 330, 342, 343, 345, 356, 358, 359, 361, 362, 373, 382, 384, 385, 386, 387, 389, 399, 400, 401, 402, 413, 415, 418, 419, 421, 424, 430, 433, 434, and 443, according to EU numbering.

[CLAIMS]

[Claim 1]

An antibody comprising an antigen-binding domain whose antigen-binding activity changes according to hydrogen ion concentration (pH) conditions, wherein

(i) a modified light chain comprising an amino acid sequence in which amino acid residues at positions 18, 24, 45, 79, and 107, according to Kabat numbering, in the amino acid sequence of SEQ ID NO: 32 are substituted with Arg (R), Arg (R), Lys (K), Gln (Q), and Lys (K), respectively, and

(ii) a modified heavy chain comprising an amino acid sequence in which amino acid residues at positions 16, 43, 64, and 105, according to Kabat numbering, in the amino acid sequence of SEQ ID NO: 24, 26, 28 or 30 are substituted with Gln (Q), Arg (R), Lys (K), and Gln (Q), respectively.

[Claim 2]

The antibody of claim 1, wherein the antibody binds to a soluble antigen.

[Claim 3]

The antibody of claim 1, wherein a ratio of its K_D in an acidic pH range to that in a neutral pH range, K_D (acidic pH range) / K_D (neutral pH range), for the antigen, is 2 or higher.

[Claim 4]

The antibody of any one of claims 1 to 3, which can promote elimination of an antigen from plasma as compared to an antibody before the modification, or wherein an extracellular matrix-binding activity of the antibody is enhanced as compared to an antibody before the modification.

[Claim 5]

The antibody of any one of claims 1 to 4, wherein the antibody is an IgG antibody.

[Claim 6]

A pharmaceutical composition comprising the antibody of any one of claims 1 to 5.

[Claim 7]

The pharmaceutical composition of claim 6, which is for promoting elimination of an antigen from plasma or which is for enhancing binding to an extracellular matrix.

[Claim 8]

A nucleic acid encoding the antibody of any one of claims 1 to 5.

[Claim 9]

A vector comprising the nucleic acid of claim 8.

[Claim 10]

A host cell comprising the vector of claim 9.

[Claim 11]

A method for producing an antibody comprising an antigen-binding domain whose antigen-binding activity changes according to hydrogen ion concentration (pH) conditions, wherein the method comprises culturing the host cell of claim 10 and collecting the antibody from the cell culture.

[Claim 12]

The method of claim 11, which further comprises any one or more of:

- (a) selecting an antibody which can promote elimination of an antigen from plasma;
- (b) selecting an antibody with enhanced binding activity to an extracellular matrix;
- (c) selecting an antibody with enhanced Fc γ R-binding activity under a neutral pH condition;
- (d) selecting an antibody with enhanced Fc γ RIIb-binding activity under a neutral pH condition;
- (e) selecting an antibody with maintained or enhanced Fc γ RIIb-binding activity and decreased binding activity to one or more activating Fc γ R, selected from the group consisting of Fc γ RIa, Fc γ RIb, Fc γ RIc, Fc γ RIIIa, Fc γ RIIIb and Fc γ RIIIa;
- (f) selecting an antibody with enhanced FcRn-binding activity under a neutral pH condition;
- (g) selecting an antibody with an increased isoelectric point (pI);
- (h) confirming the isoelectric point (pI) of the collected antibody, and then selecting an antibody with an increased isoelectric point (pI); and
- (i) selecting an antibody whose antigen-binding activity is changed or increased according to ion concentration conditions; as compared to a reference antibody.