antigen-binding domain of an antigen-binding molecule whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range. Still another objective of the present invention is to provide antigen-binding molecules that exhibit improved pharmacokinetics or impaired *in vivo* immune response when administered to animals. Yet another objective of the present invention is to provide methods for producing such antigen-binding molecules as well as pharmaceutical compositions comprising as an active ingredient the antigen-binding molecules.

[Means for Solving the Problems]

The present inventors conducted dedicated studies to achieve the above-described objectives. As a result, the present inventors revealed that an antigen-binding molecule that comprises the antigen-binding domain of an antigen-binding molecule whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range formed a hetero complex consisting of four molecules: antigen-binding molecule/two molecules of FcRn/activating Fcγ receptor (Fig. 48). The present inventors also demonstrated that the tetramer formation adversely affected the pharmacokinetics and immune response. The present inventors demonstrated that the pharmacokinetics of an antigen-binding molecule was improved by modifying the Fc region of such antigen-binding molecule into an Fc region that in a neutral pH range does not form a hetero tetramer complex comprising two molecules of FcRn and an activating Fcγ receptor. The present inventors also demonstrated that the immune response in animals administered with an antigen-binding molecule could be altered by modifying the Fc region of such an antigen-binding molecule into an Fc region that in a neutral pH range does not form a tetramer complex comprising two molecules of FcRn and an activating Fcγ receptor. The present inventors also demonstrated that immune response to the antigen-binding molecule was reduced by modification into an Fc region that in a neutral pH range does not form a hetero tetramer complex comprising two molecules of FcRn and an activating Fcγ receptor. Furthermore, the present inventors discovered antigen-binding molecules and methods for producing them, and in addition found that when administered, pharmaceutical compositions comprising as an active ingredient such an antigen-binding molecule or an antigen-binding molecule produced by a production method of the present invention had superior properties such as improved pharmacokinetics and reduction of immune response in the administered living organism as compared to conventional antigen-binding molecules; and thereby completed the present invention.

In an aspect, there is provided a method of either (a) or (b) below, wherein the method comprises modifying the Fc region of an IgG-type antibody comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range into an Fc region that does not form a hetero complex comprising two molecules of FcRn and one molecule of activating Fcγ receptor in a neutral pH range,

wherein the ion concentration

(i) is hydrogen ion concentration (pH), and the antigen-binding activity is lower at pH 5.8 than at pH 7.4, wherein the ratio of (a) the KD value for antigen binding by the antibody at pH 5.8, to (b) the KD value for antigen binding by the antibody at pH 7.4 (KD (pH 5.8) / KD (pH 7.4)) is 2 or more; or

(ii) is calcium ion concentration and the antigen-binding activity is lower at a first calcium ion concentration in the range of 0.1 uM to 30 uM than at a second calcium ion concentration in the range of 100 uM to 10 mM, wherein the ratio of (a) the KD value for antigen binding by the antibody at the first calcium ion concentration, to (b) the KD value for antigen binding by the antibody at the second calcium ion concentration (KD (first calcium ion concentration) / KD (second calcium ion concentration)) is 2 or more;

(a) a method for improving pharmacokinetics of an IgG-type antibody; and

(b) a method for reducing immunogenicity of an IgG-type antibody.

In another aspect, there is provided an IgG-type antibody comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region that has FcRn-binding activity in a neutral pH range, wherein the Fc region comprises one or more amino acids selected from:

Ala at amino acid position 234;

Ala, Lys, or Arg at amino acid position 235;

Arg at amino acid position 236;

Arg at amino acid position 238;

Lys at amino acid position 239;

Phe at amino acid position 270;

Ala at amino acid position 297;

Gly at amino acid position 298;

Gly at amino acid position 325;

Arg at amino acid position 328; and

Lys or Arg at amino acid position 329; wherein the amino acids are indicated by EU numbering,

wherein the ion concentration

(i) is hydrogen ion concentration (pH), and the antigen-binding activity is lower at pH 5.8 than at pH 7.4, wherein the ratio of (a) the KD value for antigen binding by the antibody at pH 5.8, to (b) the KD value for antigen binding by the antibody at pH 7.4 (KD (pH 5.8) / KD (pH 7.4)) is 2 or more, wherein the antigen-binding domain comprises at least one His residue; or

(ii) is calcium ion concentration and the antigen-binding activity is lower at a first calcium ion concentration in the range of 0.1 uM to 30 uM than at a second calcium ion concentration in the range of 100 uM to 10 mM, wherein the ratio of (a) the KD value for antigen binding by the antibody at the first calcium ion concentration, to (b) the KD value for antigen binding by the antibody at the second calcium ion concentration (KD (first calcium ion concentration) / KD (second calcium ion concentration)) is 2 or more.

In another aspect, there is provided an IgG-type antibody comprising an antigen-binding domain whose antigen-binding activity varies depending on ion concentration and an Fc region in which one of the two polypeptides constituting the Fc region has FcRn-binding activity in a neutral pH range and the other does not have FcRn-binding activity in a neutral pH range, wherein the ion concentration

(i) is hydrogen ion concentration (pH), and the antigen-binding activity is lower at pH 5.8 than at pH 7.4, wherein the ratio of (a) the KD value for antigen binding by the antibody at pH 5.8, to (b) the KD value for antigen binding by the antibody at pH 7.4 (KD (pH 5.8) / KD (pH 7.4)) is 2 or more, wherein the antigen-binding domain comprises at least one His residue ; or

(ii) is calcium ion concentration and the antigen-binding activity is lower at a first calcium ion concentration in the range of 0.1 uM to 30 uM than at a second calcium ion concentration in the range of 100 uM to 10 mM, wherein the ratio of (a) the KD value for antigen binding by the antibody at the first calcium ion concentration, to (b) the KD value for antigen binding by the antibody at the second calcium ion concentration (KD (first calcium ion concentration) / KD (second calcium ion concentration)) is 2 or more.

In another aspect, there is provided a polynucleotide encoding the IgG-type antibody as defined above.

In another aspect, there is provided a vector which is operably linked to the polynucleotide as defined above.

In another aspect, there is provided a cell introduced with the vector as defined above.

In another aspect, there is provided a method for producing the IgG-type antibody as defined above, which comprises the step of collecting the IgG-type antibody from a culture of the cell as defined above.

In another aspect, there is provided a pharmaceutical composition which comprises as an active ingredient the IgG-type antibody as defined above or an IgG-type antibody obtained by the production method as defined above.

TMore specifically, the present inventiondisclosure provides the following.

[1] A method of either (a) or (b) below, wherein the method comprises modifying the Fc region of an antigen-binding molecule comprising an antigen-binding domain whose antigen-binding

[36] The antigen-binding molecule of any one of [29] to [33], wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies depending on pH.
[37] The antigen-binding molecule of [36], wherein the antigen-binding domain is an antigen-binding domain whose antigen-binding activity varies in a way that the antigen-binding activity in an acidic pH range is lower than the antigen-binding activity in a neutral pH range.
[38] The antigen-binding molecule of any one of [29] to [37], wherein the antigen-binding domain is an antibody variable region.
[39] The antigen-binding molecule of any one of [29] to [38], wherein the antigen-binding molecule is an antibody.
[40] A polynucleotide encoding the antigen-binding molecule of any one of [29] to [39].
[41] A vector which is operably linked to the polynucleotide of [40].
[42] A cell introduced with the vector of [41].
[43] A method for producing the antigen-binding molecule of any one of [29] to [39], which comprises the step of collecting the antigen-binding molecule from a culture of the cell of [42].
[44] A pharmaceutical composition which comprises as an active ingredient the antigen-binding molecule of any one of [29] to [39] or an antigen-binding molecule obtained by the production method of [43].

Furthermore, the present ~~invention~~disclosure relates to kits for use in the methods of the present ~~invention~~disclosure, which comprise an antigen-binding molecule of the present ~~invention~~disclosure or an antigen-binding molecule produced by a production method of the present ~~invention~~disclosure. The present ~~invention~~disclosure also relates to agents for improving the pharmacokinetics of an antigen-binding molecule and agents for impairing the immunogenicity of an antigen-binding molecule, which comprise as an active ingredient an antigen-binding molecule of the present ~~invention~~disclosure or an antigen-binding molecule produced by a production method of the present ~~invention~~disclosure. The present ~~invention~~disclosure also relates to methods for treating immune/inflammatory diseases, which comprise the step of administering to a subject an antigen-binding molecule of the present ~~invention~~disclosure or an antigen-binding molecule produced by a production method of the present ~~invention~~disclosure. In addition, the present ~~invention~~disclosure relates to the use of antigen-binding molecules of the present ~~invention~~disclosure or antigen-binding molecules produced by a production method of the present ~~invention~~disclosure in producing agents for improving the pharmacokinetics of antigen-binding molecules and agents for impairing the immunogenicity of antigen-binding molecules. The present ~~invention~~disclosure also relates to antigen-binding molecules of the present ~~invention~~disclosure or antigen-binding molecules produced by a production method of the present ~~invention~~disclosure for use in the methods of the present ~~invention~~disclosure.

[Effects of the Invention]

The present ~~invention~~disclosure provides methods for improving pharmacokinetics of antigen-binding molecules and methods for impairing the immunogenicity of antigen-binding molecules. The present ~~invention~~disclosure enables antibody therapy without causing unfavorable *in vivo* effects as compared to general antibodies.

Brief Description of the Drawings

Fig. 1 is a diagram showing effects on a soluble antigen of an existing neutralizing antibody and an antibody that binds to an antigen in a pH-dependent manner and exhibits augmented FcRn binding under a neutral condition.

Fig. 2 is a graph showing a plasma concentration time course after intravenous or subcutaneous administration of Fv4-IgG1 or Fv4-IgG1-F1 to normal mice.

Fig. 3 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to human FcγRIa.

Fig. 4 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to human FcγRIIa(R).

Fig. 5 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to human FcγRIIa(H).

Fig. 6 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to human FcγRIIb.

Fig. 7 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to human FcγRIIIa(F).

Fig. 8 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to mouse FcγRI.

Fig. 9 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to mouse FcγRIIb.

Fig. 10 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to mouse FcγRIII.

Fig. 11 is a graph demonstrating that in a human FcRn-bound state, Fv4-IgG1-F157 binds to mouse FcγRIV.

Fig. 12 is a graph demonstrating that in a mouse FcRn-bound state, Fv4-IgG1-F20 binds to mouse FcγRI, mouse FcγRIIb, mouse FcγRIII, and mouse FcγRIV.

Fig. 13 is a graph demonstrating that in a mouse FcRn-bound state, mPM1-mIgG1-mF3 binds to mouse FcγRIIb and mouse FcγRIII.

Fig. 14 is a graph showing a plasma concentration time course of Fv4-IgG1-F21, Fv4-IgG1-F140, Fv4-IgG1-F157, and Fv4-IgG1-F424 in human FcRn transgenic mice.

Fig. 15 is a graph showing a plasma concentration time course of Fv4-IgG1 and