(c) the amino acid at position 264 of the Fc region according to EU numbering;

(d) the amino acid at position 267 of the Fc region according to EU numbering; and

(e) the amino acid at position 268 of the Fc region according to EU numbering;

[14] the variant of [13] above, wherein the amino acid alteration is a combination of amino acid alterations of any one of (1) to (4) below:

(1) amino acids at positions 237, 238, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering;

(2) amino acids at positions 233, 237, 238, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering;

(3) amino acids at positions 238, 267, 268, 271, 327, 330, and 331 of the Fc region according to EU numbering; and

(4) amino acids at positions 238, 264, 267, 271, 327, 330, and 331 of the Fc region according to EU numbering;

[15] an Fc region variant, wherein the amino acid at position 238 is Asp, the amino acid at position 271 is Gly, the amino acid at position 327 is Gly, the amino acid at position 330 is Ser, and the amino acid at position 331 is Ser in the Fc region according to EU numbering, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region;

[16] the variant of [15] above, wherein the variant further comprises any one of the amino acids of (a) to (~~h~~e) below:

(a) Asp at amino acid position 233 of the Fc region according to EU numbering;

(b) Asp at amino acid position 237 of the Fc region according to EU numbering;

(c) Ile at amino acid position 264 of the Fc region according to EU numbering;

(d) Ala at amino acid position 267 of the Fc region according to EU numbering; and

(e) Asp or Glu at amino acid position 268 of the Fc region according to EU numbering;

[17] an Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at position 271 is Gly in the Fc region according to EU numbering, wherein the variant also comprises the amino acids of any one of (1) to (4) below:

(1) Asp at amino acid position 237, Asp at amino acid position 238, Asp or Glu at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering;

(2) Asp at amino acid position 233, Asp at amino acid position 237, Asp at amino acid position 238, Asp at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and, Ser at amino acid position 331 of the Fc region according to EU numbering;

(3) Asp at amino acid position 238, Ala at amino acid position 267, Glu at amino acid position

Fig. 1 shows the results of analysis by gel filtration chromatography which confirm the pH-dependent formation of a large immune complex by human IgE and a pH-dependent anti-IgE antibody, clone 278.

Fig. 2 shows changes in the human IgE concentration in normal mouse plasma for the group to which human IgE alone was administered, the human IgE + clone 278 antibody-administered group, and the human IgE + ~~clone 278~~Xolair antibody-administered group.

Fig. 3 shows changes in the antibody concentration in normal mouse plasma for the human IgE + clone 278-administered group and the human IgE + Xolair antibody-administered group.

Fig. 4 shows changes in the human IgE concentration in normal mouse plasma for the group to which human IgE alone was administered, the human IgE + 278-IgG1 antibody-administered group, and the human IgE + 278-F760 antibody-administered group.

Fig. 5 shows changes in the normal mouse antibody concentration for the human IgE + 278-IgG1 antibody-administered group and the human IgE + 278-F760 antibody-administered group.

Fig. 6 shows results of using the IL-8 expression level as an indicator to evaluate DC activation by an Fc variant.

Fig. 7 confirms the expression of CD62p (p-selectin) on the surface of a washed platelet membrane to which Fc variants were added. The case of 5c8-F648 addition and ADP stimulation is shown by a solid line, and the filled area shows the case of 5c8-F600 addition and ADP stimulation.

Fig. 8 confirms the expression of activated integrin (PAC-1) on the surface of a washed platelet membrane to which Fc variants were added. The case of 5c8-F648 addition and ADP stimulation is shown by a solid line, and the filled area shows the case of 5c8-F600 addition and ADP stimulation.

Fig. 9 shows how antibodies with a pH-dependent binding property bind repeatedly to soluble antigens: (i) an antibody binds to soluble antigens; (ii) the antibody is taken up non-specifically into the cell by pinocytosis; (iii) the antibody binds to FcRn in the endosome, and then the soluble antigens dissociate from the antibody; (iv) the soluble antigens translocate to the lysosome and are then degraded; (v) the antibody from which the soluble antigens have dissociated is recycled into the plasma by FcRn; and (vi) the recycled antibody can bind again to soluble antigens.

Fig. 10 shows how enhancing FcRn binding under neutral conditions further improves the effects of antibodies with a pH-dependent binding property to repeatedly bind to antigens: (i) an antibody binds to soluble antigens; (ii) the antibody is taken up into cells by pinocytosis *via* FcRn; (iii) the soluble antigens dissociate from the antibody in the endosome; (iv) the soluble

when assay is performed with substantially the same amount of a polypeptide containing the Fc region of the native IgG (also referred to as a polypeptide containing the parent Fc region or a parent polypeptide) and a polypeptide which includes amino acid alterations of the present invention in the Fc region (a polypeptide containing an Fc region variant).

Whether or not an Fc region variant of the present invention maintains the FcγRIIb-binding activity of the Fc region of a native IgG can be determined by comparing the KD value for FcγRIIb of the polypeptide comprising the Fc region variant of the present invention with the KD value for FcγRIIb of the polypeptide containing the Fc region of a native IgG, which can be determined, for example, according to the above-mentioned examples. Specifically, when the KD value for the polypeptide containing an Fc region variant of the present invention is a value equivalent to or less than that of a polypeptide containing the parent Fc region, the polypeptide containing the Fc region variant of the present invention can be determined to have maintained its FcγRIIb-binding activity in comparison to a polypeptide containing the parent Fc region ~~variant~~. Whether or not the activating FcγR-binding activity of an Fc region variant of the present invention is decreased in comparison to that of a native IgG Fc region can be determined in a similar manner, for example, by comparing the KD value for an activating FcγR of the polypeptide comprising the Fc region variant of the present invention with the KD value for the activating FcγR of the polypeptide containing the Fc region of a native IgG, as determined according to the above-mentioned examples. Specifically, when the KD value of the polypeptide comprising the Fc region variant of the present invention is enhanced compared to that of the polypeptide comprising the parent Fc region, the polypeptide comprising the Fc region variant of the present invention can be determined to have a reduced binding activity for activating FcγR in comparison to that of the polypeptide comprising the parent Fc region ~~variant~~. In particular, since the FcγRIIa (R type)-binding activity is more easily correlated with the FcγRIIb-binding activity than with binding activities for other activating FcγRs, finding amino acid alterations that can decrease the FcγRIIa (R type)-binding activity while maintaining the FcγRIIb-binding activity is the most difficult task in selectively decreasing the binding activities for activating FcγRs other than FcγRIIb.

An equivalent or maintained FcγRIIb-binding activity means that, for example, in the KD values determined by the measurement method described above, the KD ratio of [KD value for FcγRIIb of the polypeptide comprising the parent Fc region] / [KD value for FcγRIIb of the polypeptide comprising the Fc region variant] is preferably at least 0.75, more preferably at least 0.8, even more preferably at least 0.9. Furthermore, a value of about 5 is sufficient for the KD ratio, and a higher value is not necessary for determining that the FcγRIIb-binding activity is equivalent or maintained.

Decrease, reduction or attenuation of binding activities for activating FcγRs means that,

EU numbering; and
(4) amino acids at positions 238, 264, 267, 271, 327, 330, and 331 of the Fc region according to EU numbering.

15. An Fc region variant, wherein the amino acid at position 238 is Asp, the amino acid at position 271 is Gly, the amino acid at position 327 is Gly, the amino acid at position 330 is Ser, and the amino acid at position 331 is Ser in the Fc region according to EU numbering, wherein an FcγRIIb-binding activity of the variant is maintained and binding activities of the variant to all activating FcγRs are decreased when compared to those of a native IgG Fc region.

16. The variant of claim 15, wherein the variant further comprises any one of the amino acids of (a) to (~~h~~e) below:
(a) Asp at amino acid position 233 of the Fc region according to EU numbering;
(b) Asp at amino acid position 237 of the Fc region according to EU numbering;
(c) Ile at amino acid position 264 of the Fc region according to EU numbering;
(d) Ala at amino acid position 267 of the Fc region according to EU numbering; and
(e) Asp or Glu at amino acid position 268 of the Fc region according to EU numbering.

17. An Fc region variant, wherein the amino acid at position 238 is Asp and the amino acid at position 271 is Gly in the Fc region according to EU numbering, wherein the variant also comprises the amino acids of any one of (1) to (4) below:
(1) Asp at amino acid position 237, Asp at amino acid position 238, Asp or Glu at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering;
(2) Asp at amino acid position 233, Asp at amino acid position 237, Asp at amino acid position 238, Asp at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and, Ser at amino acid position 331 of the Fc region according to EU numbering;
(3) Asp at amino acid position 238, Ala at amino acid position 267, Glu at amino acid position 268, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering; and
(4) Asp at amino acid position 238, Ile at amino acid position 264, Ala at amino acid position 267, Gly at amino acid position 271, Gly at amino acid position 327, Ser at amino acid position 330, and Ser at amino acid position 331 of the Fc region according to EU numbering.

18. The Fc region variant of any one of claims 1 to 17, wherein the variant has an FcγRIIb-