CLAIMS

1. A polypeptide comprising an antibody Fc region, wherein the Fc region comprises an amino acid modification at position 235 and 239 (EU numbering), and wherein the polypeptide has improved stability and decreased FcγR-binding activity as compared to those of a parent polypeptide.

2. The polypeptide of claim 1, wherein the amino acid modification at position 235 (EU numbering) is a substitution with Lys or Arg and the amino acid modification at position 239 (EU numbering) is a substitution with Met, Lys, Arg, Thr, His or Gln.

3. The polypeptide of claim 1 or 2, wherein the amino acid modification at position 235 (EU numbering) is a substitution with Arg and the amino acid modification at position 239 (EU numbering) is a substitution with Lys.

4. The polypeptide of any one of claims 1 to 3, wherein the stability is assessed or determined using melting temperature (Tm) as an index.

5. The polypeptide of any one of claims 1 to 4, wherein the Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 236 (EU numbering), position 237 (EU numbering), position 238 (EU numbering), position 247 (EU numbering), position 250 (EU numbering), position 265 (EU numbering), position 266 (EU numbering), position 267 (EU numbering), position 268 (EU numbering), position 269 (EU numbering), position 270 (EU numbering), position 271 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), position 300 (EU numbering), position 307 (EU numbering), position 309 (EU numbering), position 315 (EU numbering), position 324 (EU numbering), position 325 (EU numbering), position 326 (EU numbering), position 327 (EU numbering), position 329 (EU numbering), position 330 (EU numbering), position 333 (EU numbering), position 335 (EU numbering), position 337 (EU numbering), position 360 (EU numbering), position 385 (EU numbering), position 386 (EU numbering), position 387 (EU numbering), position 389 (EU numbering), position 428 (EU numbering), and position 433 (EU numbering).

6. The polypeptide of any one of claims 1 to 4, wherein the Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 266 (EU numbering), position 267 (EU numbering),

position 268 (EU numbering), position 269 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), position 300 (EU numbering), position 324 (EU numbering), position 325 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering).

7. The polypeptide of any one of claims 1 to 4, wherein the Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 267 (EU numbering), position 268 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

8. The polypeptide of any one of claims 5 to 7, wherein the amino acid modification(s) further comprised in the Fc region is one or more amino acid modification(s) selected from the group consisting of:
substitution of the amino acid at position 234 (EU numbering) with Lys or Arg;
substitution of the amino acid at position 267 (EU numbering) with Pro;
substitution of the amino acid at position 268 (EU numbering) with Met or Lys;
substitution of the amino acid at position 270 (EU numbering) with Phe;
substitution of the amino acid at position 295 (EU numbering) with Met;
substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with Gly, His or Met.

9. The polypeptide of any one of claims 1 to 4, wherein the Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 268 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

10. The polypeptide of claim 5 or 9, wherein the amino acid modification(s) further comprised in the Fc region is one or more amino acid modification(s) selected from the group consisting of:
substitution of the amino acid at position 234 (EU numbering) with Lys;
substitution of the amino acid at position 268 (EU numbering) with Lys or His;
substitution of the amino acid at position 270 (EU numbering) with Phe or Asp;
substitution of the amino acid at position 295 (EU numbering) with Met;

substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with His or Gly.

11. The polypeptide of claim 5, 9 or 10, wherein the amino acid modification(s) further comprised in the Fc region is one or more amino acid modification(s) selected from the group consisting of:
substitution of the amino acid at position 234 (EU numbering) with Lys;
substitution of the amino acid at position 268 (EU numbering) with Lys;
substitution of the amino acid at position 270 (EU numbering) with Phe;
substitution of the amino acid at position 295 (EU numbering) with Met;
substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with His or Gly.

12. The polypeptide of any one of claims 1 to 4, wherein the Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

13. The polypeptide of claim 5 or 12, wherein the amino acid modification(s) further comprised in the Fc region is one or more amino acid modification(s) selected from the group consisting of:
substitution of the amino acid at position 234 (EU numbering) with Lys;
substitution of the amino acid at position 295 (EU numbering) with Met;
substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with His or Gly.

14. A method for improving stability and decreasing FcγR-binding activity of a polypeptide comprising an antibody Fc region as compared to those of a parent polypeptide by introducing at least two amino acid modification comprising at position 235 and 239 (EU numbering) of the Fc region.

15. The method of claim 14, wherein the stability is assessed or determined using melting temperature (Tm) as an index.

16. A method of producing a polypeptide comprising an antibody Fc region, which has at least two amino acid modification in the Fc region, and has improved stability and decreased FcγR-binding activity as compared to those of a parent polypeptide, wherein the method comprises the steps of:
(a) introducing at least two amino acid modification to a polypeptide comprising an antibody Fc region comprising at position 235 and 239 (EU numbering) of the Fc region;
(b) determining the stability and FcγR-binding activity of the polypeptide modified in step (a); and
(c) selecting a polypeptide with improved stability and decreased FcγR-binding activity as compared to those of the parent polypeptide.

17. A method of producing a polypeptide comprising an antibody Fc region, which has at least two amino acid modification in the Fc region, and has improved stability and decreased FcγR-binding activity as compared to those of a parent polypeptide, wherein the method comprises the steps of:
(a) modifying a nucleic acid so as to encode a polypeptide comprising at least two amino acid modification at position 235 and 239 (EU numbering) of the Fc region of the parent polypeptide;
(b) introducing the modified nucleic acid into a host cell and culturing the cell to induce expression of the nucleic acid; and
(c) collecting the polypeptide from the host cell culture.

18. The method of any one of claims 14 to 17, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 236 (EU numbering), position 237 (EU numbering), position 238 (EU numbering), position 247 (EU numbering), position 250 (EU numbering), position 265 (EU numbering), position 266 (EU numbering), position 267 (EU numbering), position 268 (EU numbering), position 269 (EU numbering), position 270 (EU numbering), position 271 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), position 300 (EU numbering), position 307 (EU numbering), position 309 (EU numbering), position 315 (EU numbering), position 324 (EU numbering), position 325 (EU numbering), position 326 (EU numbering), position 327 (EU numbering), position 329 (EU numbering), position 330 (EU numbering), position 333 (EU numbering), position 335 (EU numbering), position 337 (EU numbering), position 360 (EU numbering), position 385 (EU numbering), position 386 (EU numbering), position 387 (EU numbering), position 389 (EU numbering), position 428 (EU numbering), and position 433 (EU numbering) of the Fc region.

19. The method of any one of claims 14 to 17, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 266 (EU numbering), position 267 (EU numbering), position 268 (EU numbering), position 269 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), position 300 (EU numbering), position 324 (EU numbering), position 325 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering) of the Fc region.

20. The method of any one of claims 14 to 17, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 267 (EU numbering), position 268 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering) of the Fc region.

21. The method of any one of claims 18 to 20, wherein the amino acid modification(s) further introduced in the Fc region is one or more amino acid modification(s) selected from the group consisting of:
substitution of the amino acid at position 234 (EU numbering) with Lys or Arg;
substitution of the amino acid at position 267 (EU numbering) with Pro;
substitution of the amino acid at position 268 (EU numbering) with Met or Lys;
substitution of the amino acid at position 270 (EU numbering) with Phe;
substitution of the amino acid at position 295 (EU numbering) with Met;
substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with Gly, His or Met.

22. The method of any one of claims 14 to 17, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 268 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering) of the Fc region.

23. The method of any one of claims 18 or 22, wherein the amino acid modification(s) further introduced in the Fc region is one or more amino acid modification(s) selected from the group consisting of:

substitution of the amino acid at position 234 (EU numbering) with Lys;
substitution of the amino acid at position 268 (EU numbering) with Lys or His;
substitution of the amino acid at position 270 (EU numbering) with Phe or Asp;
substitution of the amino acid at position 295 (EU numbering) with Met;
substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with His or Gly.

24. The method of any one of claims 18, 22 and 23, wherein the amino acid modification(s) further introduced in the Fc region is one or more amino acid modification(s) selected from the group consisting of:
substitution of the amino acid at position 234 (EU numbering) with Lys;
substitution of the amino acid at position 268 (EU numbering) with Lys;
substitution of the amino acid at position 270 (EU numbering) with Phe;
substitution of the amino acid at position 295 (EU numbering) with Met;
substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with His or Gly.

25. The method of any one of claims 14 to 17, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering) of the Fc region.

26. The method of claim 18 or 25, wherein the amino acid modification(s) further introduced in the Fc region is one or more amino acid modification(s) selected from the group consisting of:
substitution of the amino acid at position 234 (EU numbering) with Lys;
substitution of the amino acid at position 295 (EU numbering) with Met;
substitution of the amino acid at position 296 (EU numbering) with Gly;
substitution of the amino acid at position 298 (EU numbering) with Gly; and
substitution of the amino acid at position 325 (EU numbering) with His or Gly.

27. The method of any one of claims 14 to 26, wherein the amino acid modification is modification in a polypeptide comprising an Fc region of human IgG.

28. A nucleic acid encoding a polypeptide comprising an antibody Fc region, which comprises an amino acid modification at position 235 and 239 (EU numbering), and has improved stability and decreased FcγR-binding activity as compared to those of a parent polypeptide.

29. A vector comprising the nucleic acid of claim 28.

30. A host cell transformed with the vector of claim 29.

31. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 13, or a polypeptide produced by the method of any one of claims 14 to 27.

32. An agent for treating or preventing an immune-inflammatory disease or cancer, which comprises the pharmaceutical composition of claim 31.

33. The agent of claim 32, wherein the immune-inflammatory disease is rheumatoid arthritis, autoimmune hepatitis, autoimmune thyroiditis, autoimmune bullous dermatosis, autoimmune adrenocortical inflammation, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, megalocytic anemia, autoimmune atrophic gastritis, autoimmune neutropenia, autoimmune orchitis, autoimmune encephalomyelitis, autoimmune receptor disease, autoimmune infertility, chronic active hepatitis, glomerulonephritis, interstitial pulmonary fibrosis, multiple sclerosis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute and chronic spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, Basedow's disease, juvenile diabetes, Addison's disease, myasthenia gravis, lenticular uveitis, systemic lupus erythematosus, allergic rhinitis, allergic dermatitis, ulcerative colitis, hypersensitivity, asthma, myodegeneration, cachexia, systemic scleroderma, localized scleroderma, Sjogren's syndrome, Behcet's disease, Reiter's syndrome, type I and type II diabetes, bone resorption disease, graft versus host reaction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, malgias due to staining, aplastic anemia, hemolytic anemia, sudden thrombocytopenia, Goodpasture's syndrome, Guillain-Barre syndrome, Hashimoto's disease, pemphigus, IgA nephropathy, pollinosis, antiphospholipid antibody syndrome, polymyositis, Wegener's sarcoma, arteritis nodosa, mixed connective tissue disease, or fibromyalgia.

34. The agent of claim 32, wherein the cancer is pancreatic cancer, prostate cancer, breast cancer, skin cancer, gastrointestinal cancer, lung cancer, hepatoma, cervical cancer, endometrial

cancer, ovarian cancer, fallopian tube cancer, vaginal cancer, liver cancer, cholangioma, bladder cancer, ureteral cancer, thyroid cancer, adrenal carcinoma, renal cancer, other glandular tissue cancers, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, angiosarcoma, fibrosarcoma, malignant peripheral nerve tumor, gastrointestinal stromal tumor, desmoid tumor, Ewing's sarcoma, osteosarcoma, chondrosarcoma, leukemia, lymphoma, myeloma, or other solid organ tumors.