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Summary

[Problems to be Solved by the Present Disclosure]

The present disclosure was achieved in view of the above circumstances. An objective of the present disclosure is to provide polypeptides whose stability has been improved by modifying amino acids in the antibody Fc region.

In one aspect, there is provided a polypeptide comprising a~~n~~ modified antibody Fc region, wherein the modified Fc region comprises an amino acid modification at position 234 (EU numbering) ~~at least one amino acid has been modified in a loop region of the Fc region~~, and wherein the polypeptide has improved thermal stability measured by melting temperature (Tm) as compared to that of a parent polypeptide.

In another aspect, there is provided a method for improving thermal stability measured by melting temperature (Tm) of a polypeptide comprising a~~n~~ modified antibody Fc region as compared to that of a parent polypeptide by introducing ~~at least one~~an amino acid modification at position 234 (EU numbering)~~to a loop region of the Fc region~~.

In another ~~aspect~~embodiment, there is provided a method for producing a polypeptide comprising an antibody Fc region, which has at least one amino acid modification in a loop region of the Fc region, and has improved stability as compared to that of a parent polypeptide, wherein the method comprises the steps of: (a) introducing at least one amino acid modification to a polypeptide comprising an antibody Fc region at a loop region of the Fc region; (b) determining the stability of the polypeptide modified in step (a); and (c) selecting a polypeptide with improved stability as compared to that of the parent polypeptide.

In another ~~aspect~~embodiment, there is provided a method for producing a polypeptide comprising an antibody Fc region, which has at least one amino acid modification in a loop region of the Fc region, and has improved stability as compared to that of a parent polypeptide, wherein the method comprises the steps of: (a) modifying a nucleic acid encoding the polypeptide so as to improve its stability as compared to that 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.

In another aspect, there is provided a nucleic acid encoding a polypeptide comprising an antibody Fc region, which comprises an amino acid modification at position 234 (EU numbering)~~has at least one amino acid modification in a loop region of the Fc region~~, and has improved stability as compared to that of a parent polypeptide.

In another aspect, there is provided a vector comprising the nucleic acid as defined above.

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

CLAIMS

1. A polypeptide comprising an antibody Fc region, wherein at least one amino acid has been modified in a loop region of the Fc region, and the polypeptide has improved stability as compared to that of a parent polypeptide.

2. The polypeptide of claim 1, wherein the stability is assessed or determined using melting temperature (Tm) as an index.

3. The polypeptide of claim 1 or 2, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 236 (EU numbering), position 237 (EU numbering), position 238 (EU numbering), position 239 (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).

4. The polypeptide of any one of claims 1 to 3, which further has FcγR-binding activity that is maintained or enhanced as compared to that of a parent polypeptide.

5. The polypeptide of any one of claims 1 to 3, which further has FcγR-binding activity that is decreased as compared to that of a parent polypeptide.

6. The polypeptide of any one of claims 1 to 5, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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 and 6, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 266 (EU numbering), position 268 (EU numbering), position 269 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 300 (EU numbering), position 324 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering).

8. The polypeptide of any one of claims 1 to 4, 6, and 7, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 234 (EU numbering) with Ile, substitution of the amino acid at position 266 (EU numbering) with Ile, substitution of the amino acid at position 268 (EU numbering) with Gln, substitution of the amino acid at position 269 (EU numbering) with Asp, substitution of the amino acid at position 270 (EU numbering) with Glu, substitution of the amino acid at position 295 (EU numbering) with Met or Leu, substitution of the amino acid at position 300 (EU numbering) with Glu, substitution of the amino acid at position 324 (EU numbering) with His, substitution of the amino acid at position 326 (EU numbering) with Ser or Ala, and substitution of the amino acid at position 330 (EU numbering) with His or Tyr.

9. The polypeptide of any one of claims 1 to 3, 5 and 6, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid positions selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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).

10. The polypeptide of any one of claims 1 to 3, 5, 6, and 9, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, substitution of the amino acid at position 239 (EU numbering) with Lys, 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.

11. The polypeptide of any one of claims 1 to 4, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 295 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering).

12. The polypeptide of any one of claims 1 to 4 and 11, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 295 (EU numbering) with Met or Leu, substitution of the amino acid at position 326 (EU numbering) with Ser or Ala, and substitution of the amino acid at position 330 (EU numbering) with His or Tyr.

13. The polypeptide of any one of claims 1 to 3 and 5, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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).

14. The polypeptide of any one of claims 1 to 3, 5, and 13, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, substitution of the amino acid at position 239 (EU numbering) with Lys or Ser, 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.

15. The polypeptide of any one of claims 1 to 3 and 5, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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).

16. The polypeptide of any one of claims 1 to 3, 5, and 15, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, substitution of the amino acid at position 239 (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.

17. The polypeptide of any one of claims 1 to 3 and 5, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

18. The polypeptide of any one of claims 1 to 3, 5, and 17, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications 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 235 (EU numbering) with Lys and Arg, substitution of the amino acid at position 239 (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.

19. The polypeptide of any one of claims 1 to 3 and 5, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s)

selected from the group consisting of position 234 (EU numbering), position 235 (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).

20. The polypeptide of any one of claims 1 to 3, 5, and 19, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, 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.

21. The polypeptide of any one of claims 1 to 3 and 5, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

22. The polypeptide of any one of claims 1 to 3, 5, and 21, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, 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.

23. The polypeptide of any one of claims 1 to 4, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 247 (EU numbering), position 250 (EU numbering), position 307 (EU numbering), position 309 (EU numbering), position 315 (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).

24. The polypeptide of any one of claims 1 to 4, and 23, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 247 (EU numbering) with Val, substitution of the amino acid at position 250 (EU numbering) with Phe, Ile, Met, Val, Trp, or Tyr, substitution of the amino acid at position 307 (EU numbering) with Ala, Gln, or Pro, substitution of the amino acid at position 309 (EU numbering) with Ala, Arg, or Pro, substitution of the amino acid at position 315 (EU numbering) with Ala, substitution of the amino acid at position 360 (EU numbering) with His, substitution of the amino acid at position 385 (EU numbering) with Asp, substitution of the amino acid at position 386 (EU numbering) with Pro, substitution of the amino acid at position 387 (EU numbering) with Glu, substitution of the amino acid at position 389 (EU numbering) with Ser, substitution of the amino acid at position 428 (EU numbering) with His, Trp, Tyr, or Phe, and substitution of the amino acid at position 433 (EU numbering) with Lys.

25. The polypeptide of any one of claims 1 to 3 and 5, wherein at least one or more amino acid mutations have been introduced into the loop region of the Fc region at amino acid position 298 (EU numbering) or position 309 (EU numbering).

26. The polypeptide of any one of claims 1 to 3, 5, and 25, wherein the amino acid modifications in the loop region of the Fc region are at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 298 (EU numbering) with Gly and substitution of the amino acid at position 309 (EU numbering) with Asp.

27. A method for improving stability of a polypeptide comprising an antibody Fc region as compared to that of a parent polypeptide by introducing at least one amino acid modification to a loop region of the Fc region.

28. The method of claim 27, wherein the stability is assessed or determined using melting temperature (Tm) as an index.

29. A method for producing a polypeptide comprising an antibody Fc region, which has at least one amino acid modification in a loop region of the Fc region, and has improved stability as compared to that of a parent polypeptide, wherein the method comprises the steps of:
(a) introducing at least one amino acid modification to a polypeptide comprising an antibody Fc region at a loop region of the Fc region;
(b) determining the stability of the polypeptide modified in step (a); and
(c) selecting a polypeptide with improved stability as compared to that of the parent polypeptide.

30. A method for producing a polypeptide comprising an antibody Fc region, which has at least one amino acid modification in a loop region of the Fc region, and has improved stability as compared to that of a parent polypeptide, wherein the method comprises the steps of:
(a) modifying a nucleic acid encoding the polypeptide so as to improve its stability as compared to that 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.

31. The method of any one of claims 27 to 30, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 236 (EU numbering), position 237 (EU numbering), position 238 (EU numbering), position 239 (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).

32. The method of any one of claims 27 to 31, which further comprises the step of introducing a modification to maintain or enhance FcγR-binding activity as compared to that of the parent polypeptide.

33. The method of any one of claims 27 to 31, which further comprises the step of introducing a modification to reduce FcγR-binding activity as compared to that of the parent polypeptide.

34. The method of any one of claims 27 to 33, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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).

35. The method of any one of claims 27 to 32 and 34, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 266 (EU numbering), position 268 (EU numbering), position 269 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 300 (EU numbering), position 324 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering).

36. The method of any one of claims 27 to 32, 34, and 35, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 234 (EU numbering) with Ile, substitution of the amino acid at position 266 (EU numbering) with Ile, substitution of the amino acid at position 268 (EU numbering) with Gln, substitution of the amino acid at position 269 (EU numbering) with Asp, substitution of the amino acid at position 270 (EU numbering) with Glu, substitution of the amino acid at position 295 (EU numbering) with Met or Leu, substitution of the amino acid at position 300 (EU numbering) with Glu, substitution of the amino acid at position 324 (EU numbering) with His, substitution of the amino acid at position 326 (EU numbering) with Ser or Ala, and substitution of the amino acid at position 330 (EU numbering) with His or Tyr.

37. The method of any one of claims 27 to 31, 33, and 34, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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).

38. The method of any one of claims 27 to 31, 33, 34, and 37, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, substitution of the amino acid at position 239 (EU numbering) with Lys, 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.

39. The method of any one of claims 27 to 32, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 295 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering).

40. The method of any one of claims 27 to 32 and 39, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 295 (EU numbering) with Met or Leu, substitution of the amino acid at position 326 (EU numbering) with Ser or Ala, and substitution of the amino acid at position 330 (EU numbering) with His or Tyr.

41. The method of any one of claims 27 to 31 and 33, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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).

42. The method of any one of claims 27 to 31, 33, and 41, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, substitution of the amino acid at position 239 (EU numbering) with Lys or Ser, 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.

43. The method of any one of claims 27 to 31 and 33, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (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).

44. The method of any one of claims 27 to 31, 33, and 43, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, substitution of the amino acid at position 239 (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.

45. The method of any one of claims 27 to 31 and 33, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 239 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

46. The method of any one of claims 27 to 31, 33, and 45, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, substitution of

the amino acid at position 239 (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.

47. The method of any one of claims 27 to 31 and 33, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (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).

48. The method of any one of claims 27 to 31, 33, and 47, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, 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.

49. The method of any one of claims 27 to 31 and 33, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 234 (EU numbering), position 235 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

50. The method of any one of claims 27 to 31, 33, and 49, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications 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 235 (EU numbering) with Lys or Arg, 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.

51. The method of any one of claims 27 to 32, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position(s) selected from the group consisting of position 247 (EU numbering), position 250 (EU numbering), position 307 (EU numbering), position 309 (EU numbering), position 315 (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).

52. The method of any one of claims 27 to 32 and 51, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 247 (EU numbering) with Val, substitution of the amino acid at position 250 (EU numbering) with Phe, Ile, Met, Val, Trp, or Tyr, substitution of the amino acid at position 307 with Ala, Gln, or Pro, substitution of the amino acid at position 309 with Ala, Arg, or Pro, substitution of the amino acid at position 315 with Ala, substitution of the amino acid at position 360 with His, substitution of the amino acid at position 385 with Asp, substitution of the amino acid at position 386 with Pro, substitution of the amino acid at position 387 with Glu, substitution of the amino acid at position 389 with Ser, substitution of the amino acid at position 428 with His, Trp, Tyr, or Phe, and substitution of the amino acid at position 433 with Lys.

53. The method of any one of claims 27 to 31 and 33, wherein at least one or more amino acid mutations are introduced into the loop region of the Fc region at amino acid position 298 (EU numbering) or position 309 (EU numbering).

54. The method of any one of claims 27 to 31, 33, and 53, wherein the amino acid modification in the loop region of the Fc region is at least one or more amino acid modifications selected from the group consisting of substitution of the amino acid at position 298 with Gly and substitution of the amino acid at position 309 with Asp.

55. The method of any one of claims 27 to 54, wherein the modification is modification in a polypeptide comprising an Fc region of human IgG.

56. A nucleic acid encoding a polypeptide comprising an antibody Fc region, which has at least one amino acid modification in a loop region of the Fc region, and has improved stability as compared to that of a parent polypeptide.

57. A vector comprising the nucleic acid of claim 56.

58. A host cell transformed with the vector of claim 57.

59. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 26, or a polypeptide produced by the method of any one of claims 27 to 55.

60. An agent for treating or preventing an immune-inflammatory disease or cancer, which comprises the pharmaceutical composition of claim 59.

61. The agent of claim 60, 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.

62. The agent of claim 60, 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.

63. Use of the pharmaceutical composition of claim 59 in the preparation of an agent for treating or preventing an immune-inflammatory disease or cancer.

CLAIMS

1. A polypeptide comprising a modified antibody Fc region, wherein the modified antibody Fc region comprises an amino acid modification at position 234 (EU numbering), and wherein the polypeptide has improved thermal stability measured by melting temperature (Tm) as compared to that of a parent polypeptide.

2. The polypeptide of claim 1, wherein the amino acid modification at position 234 (EU numbering) is a substitution with Gly, Ala, Val, Phe, Pro, Met, Ile, Lys, Arg, Ser, Thr, Tyr, His, Asn, Gln or Trp.

3. The polypeptide of claim 1 or 2, wherein the modified antibody Fc region comprises further one or more amino acid modification(s) at amino acid positions(s) selected from the group consisting of position 235 (EU numbering), position 236 (EU numbering), position 237 (EU numbering), position 238 (EU numbering), position 239 (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).

4. The polypeptide of any one of claims 1 to 3, which further has FcγR-binding activity that is maintained or enhanced as compared to that of a parent polypeptide.

5. The polypeptide of any one of claims 1 to 3, which further has FcγR-binding activity that is decreased as compared to that of a parent polypeptide.

6. The polypeptide of any one of claims 1 to 3 and 5, wherein the modified antibody Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 239 (EU numbering),

position 268 (EU numbering), position 270 (EUnumbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

7. The polypeptide of any one of claims 1 to 3 and 5, wherein the modified antibody Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting position 235 (EU numbering), position 239 (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 1 to 3 and 5, wherein the modified antibody Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (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).

9. The polypeptide of any one of claims 1 to 3 and 5, wherein the modified antibody Fc region comprises further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

10. The polypeptide of any one of claims 1 to 3 and 5, wherein the modified antibody Fc region comprises further amino acid modification at position 235 (EU numbering).

11. The polypeptide of any one of claims 3, 5 and 6, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 239 (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) is selected from the group consisting of
a) at position 235 (EU numbering) is a substitution with Lys or Arg;
b) at position 239 (EU numbering) is a substitution with Lys;
c) at position 268 (EU numbering) is a substitution with Lys or His;
d) at position 270 (EU numbering) is a substitution with Phe or Asp;
e) at position 295 (EU numbering) is a substitution with Met;
f) at position 296 (EU numbering) is a substitution with Gly;
g) at position 298 (EU numbering) is a substitution with Gly; and
h) at position 325 (EU numbering) is a substitution with Gly or His.

12. The polypeptide of any one of claims 3, 5 and 7, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 239 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering) is selected from the group consisting of

a) at position 235 (EU numbering) is a substitution with Lys or Arg;

b) at position 239 (EU numbering) is a substitution with Lys;

c) at position 295 (EU numbering) is a substitution with Met;

d) at position 296 (EU numbering) is a substitution with Gly;

e) at position 298 (EU numbering) is a substitution with Gly; and

f) at position 325 (EU numbering) is a substitution with Gly or His.

13. The polypeptide of any one of claims 3, 5 and 8, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (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) is selected from the group consisting of

a) at position 235 (EU numbering) is a substitution with Lys or Arg;

b) at position 268 (EU numbering) is a substitution with Lys;

c) at position 270 (EU numbering) is a substitution with Phe;

d) at position 295 (EU numbering) is a substitution with Met;

e) at position 296 (EU numbering) is a substitution with Gly;

f) at position 298 (EU numbering) is a substitution with Gly; and

g) at position 325 (EU numbering) is a substitution with Gly or His.

14. The polypeptide of any one of claims 3, 5 and 9, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering) is selected from the group consisting of

a) at position 235 (EU numbering) is a substitution with Lys or Arg;

b) at position 295 (EU numbering) is a substitution with Met;

c) at position 296 (EU numbering) is a substitution with Gly;

d) at position 298 (EU numbering) is a substitution with Gly; and

e) at position 325 (EU numbering) is a substitution with Gly or His.

15. The polypeptide of any one of claims 3, 5 and 10, wherein the one or more amino acid modification(s) is a substitution of the amino acid at position 235 (EU numbering) with Lys or Arg.

16. A method for improving thermal stability measured by melting temperature (Tm) of a polypeptide comprising a modified antibody Fc region as compared to that of a parent polypeptide by introducing an amino acid modification at position 234 (EU numbering).

17. The method of claim 16, wherein the amino acid modification at position 234 (EU numbering) is a substitution with Gly, Ala, Val, Phe, Pro, Met, Ile, Lys, Arg, Ser, Thr, Tyr, His, Asn, Gln or Trp.

18. The method of claim 16 or 17, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 236 (EU numbering), position 237 (EU numbering), position 238 (EU numbering), position 239 (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).

19. The method of any one of claims 16 to 18, wherein the method comprises the steps of:
(a) introducing at least one amino acid modification to a polypeptide comprising an antibody Fc region at a loop region of the Fc region;
(b) determining the stability of the polypeptide modified in step (a); and
(c) selecting a polypeptide with improved stability as compared to that of the parent polypeptide.

20. The method of any one of claims 16 to 18, wherein the method comprises the steps of:

(a) modifying a nucleic acid encoding the polypeptide so as to improve its stability as compared to that 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.

21. The method of any one of claims 16 to 20, which further comprises the step of introducing a modification to maintain or enhance FcγR-binding activity as compared to that of the parent polypeptide.

22. The method of any one of claims 16 to 20, which further comprises the step of introducing a modification to reduce FcγR-binding activity as compared to that of the parent polypeptide.

23. The method of any one of claims 16 to 22 and 22, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 239 (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).

24. The method of any one of claims 16 to 20 and 22, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 239 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

25. The method of any one of claims 16 to 20 and 22, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (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).

26. The method of any one of claims 16 to 20 and 22, comprises introducing further one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

27. The method of any one of claims 16 to 20 and 22, comprises introducing further amino acid modification at position 235 (EU numbering).

28. The method of any one of claims 16 to 20, 22 and 23, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 239 (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) is selected from the group consisting of
a) at position 235 (EU numbering) is a substitution with Lys or Arg;
b) at position 239 (EU numbering) is a substitution with Lys;
c) at position 268 (EU numbering) is a substitution with Lys or His;
d) at position 270 (EU numbering) is a substitution with Phe or Asp;
e) at position 295 (EU numbering) is a substitution with Met;
f) at position 296 (EU numbering) is a substitution with Gly;
g) at position 298 (EU numbering) is a substitution with Gly; and
h) at position 325 (EU numbering) is a substitution with His or Gly.

29. The method of any one of claims 16 to 20, 22 and 24, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 239 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering) is selected from the group consisting of
a) at position 235 (EU numbering) is a substitution with Lys or Arg;
b) at position 239 (EU numbering) is a substitution with Lys;
c) at position 295 (EU numbering) is a substitution with Met;
d) at position 296 (EU numbering) is a substitution with Gly;
e) at position 298 (EU numbering) is a substitution with Gly; and
f) at position 325 (EU numbering) is a substitution with His or Gly.

30. The method of any one of claims 16 to 20, 22 and 25, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (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) is selected from the group consisting of
a) at position 235 (EU numbering) is a substitution with Lys or Arg;
b) at position 268 (EU numbering) is a substitution with Lys;

c) at position 270 (EU numbering) is a substitution with Phe;
d) at position 295 (EU numbering) is a substitution with Met;
e) at position 296 (EU numbering) is a substitution with Gly;
f) at position 298 (EU numbering) is a substitution with Gly; and
g) at position 325 (EU numbering) is a substitution with Gly or His.

31. The method of any one of claims 16 to 20, 22 and 26, wherein the one or more amino acid modification(s) at amino acid position(s) selected from the group consisting of position 235 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering) is selected from the group consisting of
a) at position 235 (EU numbering) is a substitution with Lys or Arg;
b) at position 295 (EU numbering) is a substitution with Met;
c) at position 296 (EU numbering) is a substitution with Gly;
d) at position 298 (EU numbering) is a substitution with Gly; and
e) at position 325 (EU numbering) is a substitution with Gly or His.

32. The method of any one of claims 16 to 20, 22 and 27, wherein the one or more amino acid modification(s) is a substitution of the amino acid at position 235 (EU numbering) with Lys or Arg.

33. The method of any one of claims 16 to 32, wherein the amino acid modification is modification in a polypeptide comprising an Fc region of human IgG.

34. A nucleic acid encoding a polypeptide comprising a modified antibody Fc region, which comprises an amino acid modification at position 234 (EU numbering) and has improved stability as compared to that of a parent polypeptide.

35. A vector comprising the nucleic acid of claim 34.

36. A host cell transformed with the vector of claim 35.

37. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 2615, or a polypeptide produced by the method of any one of claims 16 to 33.

38. An agent for treating or preventing an immune-inflammatory disease or cancer, which comprises the pharmaceutical composition of claim 37.

39. The agent of claim 38, 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.

40. The agent of claim 38, 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.

41. Use of the pharmaceutical composition of claim 37 in the preparation of an agent for treating or preventing an immune-inflammatory disease or cancer.