DESCRIPTION

MODIFIED Fc REGION OF ANTIBODY

Technical Field

The present invention provides antibody Fc regions in which the amino acid sequence of a naturally-occurring antibody Fc region has been modified, antibodies containing such an Fc region, pharmaceutical compositions containing such an antibody, and methods for producing them.

Background Art

Antibodies are drawing attention as pharmaceuticals as they are highly stable in plasma and have few side effects. In particular, a number of IgG-type antibody pharmaceuticals are available on the market and many antibody pharmaceuticals are currently under development (Non-patent Documents 1 and 2).

Recently, active research has been conducted on enhancing antibody functions by introducing artificial amino acid modification into antibody Fc regions. Specifically, Fc regions with improved pharmacokinetics, Fc regions with enhanced ADCC activity, which is an effector function, and Fc regions with reduced ADCC activity in neutralizing antibodies have been studied (Non-Patent Documents 3-6). However, such Fc region modifications are known to cause adverse effects on physical properties of antibodies. For example, a modified Fc region with enhanced ADCC activity has been reported to show a decrease in melting temperature by approximately 20°C (Non-Patent Document 6). Furthermore, there are reports that modified Fc regions with reduced ADCC activity show a decrease in melting temperature by approximately 5°C, readily undergo digestion by hydrolases, and readily degrade under acidic conditions (Non-Patent Documents 7-9). Furthermore, modified Fc regions with improved retention in blood have been reported to show reduced thermal stability and storage stability (Patent Document 1).

Thus, in most of the modified Fc regions discovered so far, the enhancement of their functions has resulted in loss of their excellent stability, which is one of the advantages of antibodies.

As an effort to improve stability, there is a report of a technique for amino acid modification in the CH2 domain to introduce cysteines (Non-Patent Document 10). It has been reported that formation of new disulfide bonds by introduction of cysteines increases the thermal stability by approximately 10°C to 20°C. In this report, however, only the CH2 domain was evaluated for thermal stability; therefore, the thermal stability of the IgG form is unknown.

Furthermore, the formation of additional disulfide bonds is expected to cause an increase in heterogeneity.

As described above, there has so far been no report on an Fc region that is excellent in both activity and stability.

Prior art documents related to the present invention are shown below:

Prior Art Documents

[Patent Documents]

[Patent Document 1] WO2007/092772

[Patent Document 2] WO2010/085682

[Non-patent Documents]

[Non-patent Document 1] Monoclonal antibody successes in the clinic, Janice M Reichert, Clark J Rosensweig, Laura B Faden & Matthew C Dewitz, Nature Biotechnology 23, 1073-1078 (2005)

[Non-patent Document 2] Pavlou AK, Belsey MJ., The therapeutic antibodies market to 2008., Eur J Pharm Biopharm. 2005 Apr;59(3):389-96.

[Non-patent Document 3] Hinton PR, Xiong JM, Johlfs MG, Tang MT, Keller S, Tsurushita N., An engineered human IgG1 antibody with longer serum half-life., J Immunol. 2006 Jan 1;176(1):346-56

[Non-patent Document 4] Ghetie V, Popov S, Borvak J, Radu C, Matesoi D, Medesan C, Ober RJ, Ward ES., Increasing the serum persistence of an IgG fragment by random mutagenesis., Nat Biotechnol. 1997 Jul;15(7):637-40

[Non-patent Document 5] Oganesyan V, Damschroder MM, Leach W, Wu H, Dall'Acqua WF., Structural characterization of a mutated, ADCC-enhanced human Fc fragment., Mol Immunol. 2008 Apr;45(7):1872-82

[Non-patent Document 6] Oganesyan V, Gao C, Shirinian L, Wu H, Dall'Acqua WF., Structural characterization of a human Fc fragment engineered for lack of effector functions., Biol Crystallogr. 2008 Jun;64(Pt 6):700-4

[Non-patent Document 7] Liu H, Bulseco GG, Sun J., Effect of posttranslational modifications on the thermal stability of a recombinant monoclonal antibody., Immunol Lett. 2006 Aug;106(2):144-53

[Non-patent Document 8] Gaza-Bulseco G, Liu H., Fragmentation of a recombinant monoclonal antibody at various pH., Pharm Res. 2008 Aug;25(8):1881-90

[Non-patent Document 9] Raju TS, Scallon BJ., Glycosylation in the Fc domain of IgG increases resistance to proteolytic cleavage by papain., Biochem Biophys Res Commun. 2006 Mar;341(3):797-803

[Non-patent Document 10] Gong R, Vu BK, Feng Y, Prieto DA, Dyba MA, Walsh JD,

Prabakaran P, Veenstra TD, Tarasov SG, Ishima R, Dimitrov DS., Engineered human antibody constant domains with increased stability., J Biol Chem. 2009 Mar;284(21):14203-14210
[Non-patent Document 11] Remmele RL Jr, Callahan WJ, Krishnan S, Zhou L, Bondarenko PV, Nichols AC, Kleemann GR, Pipes GD, Park S, Fodor S, Kras E, Brems DN., Active dimer of Epratuzumab provides insight into the complex nature of an antibody aggregate., J Pharm Sci. 2006 Jan;95(1):126-45.
[Non-patent Document 12] Rosenberg AS, Effects of Protein Aggregates: An Immunologic Perspective., AAPS J. 2006 Aug; 8(3);E501-E507

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 modified antibody Fc region, wherein the modified Fc region comprises an amino acid substitution at position 234 (EU numbering) with Ile, 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 modified antibody Fc region as compared to that of a parent polypeptide by introducing an amino acid substitution at position 234 (EU numbering) with Ile.

In another 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 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 substitution at position 234 (EU numbering) with Ile, and has improved thermal 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.

In another aspect, there is provided a pharmaceutical composition comprising the polypeptide as disclosed herein, or a polypeptide produced by the method as disclosed herein.

In another aspect, there is provided an agent for treating or preventing an immune-inflammatory disease or cancer, which comprises the pharmaceutical composition as defined above.

In another aspect, there is provided the use of the pharmaceutical composition as defined above in the preparation of an agent for treating or preventing an immune-inflammatory disease or cancer.

[Means for Solving the Problems]

The present inventors considered that, in the production of modified Fc regions, it would be desirable to enhance their function while maintaining antibody stability, or to recover stability that had been reduced due to functional enhancement.

The present inventors conducted dedicated studies, and as a result succeeded in obtaining polypeptides with an antibody Fc region which have been modified in at least one amino acid in a loop region of the Fc region and which thereby have improved stability as compared to that of a parent polypeptide.

Furthermore, by combining multiple amino acid modifications in the loop region, polypeptides with improved thermal stability and maintained or enhanced FcγR-binding activity, and polypeptides with improved thermal stability and decreased FcγR-binding activity, as compared to those of a parent polypeptide, were successfully obtained. Furthermore, polypeptides not only with improved thermal stability and adjusted FcγR-binding activity but also with decreased aggregate content were successfully obtained.

More specifically, the present disclosure relates to the following:

[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 [1], wherein the stability is assessed or determined using melting temperature (Tm) as an index;

[3] the polypeptide of [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 (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;

[53] the method of any one of [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 [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 [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 [56];

[58] a host cell transformed with the vector of [57];

[59] a pharmaceutical composition comprising the polypeptide of any one of [1] to [26], or a polypeptide produced by the method of any one of [27] to [55];

[60] an agent for treating or preventing an immune-inflammatory disease or cancer, which comprises the pharmaceutical composition of [59];

[61] the agent of [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 [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] a method for treating or preventing an immune-inflammatory disease or cancer, comprising administering to a subject the polypeptide of any one of [1] to [26], or a polypeptide produced by the method of any one of [27] to [55];

[64] the polypeptide of any one of [1] to [26] or a polypeptide produced by the method of any one of [27] to [55], for use in treatment or prevention of an immune-inflammatory disease or cancer;

[65] use of the polypeptide of any one of [1] to [26] or a polypeptide produced by the method of any one of [27] to [55] in the preparation of an agent for treating or preventing an immune-inflammatory disease or cancer; and

[66] a method for producing an agent for treating or preventing an immune-inflammatory disease or cancer, comprising the step of using the polypeptide of any one of [1] to [26] or a polypeptide produced by the method of any one of [27] to [55].

Brief Description of the Drawings

Fig. 1 shows the melting temperatures (Tm) of the produced antibodies.

Fig. 2-1 shows the chromatograms for aggregate content determination of TS20 to TS27 in which multiple modifications were combined.

Fig. 2-2 shows the chromatograms for aggregate content determination of TS28 to TS39 in which multiple modifications have been combined.

Fig. 2-3 shows the chromatograms for aggregate content determination of TS40 to TS43 in which multiple modifications have been combined.

Fig. 3 shows the relationship between the amino acid residues constituting the Fc region of IgG1, IgG2, IgG3, and IgG4 and Kabat EU numbering (which is herein also referred to as EU index).

Fig. 4 shows the sites of amino acid modification (L234-S239, D265-P271, Q295, Y296, S298, Y300, S324-S337: the shaded portions) in the loop region of the CH2 domain of Fc region B3 (SEQ ID NO: 16).

Mode for Carrying Out the Invention

The present invention provides polypeptides having an antibody Fc region whose stability has been improved as compared to that of a parent polypeptide by introducing amino acid substitutions into a loop region of the Fc region.

Furthermore, the present invention provides methods for improving stability of a polypeptide having an antibody Fc region as compared to that of a parent polypeptide by introducing amino acid substitutions to a loop region of the antibody Fc region. Furthermore, the present invention provides methods for producing a polypeptide having an antibody Fc region whose stability has been improved as compared to that of a parent polypeptide by introducing amino acid substitutions to a loop region of the Fc region.

In the present invention, polypeptides generally refer to peptides or proteins of about ten or more amino acids in length. In addition, they are typically polypeptides of biological origin, but are not particularly limited. For example, they may be polypeptides composed of artificially designed sequences. They may also be any of naturally-occurring polypeptides, synthetic polypeptides, recombinant polypeptides, and such. Moreover, polypeptides may be antibodies. Preferred examples of polypeptides of the present invention include human IgG. When an antibody used is a human IgG, the type of its constant region is not limited, and human IgG isotypes (subclasses) such as IgG1, IgG2, IgG3, or IgG4 may be used.

Herein, "parent polypeptide" refers to a polypeptide which serves as a basis or reference in the production of polypeptides having an antibody Fc region of the present invention. More specifically, it can be a polypeptide having an antibody Fc region which has not yet been modified in at least one of the amino acids of the Fc region. The parent polypeptide in the present invention may be, for example, a polypeptide having an Fc region of a naturally-occurring IgG, or may be a polypeptide having an Fc region of IgG in which a modification other than the amino acid modifications of the present invention has been made to a naturally-occurring IgG.

Naturally-occurring IgGs refer to polypeptides that include an amino acid sequence identical to those of IgGs found in nature, and belong to a class of antibodies virtually encoded by immunoglobulin gamma genes. For example, naturally-occurring human IgG refers to naturally-occurring human IgG1, naturally-occurring human IgG2, naturally-occurring human IgG3, naturally-occurring human IgG4, and such. Naturally-occurring IgGs also include mutants and such that naturally occur from them.

The Fc region of a naturally-occurring IgG refers to an Fc region containing an amino acid sequence identical to that of the Fc region derived from an IgG found in nature. The Fc regions of naturally-occurring IgGs are shown in Fig. 3 (SEQ ID NOs: 11 to 14), and refer to, for example, an Fc region derived from naturally-occurring human IgG1, an Fc region derived from naturally-occurring human IgG2, an Fc region derived from naturally-occurring human IgG3, an

Fc region derived from naturally-occurring human IgG4, and such. The Fc regions of naturally-occurring IgGs also include mutants and such that naturally occur from them.

In the present invention, amino acid positions are defined according to Kabat (Sequences of Proteins of Immunological Interest (National Institute of Health, Bethesda, Md., 1987 and 1991). Herein, the sites of amino acid modifications in the antibody Fc region are shown according to EU numbering based on Kabat's amino acid positions.

In the present invention, portions linking α helices and β sheets are called loops, and there are no rules on their length or structure. In the present invention, a portion linking two β sheets in the CH2 domain is referred to as a loop, a loop region, a loop portion, or a loop structure. Specific amino acid positions of the loop region subjected to modification in the present invention are 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).

"Fc region" refers to a region containing a fragment composed of a hinge portion or a part thereof, and CH2 and CH3 domains of an antibody molecule. An Fc region of IgG class means, for example, from cysteine at position 226 to the C terminus or from proline at position 230 to the C terminus according to Kabat's EU numbering (herein also referred to as EU index) (see Fig. 3), but is not limited thereto.

An Fc region may be obtained preferably by partially digesting IgG1, IgG2, IgG3, IgG4 monoclonal antibodies or such using a protease such as pepsin and then re-eluting a fraction adsorbed onto protein A column. The protease is not particularly limited as long as it can digest a full-length antibody so that Fab and F(ab')2 will be produced in a restrictive manner by appropriately setting the enzyme reaction conditions such as pH, and examples include pepsin and papain.

The polypeptides of the present invention include, for example, polypeptides having an Fc region with improved stability as compared to a parent polypeptide. Preferred embodiments of the polypeptides having an Fc region with improved stability as compared to a parent polypeptide include, for example, polypeptides in which at least one amino acid has been modified in a loop region of the Fc region.

The present invention provides antibody Fc regions containing an Fc region in which at least one or more amino acids have been modified in a loop region of the Fc region of an antibody (for example, human IgG (IgG1, IgG2, IgG3, and IgG4)) at amino acid positions 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) of the IgG. For example, a polypeptide with improved stability as compared to a parent polypeptide can be provided by introducing the above-mentioned modifications to human IgG.

The present invention also provides antibody Fc regions containing an Fc region in which at least one or more amino acid mutations have been introduced into a loop region of the Fc region of an antibody (for example, human IgG (IgG1, IgG2, IgG3, and IgG4)) at amino acid positions 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) of the IgG.

Herein, "stability" means, for example, thermodynamic stability of a polypeptide, but is not limited thereto. Thermodynamic stability of a polypeptide can be assessed or determined, for example, by using the melting temperature (Tm) of a CH2 domain as an index. Thus,

polypeptides of the present invention are preferably assessed or judged using melting temperature (Tm) as an index. Tm can be measured by CD (circular dichroism), DSC (differential scanning calorimetry), and DSF (differential scanning fluorimetry).

The above-mentioned methods used for evaluating thermal stability can evaluate the thermal stability of the CH2, CH3, and Fab domains individually, when a sample in the form of IgG is measured. When CH2 and CH3 of the Fc region are compared, CH2 has lower thermal stability; therefore, improving the thermal stability of CH2 may lead to improvement of thermal stability of the Fc region.

Furthermore, an IgG keeps a highly-controlled conformation, and the conformation and physical stability of the respective domains affect each other. That is, a modification introduced into a certain domain may have an effect on a different domain, resulting in changes in the conformation and physical stability of the entire IgG. Therefore, when evaluating effects of introduced modifications, a sample is desirably evaluated in the form of IgG. For the above-mentioned reasons, evaluation of thermal stability of the CH2 domain in the present specification has been carried out using modified antibodies produced in the form of IgG.

When CD is used, Tm is determined by observing the mean residue molar ellipticity (θ) changing with rising temperature. Devices for measuring CD include, for example, a circular dichroism dispersion meter (JASCO Corporation). When CD spectra are monitored at a suitable wavelength (for example, 208 nm or 222 nm) while increasing the temperature, θ increases at a certain temperature, and becomes constant at temperatures thereafter. The temperature corresponding to the midpoint between the θ at low temperatures and the θ at high temperatures is determined as Tm. For the measurement, for example, protein solutions prepared using citric acid, Tris, phosphate solution, and such may be used, and such solutions can be used at a concentration of several hundred μg/mL.

When DSC is used, Tm is determined by observing the amount of heat changing with rising temperature. Measurement devices for DSC include MicroCal VP-DSC and Micro Cal Capillary DSC (both from GE Healthcare). When a protein solution and a buffer are enclosed in measurement cells, and temperature differences between the cells are measured while raising the temperature, the reaction becomes endothermic at a certain temperature. This temperature is determined as Tm. For the measurement, for example, protein solutions prepared using citrate buffer, TBS, PBS, histidine buffer, and such may be used, and such solutions can be used at a concentration of several ten μg/mL to several hundred μg/mL.

When DSF is used, Tm is determined by observing exposure of hydrophobic residues due to rising temperature, using a fluorescent reagent (for example, SYPRO Orange) that specifically binds to hydrophobic residues. A protein solution and a fluorescence reagent are mixed at an appropriate ratio. When fluorescence intensity is measured while raising the

temperature using an RT-PCR instrument, an increase in the fluorescence intensity is observed at a certain temperature. This temperature is determined as Tm. Measurement devices for DSF include Rotor-Gene Q (QIAGEN), and CFX96 real-time PCR analysis system (Bio-Rad). For the measurements, for example, protein solutions prepared using PBS, histidine buffer, and such may be used, and such solutions can be used at a concentration of several ten μg/mL to several hundred μg/mL.

Herein, "the stability of a polypeptide is improved" means that, for example, as compared to the Tm of the CH2 domain in the Fc region of a parent polypeptide used as a control determined according to the above-mentioned methods, the Tm of the CH2 domain in the Fc region of a test polypeptide is improved by 0.1 degrees or more, preferably 0.2 degrees or more, 0.3 degrees or more, 0.4 degrees or more, 0.5 degrees or more, 1 degree or more, 2 degrees or more, 3 degrees or more, 4 degrees or more, 5 degrees or more, 10 degrees or more, or 20 degrees or more.

Furthermore, the polypeptides of the present invention may also be polypeptides having an Fc region with not only improved stability as compared to that of a parent polypeptide but also maintained or enhanced binding activity to an Fcγ receptor (which may also be herein referred to as FcγR) as compared to that of the parent polypeptide. In the present invention, examples of the polypeptides having an Fc region with not only improved stability compared to that of a parent polypeptide but also maintained or enhanced FcγR-binding activity as compared to that of the parent polypeptide include polypeptides having the amino acid positions described in any of TS1-TS8, TS20-TS27, TS44-TS50, TS52-TS55, or TS57-TS67 as shown below in the Examples.

(TS1-TS8)

Examples of the polypeptide with maintained or enhanced FcγR-binding activity as compared to that of its parent polypeptide include polypeptides in which 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 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).

Preferred polypeptides in this embodiment include polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment include polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS20-TS27)

Examples of the polypeptide with maintained or enhanced FcγR-binding activity compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to the loop region of the Fc region at amino acid positions selected from the group consisting of position 295 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are position 295 (EU numbering), position 326 (EU numbering), and position 330 (EU numbering).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment include polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS44-TS50, TS52-TS55, TS57-TS67)

Examples of the polypeptide with maintained or enhanced FcγR-binding activity compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to the loop region of the Fc region at amino acid positions 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).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment include polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

For example, when the polypeptide is an antibody, it may preferably be used as a cancer antibody, for which its effector functions are important.

Furthermore, a polypeptide of the present invention may also be a polypeptide having an Fc region with not only improved stability compared to that of its parent polypeptide but also decreased binding activity to an Fcγ receptor as compared to that of the parent polypeptide. In the present invention, examples of the polypeptide having an Fc region with not only improved stability compared to that of its parent polypeptide but also decreased FcγR-binding activity as compared to that of the parent polypeptide include polypeptides having the amino acid modification region of TS9-TS19, TS28-TS43, TS51, or TS56 as shown below in the Examples.

(TS9-TS19)

Examples of the polypeptide with decreased FcγR-binding activity as compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to 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).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment include polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS28-TS34)

Examples of the polypeptide with decreased FcγR-binding activity compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to 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 268 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment are polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS28, TS29, TS36, TS37)

Examples of the polypeptide with decreased FcγR-binding activity as compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to 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 268 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment are polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS30, TS31, TS38, TS39)

Examples of the polypeptide with decreased FcγR-binding activity compared with that of a parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to 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 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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 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.

Even more preferred polypeptides in this embodiment are polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS32, TS33, TS40, TS41)

Examples of the polypeptide with decreased FcγR-binding activity as compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to 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 268 (EU numbering), position 270 (EU numbering), position 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment are polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS34, TS35, TS42, TS43)

Examples of the polypeptide with decreased FcγR-binding activity compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations have been introduced to 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 295 (EU numbering), position 296 (EU numbering), position 298 (EU numbering), and position 325 (EU numbering).

Preferred polypeptides in this embodiment are polypeptides in which the positions of amino acid modification in the loop region of the Fc region are 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).

More preferred polypeptides in this embodiment include polypeptides in which 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.

Even more preferred polypeptides in this embodiment are polypeptides in which the amino acid modifications in the loop region of the Fc region are 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.

(TS51, TS56)

Examples of the polypeptide with decreased FcγR-binding activity compared to that of its parent polypeptide include polypeptides in which at least one or more amino acid mutations

have been introduced to the loop region of the Fc region at amino acid position 298 (EU numbering) and position 309 (EU numbering).

Preferred polypeptides in this embodiment include polypeptides in which the positions of amino acid modification in the loop region of the Fc region are position 298 (EU numbering) and position 309 (EU numbering).

More preferred polypeptides in this embodiment include polypeptides in which 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 with Asp.

Even more preferred polypeptides in this embodiment include polypeptides in which the amino acid modifications in the loop region of the Fc region are substitution of the amino acid at position 298 (EU numbering) with Gly and substitution of the amino acid at position 309 with Asp.

For example, when the polypeptide is an antibody, it may preferably be used as a neutralizing antibody.

"Fcγ receptors" refers to receptors that may bind to the Fc region of IgG1, IgG2, IgG3, and IgG4 monoclonal antibodies, and practically means any member of the family of proteins encoded by the Fcγ receptor genes. In humans, this family includes FcγRI (CD64) including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32) including isoforms FcγRIIa (including allotypes H131 (type H) and R131 (type R)), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16) including isoforms FcγRIIIa (including allotypes V158 and F158), and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2), and any human FcγRs, FcγR isoforms or allotypes yet to be discovered, but is not limited thereto. The FcγR in the present invention includes not only human-derived FcγRs, but also mouse, rat, rabbit, and monkey-derived FcγRs but is not limited thereto, and may be derived from any organism. Mouse FcγRs include FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and FcγRIII-2 (CD16-2), and any mouse FcγRs, or FcγR isoforms or allotypes yet to be discovered, but are not limited thereto. Preferred examples of Fcγ receptors in the present invention include human FcγI (CD64), FcγIIA (CD32), FcγIIB (CD32), FcγIIIA (CD16), and/or FcγIIIB (CD16).

The polynucleotide sequence and amino acid sequence of FcγI are set forth in SEQ ID NOs: 1 (NM_000566.3) and 2 (NP_000557.1), respectively;
the polynucleotide sequence and amino acid sequence of FcγIIA are set forth in SEQ ID NOs: 3 (BC020823.1) and 4 (AAH20823.1), respectively;
the polynucleotide sequence and amino acid sequence of FcγIIB are set forth in SEQ ID NOs: 5 (BC146678.1) and 6 (AAI46679.1), respectively;
the polynucleotide sequence and amino acid sequence of FcγIIIA are set forth in SEQ ID NOs: 7

(BC033678.1) and 8 (AAH33678.1), respectively; and
the polynucleotide sequence and amino acid sequence of FcγIIIB are set forth in SEQ ID NOs 9 (BC128562.1) and 10 (AAI28563.1), respectively (the RefSeq Registration number is indicated inside the parentheses).

In FcγRIIa, there are two allotypes: one where the amino acid at position 131 of FcγRIIa is histidine (type H) and the other where this amino acid is substituted with arginine (type R) (J. Exp. Med, 172: 19-25, 1990).

In the present invention, whether or not the binding activity of a polypeptide or an Fc region of the present invention towards each type of FcγR is decreased, or maintained or enhanced can be determined, for example, as shown in the present Examples. Specifically, it can be determined by using BIACORE, which is a device for interaction analysis based on the surface plasmon resonance (SPR) phenomenon, and observing whether there is a decrease or an increase in the dissociation constant (KD) value obtained by allowing each type of FcγR to flow as an analyte over a sensor chip onto which a polypeptide (antibody) has been immobilized or captured with Protein A, antigen peptide or such, or whether there is an increase or a decrease in the amount of change in the sensorgram value before and after allowing each type of FcγR to flow as an analyte over a sensor chip onto which a polypeptide (antibody) has been immobilized or captured with Protein A, antigen peptide or such.

Specifically, the binding activity of an Fc region towards an Fcγ receptor can be measured by the Amplified Luminescent Proximity Homogeneous Assay (ALPHA) Screen, the BIACORE method which utilizes the surface plasmon resonance (SPR) phenomena, or such, in addition to ELISA or fluorescence activated cell sorting (FACS) (Proc. Natl. Acad. Sci. USA (2006) 103 (11): 4005-4010).

ALPHA Screen is performed by ALPHA technology which uses two beads, a donor and an acceptor, based on the following principles. Luminescent signals are detected only when molecules bound to donor beads physically interact with molecules bound to the acceptor beads, and the two beads are in close proximity to each other. Laser-excited photosensitizer in the donor beads converts ambient oxygen to excited-state singlet oxygen. Singlet oxygen is dispersed around the donor beads, and when it reaches the adjacent acceptor beads, chemiluminescent reaction is induced in the beads, and light is ultimately emitted. When the molecules bound to the donor beads do not interact with the molecules bound to the acceptor beads, the chemiluminescent reaction does not take place because singlet oxygen produced by the donor beads does not reach the acceptor beads.

For example, a biotinylated polypeptide complex is bound to the donor beads, and Fcγ receptor tagged with glutathione S transferase (GST) is linked to the acceptor beads. In the absence of a competing polypeptide complex having a mutant Fc region, the polypeptide

complex having a wild-type Fc region interacts with the Fcγ receptor and produces 520-620 nm signals. The polypeptide complex having an untagged mutant Fc region competes with the polypeptide complex having a wild-type Fc region for interaction with the Fcγ receptor. Relative binding affinity can be determined by quantifying the decrease in fluorescence observed as a result of the competition.

Biotinylation of polypeptide complexes such as antibodies using Sulfo-NHS-biotin and such is well known. The method of expressing the Fcγ receptor and GST in a cell carrying a fusion gene produced by fusing a polynucleotide encoding the Fcγ receptor in frame with a polynucleotide encoding GST in an expressible vector, and performing purification using a glutathione column is appropriately adopted as a method for tagging an Fcγ receptor with GST. The obtained signals are preferably analyzed, for example, by fitting them to a one-site competition model which uses a non-linear regression analysis using software such as GRAPHPAD PRISM (GraphPad, San Diego).

One of the substances (the ligand) in observation of an interaction is immobilized onto a gold thin film on a sensor chip, and by shining light from the reverse side of the sensor chip so that total reflection takes place at the interface between the gold thin film and glass, a portion of reduced reflection intensity is formed in part of the reflected light (SPR signal). When the other one of the substances (the analyte) in observation of an interaction is made to flow on the sensor chip surface and the ligand binds to the analyte, the mass of the immobilized ligand molecule increases and the refractive index of the solvent on the sensor chip surface changes. The position of the SPR signal shifts as a result of this change in refractive index (on the other hand, the signal position returns when this binding dissociates). The Biacore system indicates the amount of shift mentioned above, or more specifically the time variable of mass by plotting the change in mass on the sensor chip surface on the ordinate as the measurement data (sensorgram). The amount of analyte bound to the ligand trapped on the sensor chip surface is determined from the sensorgram. Kinetic parameters such as association rate constants (ka) and dissociation rate constants (kd) are determined from the curves of the sensorgram, and the dissociation constants (KD) are determined from the ratio of these constants. In the BIACORE method, a method for measuring inhibition is preferably used. An example of the method for measuring inhibition is described in Proc. Natl. Acad. Sci USA (2006) 103 (11): 4005-4010.

In the present invention, a polypeptide with decreased FcγR-binding activity (a polypeptide whose binding activity to FcγR is decreased) refers to a polypeptide having at least one amino acid modification in the Fc region of a parent polypeptide (also called a polypeptide variant) which, when assayed in substantially the same amount as the parent polypeptide, binds to at least one type of FcγR with a substantially lower binding affinity than the parent polypeptide.

For example, when the amount of the parent polypeptide bound to each FcγR, as measured by the aforementioned method, is taken as 100, the amount of the polypeptide variant bound to each FcγR (hereinafter referred to as "binding amount ratio") is preferably decreased to 80 or less, preferably 50 or less, 40 or less, 30 or less, 20 or less, or particularly preferably 10 or less, 5 or less, 4 or less, 3 or less, 2 or less, 1 or less, or 0.1 or less.

In the present invention, a polypeptide with enhanced FcγR-binding activity (a polypeptide whose binding activity to FcγR is enhanced) refers to a polypeptide variant which, when assayed in substantially the same amount as the parent polypeptide, binds to at least one type of FcγR with a substantially higher binding affinity than the parent polypeptide.

For example, when the amount of the parent polypeptide bound to each FcγR, as measured by the aforementioned method, is taken as 100, the amount of the polypeptide variant bound to each FcγR (hereinafter referred to as "binding amount ratio") is preferably increased to 120 or more, 150 or more, 200 or more, or 300 or more.

A polypeptide with unchanged (maintained) FcγR-binding activity (a polypeptide whose binding activity to FcγR is unchanged (maintained)) refers to a polypeptide having at least one amino acid modification in the Fc region of a parent polypeptide (also called a polypeptide variant) which, when assayed in substantially the same amount as the parent polypeptide, binds to FcγR with a binding affinity substantially unchanged from or equivalent to that of the parent polypeptide.

For example, when the amount of the parent polypeptide bound to each FcγR, as measured by the aforementioned method, is taken as 100, the amount of the polypeptide variant bound to each FcγR (hereinafter referred to as "binding amount ratio") is preferably 80 or more and 120 or less.

In the present invention, polypeptides (for example, human IgG) containing the above-mentioned modifications of the present invention may be further modified in other parts of the Fc region.

For example, such modifications to other parts of the Fc region include substituting Pro at position 238 (EU numbering) with Asp and/or substituting Leu at position 328 (EU numbering) with Glu in human IgG (IgG1, IgG2, IgG3, and IgG4). Polypeptides with maintained or decreased binding activities towards FcγRI, FcγRIIIa, and both R and H allotypes of FcγRIIa, as well as enhanced FcγRIIb-binding activity in comparison with a parent polypeptide can be provided by introducing alteration of substituting Pro at position 238 (EU numbering) with Asp or substituting Leu at position 328 (EU numbering) with Glu in human IgG.

Further alterations of the Fc region can be added to human IgG containing alterations by which Pro at position 238 (EU numbering) has been substituted with Asp and/or Leu at position 328 (EU numbering) has been substituted with Glu. Here, alteration refers to any one of, or a

combination of amino acid substitutions, deletions, additions, and insertions. Additional alterations can be further included in addition to these alterations. An additional alteration can be selected from any one of, or combinations of amino acid substitutions, deletions, or modifications. For example, alterations that further decrease binding activity towards FcγRI, FcγRIIa (type H), FcγRIIa (type R), or FcγRIIIa can be added.

Preferred alterations among them are those that only reduce the binding activity towards FcγRI, FcγRIIa (type H), FcγRIIa (type R), or FcγRIIIa without reducing the binding activity toward FcγRIIb. Preferred examples of such alterations include the following amino acid substitutions:

substitution of Gly at position 237 (EU numbering) with Trp,
substitution of Gly at position 237 (EU numbering) with Phe,
substitution of Pro at position 238 (EU numbering) with Phe,
substitution of Asn at position 325 (EU numbering) with Met,
substitution of Ser at position 267 (EU numbering) with Ile,
substitution of Leu at position 328 (EU numbering) with Asp,
substitution of Ser at position 267 (EU numbering) with Val,
substitution of Leu at position 328 (EU numbering) with Trp,
substitution of Ser at position 267 (EU numbering) with Gln,
substitution of Ser at position 267 (EU numbering) with Met,
substitution of Gly at position 236 (EU numbering) with Asp,
substitution of Ala at position 327 (EU numbering) with Asn,
substitution of Asn at position 325 (EU numbering) with Ser,
substitution of Leu at position 235 (EU numbering) with Tyr,
substitution of Val at position 266 (EU numbering) with Met,
substitution of Leu at position 328 (EU numbering) with Tyr,
substitution of Leu at position 235 (EU numbering) with Trp,
substitution of Leu at position 235 (EU numbering) with Phe,
substitution of Ser at position 239 (EU numbering) with Gly,
substitution of Ala at position 327 (EU numbering) with Glu,
substitution of Ala at position 327 (EU numbering) with Gly,
substitution of Pro at position 238 (EU numbering) with Leu,
substitution of Ser at position 239 (EU numbering) with Leu,
substitution of Leu at position 328 (EU numbering) with Thr,
substitution of Leu at position 328 (EU numbering) with Ser,
substitution of Leu at position 328 (EU numbering) with Met,
substitution of Pro at position 331 (EU numbering) with Trp,

substitution of Pro at position 331 (EU numbering) with Tyr,
substitution of Pro at position 331 (EU numbering) with Phe,
substitution of Ala at position 327 (EU numbering) with Asp,
substitution of Leu at position 328 (EU numbering) with Phe,
substitution of Pro at position 271 (EU numbering) with Leu,
substitution of Ser at position 267 (EU numbering) with Glu,
substitution of Leu at position 328 (EU numbering) with Ala,
substitution of Leu at position 328 (EU numbering) with Ile,
substitution of Leu at position 328 (EU numbering) with Gln,
substitution of Leu at position 328 (EU numbering) with Val,
substitution of Lys at position 326 (EU numbering) with Trp,
substitution of Lys at position 334 (EU numbering) with Arg,
substitution of His at position 268 (EU numbering) with Gly,
substitution of His at position 268 (EU numbering) with Asn,
substitution of Ser at position 324 (EU numbering) with Val,
substitution of Val at position 266 (EU numbering) with Leu,
substitution of Pro at position 271 (EU numbering) with Gly,
substitution of Ile at position 332 (EU numbering) with Phe,
substitution of Ser at position 324 (EU numbering) with Ile,
substitution of Glu at position 333 (EU numbering) with Pro,
substitution of Tyr at position 300 (EU numbering) with Asp,
substitution of Ser at position 337 (EU numbering) with Asp,
substitution of Tyr at position 300 (EU numbering) with Gln,
substitution of Thr at position 335 (EU numbering) with Asp,
substitution of Ser at position 239 (EU numbering) with Asn,
substitution of Lys at position 326 (EU numbering) with Leu,
substitution of Lys at position 326 (EU numbering) with Ile,
substitution of Ser at position 239 (EU numbering) with Glu,
substitution of Lys at position 326 (EU numbering) with Phe,
substitution of Lys at position 326 (EU numbering) with Val,
substitution of Lys at position 326 (EU numbering) with Tyr,
substitution of Ser at position 267 (EU numbering) with Asp,
substitution of Lys at position 326 (EU numbering) with Pro,
substitution of Lys at position 326 (EU numbering) with His,
substitution of Lys at position 334 (EU numbering) with Ala,
substitution of Lys at position 334 (EU numbering) with Trp,

substitution of His at position 268 (EU numbering) with Gln,
substitution of Lys at position 326 (EU numbering) with Gln,
substitution of Lys at position 326 (EU numbering) with Glu,
substitution of Lys at position 326 (EU numbering) with Met,
substitution of Val at position 266 (EU numbering) with Ile,
substitution of Lys at position 334 (EU numbering) with Glu,
substitution of Tyr at position 300 (EU numbering) with Glu,
substitution of Lys at position 334 (EU numbering) with Met,
substitution of Lys at position 334 (EU numbering) with Val,
substitution of Lys at position 334 (EU numbering) with Thr,
substitution of Lys at position 334 (EU numbering) with Ser,
substitution of Lys at position 334 (EU numbering) with His,
substitution of Lys at position 334 (EU numbering) with Phe,
substitution of Lys at position 334 (EU numbering) with Gln,
substitution of Lys at position 334 (EU numbering) with Pro,
substitution of Lys at position 334 (EU numbering) with Tyr,
substitution of Lys at position 334 (EU numbering) with Ile,
substitution of Gln at position 295 (EU numbering) with Leu,
substitution of Lys at position 334 (EU numbering) with Leu,
substitution of Lys at position 334 (EU numbering) with Asn,
substitution of His at position 268 (EU numbering) with Ala,
substitution of Ser at position 239 (EU numbering) with Asp, and
substitution of Ser at position 267 (EU numbering) with Ala.

Furthermore, preferred alterations among these alterations are those that reduce the binding activity towards FcγRIIa (type R) without reducing the binding activity towards FcγRIIb. Preferred examples of such alterations include the following amino acid substitutions:
substitution of Gly at position 237 (EU numbering) with Trp,
substitution of Leu at position 328 (EU numbering) with Asp,
substitution of Gly at position 236 (EU numbering) with Asp,
substitution of Ala at position 327 (EU numbering) with Asn,
substitution of Ala at position 327 (EU numbering) with Gly,
substitution of Ser at position 239 (EU numbering) with Leu,
substitution of Pro at position 331 (EU numbering) with Trp,
substitution of Pro at position 331 (EU numbering) with Tyr,
substitution of Pro at position 331 (EU numbering) with Phe,
substitution of Pro at position 271 (EU numbering) with Leu,

substitution of Leu at position 328 (EU numbering) with Gln,
substitution of Tyr at position 300 (EU numbering) with Asp, and
substitution of Ser at position 239 (EU numbering) with Asn.

Furthermore, it is also possible to add alterations enhancing the binding activity towards FcγRIIb by adding other alterations of the Fc region to human IgG containing substitution of Pro at position 238 (EU numbering) with Asp and/or substitution of Leu at position 328 (EU numbering) with Glu. Preferred alterations among such alterations are those that enhance only the binding activity towards FcγRIIb without enhancing the binding activity towards FcγRI, FcγRIIa (type H), FcγRIIa (type R), or FcγRIIIa. Preferred examples of such alterations include the following amino acid substitutions:
substitution of Gly at position 237 (EU numbering) with Trp,
substitution of Gly at position 237 (EU numbering) with Phe,
substitution of Pro at position 238 (EU numbering) with Phe,
substitution of Asn at position 325 (EU numbering) with Met,
substitution of Ser at position 267 (EU numbering) with Ile,
substitution of Leu at position 328 (EU numbering) with Asp,
substitution of Ser at position 267 (EU numbering) with Val,
substitution of Leu at position 328 (EU numbering) with Trp,
substitution of Ser at position 267 (EU numbering) with Gln,
substitution of Ser at position 267 (EU numbering) with Met,
substitution of Gly at position 236 (EU numbering) with Asp,
substitution of Ala at position 327 (EU numbering) with Asn,
substitution of Asn at position 325 (EU numbering) with Ser,
substitution of Leu at position 235 (EU numbering) with Tyr,
substitution of Val at position 266 (EU numbering) with Met,
substitution of Leu at position 328 (EU numbering) with Tyr,
substitution of Leu at position 235 (EU numbering) with Trp,
substitution of Leu at position 235 (EU numbering) with Phe,
substitution of Ser at position 239 (EU numbering) with Gly,
substitution of Ala at position 327 (EU numbering) with Glu,
substitution of Ala at position 327 (EU numbering) with Gly,
substitution of Pro at position 238 (EU numbering) with Leu,
substitution of Ser at position 239 (EU numbering) with Leu,
substitution of Leu at position 328 (EU numbering) with Thr,
substitution of Leu at position 328 (EU numbering) with Ser,
substitution of Leu at position 328 (EU numbering) with Met,

substitution of Pro at position 331 (EU numbering) with Trp,
substitution of Pro at position 331 (EU numbering) with Tyr,
substitution of Pro at position 331 (EU numbering) with Phe,
substitution of Ala at position 327 (EU numbering) with Asp,
substitution of Leu at position 328 (EU numbering) with Phe,
substitution of Pro at position 271 (EU numbering) with Leu,
substitution of Ser at position 267 (EU numbering) with Glu,
substitution of Leu at position 328 (EU numbering) with Ala,
substitution of Leu at position 328 (EU numbering) with Ile,
substitution of Leu at position 328 (EU numbering) with Gln,
substitution of Leu at position 328 (EU numbering) with Val,
substitution of Lys at position 326 (EU numbering) with Trp,
substitution of Lys at position 334 (EU numbering) with Arg,
substitution of His at position 268 (EU numbering) with Gly,
substitution of His at position 268 (EU numbering) with Asn,
substitution of Ser at position 324 (EU numbering) with Val,
substitution of Val at position 266 (EU numbering) with Leu,
substitution of Pro at position 271 (EU numbering) with Gly,
substitution of Ile at position 332 (EU numbering) with Phe,
substitution of Ser at position 324 (EU numbering) with Ile,
substitution of Glu at position 333 (EU numbering) with Pro,
substitution of Tyr at position 300 (EU numbering) with Asp,
substitution of Ser at position 337 (EU numbering) with Asp,
substitution of Tyr at position 300 (EU numbering) with Gln,
substitution of Thr at position 335 (EU numbering) with Asp,
substitution of Ser at position 239 (EU numbering) with Asn,
substitution of Lys at position 326 (EU numbering) with Leu,
substitution of Lys at position 326 (EU numbering) with Ile,
substitution of Ser at position 239 (EU numbering) with Glu,
substitution of Lys at position 326 (EU numbering) with Phe,
substitution of Lys at position 326 (EU numbering) with Val,
substitution of Lys at position 326 (EU numbering) with Tyr,
substitution of Ser at position 267 (EU numbering) with Asp,
substitution of Lys at position 326 (EU numbering) with Pro,
substitution of Lys at position 326 (EU numbering) with His,
substitution of Lys at position 334 (EU numbering) with Ala,

substitution of Lys at position 334 (EU numbering) with Trp,
substitution of His at position 268 (EU numbering) with Gln,
substitution of Lys at position 326 (EU numbering) with Gln,
substitution of Lys at position 326 (EU numbering) with Glu,
substitution of Lys at position 326 (EU numbering) with Met,
substitution of Val at position 266 (EU numbering) with Ile,
substitution of Lys at position 334 (EU numbering) with Glu,
substitution of Tyr at position 300 (EU numbering) with Glu,
substitution of Lys at position 334 (EU numbering) with Met,
substitution of Lys at position 334 (EU numbering) with Val,
substitution of Lys at position 334 (EU numbering) with Thr,
substitution of Lys at position 334 (EU numbering) with Ser,
substitution of Lys at position 334 (EU numbering) with His,
substitution of Lys at position 334 (EU numbering) with Phe,
substitution of Lys at position 334 (EU numbering) with Gln,
substitution of Lys at position 334 (EU numbering) with Pro,
substitution of Lys at position 334 (EU numbering) with Tyr,
substitution of Lys at position 334 (EU numbering) with Ile,
substitution of Gln at position 295 (EU numbering) with Leu,
substitution of Lys at position 334 (EU numbering) with Leu,
substitution of Lys at position 334 (EU numbering) with Asn,
substitution of His at position 268 (EU numbering) with Ala,
substitution of Ser at position 239 (EU numbering) with Asp, and
substitution of Ser at position 267 (EU numbering) with Ala.

Furthermore, preferred alterations among these alterations are those that reduce the binding activity towards FcγRIIa (type R) without reducing the binding activity towards FcγRIIb. Preferred examples of such alterations include the following amino acid substitutions:
substitution of Gly at position 237 (EU numbering) with Trp,
substitution of Leu at position 328 (EU numbering) with Asp,
substitution of Gly at position 236 (EU numbering) with Asp,
substitution of Ala at position 327 (EU numbering) with Asn,
substitution of Ala at position 327 (EU numbering) with Gly,
substitution of Ser at position 239 (EU numbering) with Leu,
substitution of Pro at position 331 (EU numbering) with Trp,
substitution of Pro at position 331 (EU numbering) with Tyr,
substitution of Pro at position 331 (EU numbering) with Phe,

substitution of Pro at position 271 (EU numbering) with Leu,
substitution of Leu at position 328 (EU numbering) with Gln,
substitution of Tyr at position 300 (EU numbering) with Asp, and
substitution of Ser at position 239 (EU numbering) with Asn.

Furthermore, for example, amino acid substitutions that improve FcRn-binding activity (J. Immunol. 2006 Jan 1; 176(1): 346-56; J Biol Chem. 2006 Aug 18; 281(33): 23514-24; Int. Immunol. 2006 Dec; 18(12): 1759-69; Nat Biotechnol. 2010 Feb; 28(2): 157-9.; WO 2006/019447; WO 2006/053301; and WO 2009/086320), and amino acid substitutions for improving antibody heterogeneity or stability (WO 2009/041613) may be introduced into the Fc region of an antibody.

In addition to the amino acid modifications of the present invention, the following modifications can be added as necessary.

In order to regulate the plasma retention property of antibodies, it is possible to combine the amino acid modifications of the present invention with amino acid modifications for altering the antibody isoelectric point value (pI value). Modifications of the constant regions include, for example, amino acid modifications at positions 250 and 428 (EU numbering) and such described in known publications (for example, J. Immunol. 2006, 176 (1):346-356; and Nat. Biotechnol. 1997 15 (7):637-640). Modifications of the variable regions include the amino acid modifications described in WO2007/114319 and WO2009/041643. Amino acids to be modified are preferably exposed on the surface of a polypeptide having an antigen-binding activity. When a polypeptide of the present invention has a heavy chain constant region, the modifications include, for example, amino acid substitution at position 196 (EU numbering) in the amino acid sequence of the heavy chain constant region. When the heavy chain constant region is that of IgG4, the plasma retention can be enhanced, for example, by substituting lysine at position 196 with glutamine and thereby reducing the pI value. Furthermore, the plasma retention can be regulated by altering the FcRn-binding ability. Amino acid modifications that alter the FcRn-binding ability include, for example, the amino acid substitutions in the antibody heavy chain constant region described in known publications (The Journal of Biological Chemistry vol.276, No.9 6591-6604, 2001; and Molecular Cell, Vol.7, 867-877, 2001).

Modifications for improving the stability under acidic conditions

When a polypeptide of the present invention has a heavy chain constant region of IgG4, the stable four-chain structure (H2L2 structure) is preferably maintained by suppressing the dissociation of IgG4 into half-molecules under acidic conditions. Thus, arginine at amino acid position 409 (EU numbering), which plays an important role in the maintenance of the four-

chain structure (Immunology 2002, 105, 9-19), is preferably substituted with lysine, the residue of the IgG1 type, which maintains the stable four-chain structure even under acidic conditions. Such modifications can be used in combination with the amino acid modifications of the present invention.

Modifications for reducing heterogeneity

The amino acid modifications of the present invention may be combined with the methods described in WO2009/041613. Specifically, for example, when a polypeptide of the present invention has a heavy chain constant region of IgG1, it is possible to combine the modification for deleting the C-terminal two amino acids of the IgG1 heavy chain constant region, that is, glycine and lysine at positions 446 and 447 (EU numbering), with the amino acid modifications described in the present Examples so that the heterogeneity can be reduced.

Modifications for suppressing deamidation reaction

The amino acid modifications of the present invention may be combined with amino acid modifications for suppressing deamidation reaction. It has been reported that deamidation reaction tends to occur particularly at a site where asparagine (N) and glycine (G) are adjacent to each other (--NG--) (Geiger *et al.*, J. Bio. Chem. 1987; 262:785-794). When a polypeptide of the present invention has a site where asparagine and glycine are adjacent to each other, deamidation reaction can be suppressed by modifying this amino acid sequence. Specifically, for example, either or both of asparagine and glycine are substituted with other amino acids. More specifically, for example, asparagine is substituted with aspartic acid.

Preferred examples of polypeptides of the present invention include IgG antibodies. When an IgG antibody is used as the antibody, the type of constant region is not limited, and an IgG isotypes (subclasses) such as IgG1, IgG2, IgG3, and IgG4 can be used. IgG antibodies of the present invention are preferably human IgG, and more preferably human IgG1 or human IgG4. The amino acid sequences of the heavy-chain Fc regions of human IgG1 and human IgG4 are known. A plurality of allotype sequences due to genetic polymorphisms have been described in Sequences of Proteins of Immunological Interest, NIH Publication No. 91-3242 for the human IgG1 Fc region, and any of the sequences may be used in the present invention.

<Substitution>

For example, for the purpose of modifying (a)-(c) listed below, amino acid residues can be substituted with other amino acid residues:

(a) polypeptide backbone structure in the sheet-structure or helical-structure region;

(b) electric charge or hydrophobicity at the target site; or

(c) size of the side chain.

Amino acid residues are classified into the following groups based on their general side chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, and ile;

(2) neutral hydrophilic: cys, ser, thr, asn, and gln;

(3) acidic: asp and glu;

(4) basic: his, lys, and arg;

(5) residues that affect the chain orientation: gly and pro; and

(6) aromatic: trp, tyr, and phe.

Substitution between amino acid residues within each of these amino acid groups is referred to as conservative substitution, and amino acid residue substitution between different groups is referred to as non-conservative substitution. Substitutions in the present invention may be conservative substitutions or non-conservative substitutions, or a combination of conservative substitutions and non-conservative substitutions.

Amino acid sequence alterations are produced by various methods known to those skilled in the art. Such methods include the site-directed mutagenesis method (Hashimoto-Gotoh, T, Mizuno, T, Ogasahara, Y, and Nakagawa, M. (1995) An oligodeoxyribonucleotide-directed dual amber method for site-directed mutagenesis. Gene 152: 271-275; Zoller, MJ, and Smith, M. (1983) Oligonucleotide-directed mutagenesis of DNA fragments cloned into M13 vectors. Methods Enzymol. 100: 468-500; Kramer, W, Drutsa, V, Jansen, HW, Kramer, B, Pflugfelder, M, and Fritz, HJ (1984) The gapped duplex DNA approach to oligonucleotide-directed mutation construction. Nucleic Acids Res. 12: 9441-9456; Kramer W, and Fritz HJ (1987) Oligonucleotide-directed construction of mutations via gapped duplex DNA Methods. Enzymol. 154, 350-367; and Kunkel, TA (1985) Rapid and efficient site-specific mutagenesis without phenotypic selection. Proc Natl Acad Sci U S A. 82: 488-492), the PCR mutation method, and the cassette mutation method, but are not limited thereto.

Amino acid modification of the present invention includes post-translational modification. A specific post-translational modification may be addition or deletion of a sugar chain. For example, in the IgG1 Fc region consisting of the amino acid sequence of SEQ ID NO: 11, the amino acid residue at position 297 (EU numbering) may be sugar chain-modified. The sugar-chain structure for the modification is not limited. Generally, antibodies expressed in eukaryotic cells comprise glycosylation in the Fc region. Therefore, antibodies expressed in cells such as those below are normally modified by some type of sugar chain:

- antibody-producing cells of mammals
- eukaryotic cells transformed with an expression vector comprising a DNA encoding an

antibody

Eukaryotic cells shown here include yeast and animal cells. For example, CHO cells and HEK293H cells are representative animal cells used in transformation with an expression vector comprising an antibody-encoding DNA. On the other hand, the Fc regions of the present invention include those without glycosylation at this site. Antibodies whose Fc region is not glycosylated can be obtained by expressing an antibody-encoding gene in prokaryotic cells such as *Escherichia coli*.

Specifically, for example, sialic acid may be added to the sugar chain of an Fc region (MAbs. 2010 Sep-Oct; 2(5): 519-27).

<Antibody>

Furthermore, the present invention provides antibodies with an Fc region in which any of the above-mentioned amino acid sequences is altered.

The term "antibody/antibodies" in the present invention is used in the broadest sense, and as long as the desired biological activity is shown, it encompasses any antibodies such as monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies, antibody variants, antibody fragments, multispecific antibodies (for example, bispecific antibodies (which may be referred to as diabodies)), chimeric antibodies, and humanized antibodies.

The antibodies of the present invention are not limited in terms of the antigen type and origin, and may be any types of antibodies. The origin of the antibodies is not particularly limited, but examples include human antibodies, mouse antibodies, rat antibodies, and rabbit antibodies.

Methods for producing the antibodies are well known to those skilled in the art, and for example, monoclonal antibodies may be produced by the hybridoma method (Kohler and Milstein, Nature 256: 495 (1975)), or the recombination method (U.S. Patent No. 4,816,567). Alternatively, they may be isolated from a phage antibody library (Clackson *et al.*, Nature 352: 624-628 (1991); Marks *et al.*, J.Mol.Biol. 222: 581-597 (1991)). In the present invention, monoclonal antibodies include humanized antibodies and chimeric antibodies.

In addition to the above methods, B cell cloning (use for identification and cloning of the coding sequence of each antibody, isolation thereof, and construction of expression vectors for producing each antibody (particularly IgG1, IgG2, IgG3, or IgG4) etc.) as described in Bernasconi *et al.* (Science (2002) 298, 2199-2202) or WO2008/081008 is appropriately used as a method for obtaining antibody genes.

Moreover, the antibodies of the present invention may have an altered sugar chain. Examples of antibodies whose sugar chain has been altered include, for example, antibodies with

modified glycosylation (WO99/54342 and such), antibodies deficient in fucose attached to a sugar chain (WO00/61739, WO02/31140, WO2006/067847, WO2006/067913, and such), and antibodies having a sugar chain with bisecting GlcNAc (WO02/79255 and such).

A humanized antibody is also called a reshaped human antibody. Specifically, humanized antibodies prepared by grafting the CDRs of a non-human animal antibody such as a mouse antibody to a human antibody and such are known. Common genetic engineering techniques for obtaining humanized antibodies are also known. Specifically, for example, overlap extension PCR is known as a method for grafting mouse antibody CDRs to human FRs. Furthermore, it is also possible to design an amino acid sequence in which mouse CDRs have been grafted on human FRs, and then synthesize a gene of this amino acid sequence. Gene synthesis services are provided by, for example, Life Technologies, GenScript, and other companies.

A vector for expressing a humanized antibody can be produced by inserting a DNA encoding an antibody variable region in which three CDRs and four FRs are ligated and a DNA encoding a human antibody Fc region into an expression vector so that these DNAs are fused in frame. After this integration vector is transfected into a host to establish recombinant cells, these cells are cultured, and the DNA encoding the humanized antibody is expressed to produce the humanized antibody in the culture of the cells (see, European Patent Publication No. EP 239,400, and International Patent Publication No. WO 1996/002576).

As necessary, an amino acid residue in an FR may be substituted so that the CDRs of a reshaped human antibody form an appropriate antigen-binding site. For example, a mutation can be introduced into the amino acid sequence of an FR by applying the PCR method used for grafting mouse CDRs to human FRs.

A desired human antibody can be obtained by DNA immunization using a transgenic animal having the complete repertoire of human antibody genes (see International Publication Nos. WO 1993/012227, WO 1992/003918, WO 1994/002602, WO 1994/025585, WO 1996/034096, and WO 1996/033735) as an animal for immunization.

Furthermore, technologies for obtaining a human antibody by panning using a human antibody library are known. For example, a human antibody V region is expressed on the surface of a phage as a single-chain antibody (scFv) by the phage display method. The scFv-expressing phage that binds to the antigen can be selected. The DNA sequence that encodes the V region of the antigen-bound human antibody can be determined by analyzing the genes of the selected phage. After determining the DNA sequence of the scFv that binds to the antigen, an expression vector can be prepared by fusing the V-region sequence in-frame with the sequence of a desired human antibody C region, and then inserting this into a suitable expression vector. The expression vector is introduced into suitable expression cells such as those described above, and

the human antibody can be obtained by expressing the human antibody-encoding gene. These methods are already known (see, International Publication Nos. WO 1992/001047, WO 1992/020791, WO 1993/006213, WO 1993/011236, WO 1993/019172, WO 1995/001438, and WO 1995/15388).

Herein, there is no particular limitation on the antigen, and it may be any antigens. Examples of such antigens preferably include ligands (cytokines, chemokines, and such), receptors, cancer antigens, MHC antigens, differentiation antigens, immunoglobulins, and immune complexes partly containing immunoglobulins.

Examples of cytokines include interleukins 1 to 18, colony stimulating factors (G-CSF, M-CSF, GM-CSF, etc.), interferons (IFN-α, IFN-β, IFN-γ, etc.), growth factors (EGF, FGF, IGF, NGF, PDGF, TGF, HGF, etc.), tumor necrosis factors (TNF-α and TNF-β), lymphotoxin, erythropoietin, leptin, SCF, TPO, MCAF, and BMP.

Examples of chemokines include CC chemokines such as CCL1 to CCL28, CXC chemokines such as CXCL1 to CXCL17, C chemokines such as XCL1 and XCL2, and CX3C chemokines such as CX3CL1.

Examples of receptors include receptors belonging to receptor families such as the hematopoietic growth factor receptor family, cytokine receptor family, tyrosine kinase-type receptor family, serine/threonine kinase-type receptor family, TNF receptor family, G protein-coupled receptor family, GPI anchor-type receptor family, tyrosine phosphatase-type receptor family, adhesion factor family, and hormone receptor family. The receptors belonging to these receptor families and their characteristics have been described in many documents such as Cooke BA., King RJB., van der Molen HJ. ed. New Comprehesive Biochemistry Vol.18B "Hormones and their Actions Part II" pp.1-46 (1988) Elsevier Science Publishers BV; Patthy (Cell (1990) 61 (1): 13-14); Ullrich *et al.* (Cell (1990) 61 (2): 203-212); Massagué (Cell (1992) 69 (6): 1067-1070); Miyajima *et al.* (Annu. Rev. Immunol. (1992) 10: 295-331); Taga *et al.* (FASEB J. (1992) 6, 3387-3396); Fantl *et al.* (Annu. Rev. Biochem. (1993), 62: 453-481); Smith *et al.* (Cell (1994) 76 (6): 959-962); and Flower DR. (Biochim. Biophys. Acta (1999) 1422 (3): 207-234).

Examples of specific receptors belonging to the above-mentioned receptor families preferably include human or mouse erythropoietin (EPO) receptors (Blood (1990) 76 (1): 31-35; and Cell (1989) 57 (2): 277-285), human or mouse granulocyte-colony stimulating factor (G-CSF) receptors (Proc. Natl. Acad. Sci. USA. (1990) 87 (22): 8702-8706, mG-CSFR; Cell (1990) 61 (2): 341-350), human or mouse thrombopoietin (TPO) receptors (Proc Natl Acad Sci U S A. (1992) 89 (12): 5640-5644; EMBO J. (1993) 12(7): 2645-53), human or mouse insulin receptors (Nature (1985) 313 (6005): 756-761), human or mouse Flt-3 ligand receptors (Proc. Natl. Acad. Sci. USA. (1994) 91 (2): 459-463), human or mouse platelet-derived growth factor (PDGF) receptors (Proc. Natl. Acad. Sci. USA. (1988) 85 (10): 3435-3439), human or mouse interferon

(IFN)-α and β receptors (Cell (1990) 60 (2): 225-234; and Cell (1994) 77 (3): 391-400), human or mouse leptin receptors, human or mouse growth hormone (GH) receptors, human or mouse interleukin (IL)-10 receptors, human or mouse insulin-like growth factor (IGF)-I receptors, human or mouse leukemia inhibitory factor (LIF) receptors, and human or mouse ciliary neurotrophic factor (CNTF) receptors.

Cancer antigens are antigens that are expressed as cells become malignant, and they are also called tumor-specific antigens. Abnormal sugar chains that appear on cell surfaces or protein molecules when cells become cancerous are also cancer antigens, and they are also called sugar-chain cancer antigens. Examples of cancer antigens preferably include GPC3 which is a receptor belonging to the GPI anchor-type receptor family mentioned above, and is also expressed in several cancers including liver cancer (Int J Cancer. (2003) 103 (4): 455-65), as well as EpCAM which is expressed in several cancers including lung cancer (Proc Natl Acad Sci USA. (1989) 86 (1): 27-31), CA19-9, CA15-3, and sialyl SSEA-1 (SLX).

MHC antigens are roughly classified into MHC class I antigens and MHC class II antigens. MHC class I antigens include HLA-A, -B, -C, -E, -F, -G, and -H, and MHC class II antigens include HLA-DR, -DQ, and -DP.

Differentiation antigens may include CD1, CD2, CD4, CD5, CD6, CD7, CD8, CD10, CD11a, CD11b, CD11c, CD13, CD14, CD15s, CD16, CD18, CD19, CD20, CD21, CD23, CD25, CD28, CD29, CD30, CD32, CD33, CD34, CD35, CD38, CD40, CD41a, CD41b, CD42a, CD42b, CD43, CD44, CD45, CD45RO, CD48, CD49a, CD49b, CD49c, CD49d, CD49e, CD49f, CD51, CD54, CD55, CD56, CD57, CD58, CD61, CD62E, CD62L, CD62P, CD64, CD69, CD71, CD73, CD95, CD102, CD106, CD122, CD126, and CDw130.

Immunoglobulins include IgA, IgM, IgD, IgG, and IgE. Immunocomplexes at least contain any component of an immunoglobulin.

Variable regions that constitute the antibodies of the present invention may be variable regions that recognize any antigen. One or more amino acid residue alterations are allowed in the amino acid sequences constituting the antibody variable regions as long as their antigen-binding activities are maintained. When altering a variable region amino acid sequence, there is no particularly limitation on the site of alteration and number of amino acids altered. For example, amino acids present in CDR and/or FR can be altered appropriately. When altering amino acids in a variable region, the binding activity is preferably maintained without particular limitation; and for example, as compared to before alteration, the binding activity is 50% or more, preferably 80% or more, and more preferably 100% or more. Furthermore, the binding activity may be increased by amino acid alterations. For example, the binding activity may be 2-, 5-, 10-times higher or such than that before alteration.

When the antigen is a soluble antigen, KD (dissociation constant) can be used as a value representing the antigen-binding activity of an antibody of the present invention. When the antigen is a membrane antigen, apparent KD (apparent dissociation constant) can be used. KD (dissociation constant) and apparent KD (apparent dissociation constant) can be determined by methods known to those skilled in the art, such as Biacore (GE Healthcare), Scatchard plot, and flow cytometer.

As another index for comparing the antigen-binding activity of the antibodies of the present invention, for example, k_d (dissociation rate constant) can be used when the antigen is a soluble antigen, whilst apparent k_d (apparent dissociation rate constant) can be used when the antigen is a membrane antigen. k_d (dissociation rate constant) and apparent k_d (apparent dissociation rate constant) can be determined by methods known to those skilled in the art, such as Biacore (GE Healthcare) and flow cytometer.

In the antibodies of the present invention, alteration of amino acid sequence may be at least one of amino acid residue substitution, addition, deletion, and modification. There is no particular limitation on positions to be altered and the number of amino acids to be altered. Generally, 50 amino acids or less, preferably 30 amino acids or less, more preferably 10 amino acids or less (for example, 5 amino acids or less, or 3 amino acids or less) may be altered. Alternatively, for example, alteration of 20% or less amino acid residues, or specifically 10% or less amino acid residues (for example, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% or less) in the whole amino acid sequence is acceptable. In other words, antibodies containing an amino acid sequence sharing a homology (identity) of preferably 80% or higher, more preferably 90% or higher (for example, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or higher) with the original amino acid sequence are also included in the antibodies of the present invention.

For example, the modification of the N-terminal glutamine of a variable region into pyroglutamic acid by pyroglutamylation is a modification well known to those skilled in the art. Thus, when the heavy-chain N terminus is glutamine, the antibodies of the present invention also include the variable regions in which the glutamine is modified to pyroglutamic acid.

Antibody variable regions of the present invention may have any sequences, and they may be antibody variable regions of any origin, such as mouse antibodies, rat antibodies, rabbit antibodies, goat antibodies, camel antibodies, humanized antibodies produced by humanizing these non-human antibodies, and human antibodies. "Humanized antibodies", also referred to as "reshaped human antibodies", are antibodies in which the complementarity determining regions (CDRs) of an antibody derived from a non-human mammal, for example, a mouse antibody, are transplanted into the CDRs of a human antibody. Methods for identifying CDRs are known (Kabat *et al.*, Sequence of Proteins of Immunological Interest (1987), National Institute of Health, Bethesda, Md.; Chothia *et al.*, Nature (1989) 342: 877). Their common genetic

recombination techniques are also known (see, European Patent Application Publication No. EP 125023 and WO 96/02576). Furthermore, these antibodies may have various amino acid substitutions introduced into their variable regions to improve their antigen binding, pharmacokinetics, stability, and antigenicity. Variable regions of the antibodies of the present invention may be able to bind antigens repeatedly due to their pH dependability in antigen binding (WO 2009/125825).

There are κ chain and λ chain types in antibody light-chain constant regions, but any light chain constant regions may be used. Furthermore, light-chain constant regions of the present invention may be light-chain constant regions with amino acid alterations such as substitutions, deletions, additions, and/or insertions.

For the heavy chain Fc regions of an antibody of the present invention, for example, heavy chain Fc regions of human IgG antibodies may be used. Preferred heavy chain Fc regions are those of human IgG1 antibodies and human IgG4 antibodies.

Furthermore, polypeptides of the present invention may be made into Fc fusion protein molecules by linking to other proteins, physiologically active peptides, and such.

Examples of the other proteins and biologically active peptides include receptors, adhesion molecules, ligands, and enzymes, but are not limited thereto.

Preferred examples of Fc fusion protein molecules of the present invention include proteins with Fc region fused to a receptor protein that binds to a target, and such examples include TNFR-Fc fusion protein, IL1R-Fc fusion protein, VEGFR-Fc fusion protein, and CTLA4-Fc fusion protein (Nat Med. 2003 Jan; 9(1): 47-52; BioDrugs. 2006; 20(3): 151-60). Furthermore, a protein to be fused to a polypeptide of the present invention may be any molecule as long as it binds to a target molecule, and examples include scFv molecules (WO 2005/037989), single-domain antibody molecules (WO 2004/058821; WO 2003/002609), antibody-like molecules (Current Opinion in Biotechnology 2006, 17: 653-658; Current Opinion in Biotechnology 2007, 18: 1-10; Current Opinion in Structural Biology 1997, 7: 463-469; and Protein Science 2006, 15: 14-27) such as DARPins (WO 2002/020565), Affibody (WO 1995/001937), Avimer (WO 2004/044011; WO 2005/040229), and Adnectin (WO 2002/032925). Furthermore, antibodies and Fc fusion protein molecules may be multispecific antibodies that bind to multiple types of target molecules or epitopes.

Furthermore, the antibodies of the present invention include antibody modification products. Such antibody modification products include, for example, antibodies linked with various molecules such as polyethylene glycol (PEG) and cytotoxic substances. Such antibody modification products can be obtained by chemically modifying antibodies of the present invention. Methods for modifying antibodies are already established in this field.

The antibodies of the present invention may also be bispecific antibodies. "Bispecific antibody" refers to an antibody that has in a single molecule variable regions that recognize different epitopes. The epitopes may be present in a single molecule or in different molecules.

The polypeptides of the present invention can be prepared by the methods known to those skilled in the art. For example, the antibodies can be prepared by the methods described below, but the methods are not limited thereto

A DNA encoding an antibody heavy chain in which one or more amino acid residues in the Fc region have been substituted with other amino acids of interest and DNA encoding an antibody light chain, are expressed. A DNA encoding a heavy chain in which one or more amino acid residues in the Fc region are substituted with other amino acids of interest can be prepared, for example, by obtaining a DNA encoding the Fc region of a natural heavy chain, and introducing an appropriate substitution so that a codon encoding a particular amino acid in the Fc region encodes another amino acid of interest.

Alternatively, a DNA encoding a heavy chain in which one or more amino acid residues in the Fc region are substituted with other amino acids of interest can also be prepared by designing and then chemically synthesizing a DNA encoding a protein in which one or more amino acid residues in the Fc region of the natural heavy chain are substituted with other amino acids of interest. The position and type of amino acid substitution are not particularly limited. Furthermore, alteration is not limited to substitution, and alteration may be any of deletion, addition, or insertion, or combination thereof.

Alternatively, a DNA encoding a heavy chain in which one or more amino acid residues in the Fc region are substituted with other amino acids of interest can be prepared as a combination of partial DNAs. Such combinations of partial DNAs include, for example, the combination of a DNA encoding a variable region and a DNA encoding an Fc region, and the combination of a DNA encoding an Fab region and a DNA encoding an Fc region, but are not limited thereto. Furthermore, a DNA encoding a light chain can similarly be prepared as a combination of partial DNAs.

Methods for expressing the above-described DNAs include the methods described below. For example, a heavy chain expression vector is constructed by inserting a DNA encoding a heavy chain variable region into an expression vector along with a DNA encoding a heavy chain Fc region. Likewise, a light chain expression vector is constructed by inserting a DNA encoding a light chain variable region into an expression vector along with a DNA encoding a light chain Fc region. Alternatively, these heavy and light chain genes may be inserted into a single vector.

When inserting a DNA encoding the antibody of interest into an expression vector, the DNA is inserted so that the antibody is expressed under the control of an expression-regulating

region such as an enhancer or promoter. Next, host cells are transformed with this expression vector to express the antibody. In such cases, an appropriate combination of host and expression vector may be used.

Examples of the vectors include M13 vectors, pUC vectors, pBR322, pBluescript, and pCR-Script. Alternatively, when aiming to subclone and excise cDNA, in addition to the vectors described above, pGEM-T, pDIRECT, pT7, and such can be used.

Expression vectors are particularly useful when using vectors for producing the polypeptides of the present invention. For example, when a host cell is *E. coli* such as JM109, DH5α, HB101, and XL1-Blue, the expression vectors must carry a promoter that allows efficient expression in *E. coli*, for example, lacZ promoter (Ward *et al.*, Nature (1989) 341: 544-546; FASEB J. (1992) 6: 2422-2427; its entirety are incorporated herein by reference), araB promoter (Better *et al.*, Science (1988) 240: 1041-1043; its entirety are incorporated herein by reference), T7 promoter, or such. Such vectors include pGEX-5X-1 (Pharmacia), "QIAexpress system" (Qiagen), pEGFP, or pET (in this case, the host is preferably BL21 that expresses T7 RNA polymerase) in addition to the vectors described above.

The vectors may contain signal sequences for polypeptide secretion. As a signal sequence for polypeptide secretion, a pelB signal sequence (Lei, S. P. *et al* J. Bacteriol. (1987) 169: 4379; its entirety are incorporated herein by reference) may be used when a polypeptide is secreted into the *E. coli* periplasm. The vector can be introduced into host cells by lipofectin method, calcium phosphate method, and DEAE-Dextran method, for example.

In addition to *E. coli* expression vectors, the vectors for producing the polypeptides of the present invention include mammalian expression vectors (for example, pcDNA3 (Invitrogen), pEGF-BOS (Nucleic Acids. Res. 1990, 18(17): p5322; its entirety are incorporated herein by reference), pEF, and pCDM8), insect cell-derived expression vectors (for example, the "Bac-to-BAC baculovirus expression system" (Gibco-BRL) and pBacPAK8), plant-derived expression vectors (for example, pMH1 and pMH2), animal virus-derived expression vectors (for example, pHSV, pMV, and pAdexLcw), retroviral expression vectors (for example, pZIPneo), yeast expression vectors (for example, "Pichia Expression Kit" (Invitrogen), pNV11, and SP-Q01), and *Bacillus subtilis* expression vectors (for example, pPL608 and pKTH50), for example.

When aiming for expression in animal cells such as CHO, COS, and NIH3T3 cells, the vectors must have a promoter essential for expression in cells, for example, SV40 promoter (Mulligan *et al.*, Nature (1979) 277: 108; its entirety are incorporated herein by reference), MMTV-LTR promoter, EF1α promoter (Mizushima *et al.*, Nucleic Acids Res. (1990) 18: 5322; its entirety are incorporated herein by reference), CAG promoter (Gene. (1990) 18: 5322; its entirety are incorporated herein by reference), and CMV promoter, and more preferably they have a gene for selecting transformed cells (for example, a drug resistance gene that allows

evaluation using an agent (neomycin, G418, or such)). Vectors with such characteristics include pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, and pOP13, for example.

In addition, the following method can be used for stable gene expression and gene copy number amplification in cells: CHO cells deficient in a nucleic acid synthesis pathway are introduced with a vector that carries a DHFR gene which compensates for the deficiency (for example, pCHOI), and the vector is amplified using methotrexate (MTX). Alternatively, the following method can be used for transient gene expression: COS cells with a gene expressing SV40 T antigen on their chromosome are transformed with a vector with an SV40 replication origin (pcD and such). Replication origins derived from polyoma virus, adenovirus, bovine papilloma virus (BPV), and such can also be used. To amplify gene copy number in host cells, the expression vectors may further carry selection markers such as aminoglycoside transferase (APH) gene, thymidine kinase (TK) gene, *E. coli* xanthine-guanine phosphoribosyltransferase (Ecogpt) gene, and dihydrofolate reductase (dhfr) gene.

Antibodies can be collected, for example, by culturing transformed cells, and then separating the antibodies from the inside of the transformed cells or from the culture media. Antibodies can be separated and purified using an appropriate combination of methods such as centrifugation, ammonium sulfate fractionation, salting out, ultrafiltration, 1q, FcRn, protein A, protein G column, affinity chromatography, ion exchange chromatography, and gel filtration chromatography.

Furthermore, the present invention provides methods for altering a polypeptide to produce a polypeptide with improved stability as compared to the parent polypeptide. Thus, the present invention relates to methods for improving the stability of a polypeptide having an antibody Fc region as compared to the parent polypeptide by introducing at least one amino acid alteration in a loop region of the Fc region. In the present methods, melting temperature (Tm) is preferably used as an index for evaluating or judging the stability.

In addition, the present invention provides methods for producing a polypeptide with improved stability as compared to a parent polypeptide.

As an embodiment of the production methods of the present invention, for example, a method for producing a polypeptide which has an antibody Fc region, at least one of whose amino acids in a loop region of the Fc region is altered, and which has improved stability as compared to the parent antibody, is provided.

For example, such methods include methods including the following steps:

(a) adding at least one amino acid alteration to the Fc region of a polypeptide having an antibody Fc region;

(b) measuring the stability of the polypeptide altered in step (a); and

(c) selecting a polypeptide with improved stability as compared to the parent polypeptide.

Preferred embodiments include a method for producing a polypeptide which has antibody Fc region, at least one of whose amino acids in a loop region of the Fc region is altered, and which has improved stability as compared to the parent polypeptide, wherein the method includes the following steps:

(a) altering a nucleic acid encoding the polypeptide so that its stability is improved as compared to the parent peptide;

(b) introducing the nucleic acid into host cells and culturing them to induce expression; and

(c) collecting the polypeptide from the host cell culture.

Furthermore, polypeptides (antibodies) and Fc fusion protein molecules produced by this production method are also included in the present invention.

In preferred embodiments of the above-mentioned methods, for example, a nucleic acid encoding a polypeptide having an Fc region of antibody (such as human IgG) such that at least one or more amino acids are altered at amino acid position(s) of the loop region of the Fc region 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).

In the above-mentioned methods or production methods (which may be simply referred to as "methods"), it is preferred to further reduce the binding activity towards FcγR. In order to make modifications to maintain or enhance the binding activity towards FcγR as compared to the parent polypeptide, for example, the steps of altering the amino acid alteration sites of TS1-TS8, TS20-TS27, TS44-TS50, TS52-TS55, and TS57-TS67 as shown in the Examples described below, may be included.

Alternatively, it is preferred to further maintain or enhance the binding activity towards FcγR in the above-mentioned methods. In order to make modifications to reduce the binding activity towards FcγR as compared to the parent polypeptide, for example, the steps of altering

the amino acid alteration sites of TS9-19, TS28-43, TS51, and TS56 as shown in the Examples described below, may be included.

The alteration sites of TS1-TS67 are as mentioned above.

In the above-mentioned methods, for example, it is preferred to alter amino acids in a polypeptide that has an Fc region of antibody (such as human IgG).

Furthermore, the present invention provides nucleic acids encoding a polypeptide which has an antibody Fc region, at least one of whose amino acids in a loop region of the Fc region is altered, and which has improved stability as compared to the parent polypeptide. The nucleic acids of the present invention may be in any form such as DNA and RNA.

The present invention also provides vectors carrying the above-described nucleic acids of the present invention. The type of vector can be appropriately selected by those skilled in the art depending on the host cells to be introduced with the vector. The vectors include, for example, those described above.

Furthermore, the present invention relates to host cells transformed with the above-described vectors of the present invention. Appropriate host cells can be selected by those skilled in the art. The host cells include, for example, those described above.

<Pharmaceutical compositions>

The present invention provides pharmaceutical compositions comprising a polypeptide or Fc fusion protein molecule of the present invention.

The pharmaceutical compositions of the present invention can be formulated, in addition to a polypeptide or Fc-fusion protein molecule of the present invention described above, with pharmaceutically acceptable carriers by known methods. For example, the compositions can be used parenterally, when the antibodies are formulated in a sterile solution or suspension for injection using water or any other pharmaceutically acceptable liquid. For example, the compositions can be formulated by appropriately combining the antibodies or Fc-fusion protein molecules with pharmaceutically acceptable carriers or media, specifically, sterile water or physiological saline, vegetable oils, emulsifiers, suspending agents, surfactants, stabilizers, flavoring agents, excipients, vehicles, preservatives, binding agents, and such, by mixing them at a unit dose and form required by generally accepted pharmaceutical implementations. Specific examples of the carriers include light anhydrous silicic acid, lactose, crystalline cellulose, mannitol, starch, carmellose calcium, carmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylacetal diethylaminoacetate, polyvinylpyrrolidone, gelatin, medium-chain triglyceride, polyoxyethylene hardened castor oil 60, saccharose, carboxymethyl cellulose, corn starch, inorganic salt, and such. The content of the active ingredient in such a formulation is adjusted so that an appropriate dose within the required range

can be obtained.

Sterile compositions for injection can be formulated using vehicles such as distilled water for injection, according to standard protocols.

Aqueous solutions used for injection include, for example, physiological saline and isotonic solutions containing glucose or other adjuvants such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride. These can be used in conjunction with suitable solubilizers such as alcohol, specifically ethanol, polyalcohols such as propylene glycol and polyethylene glycol, and non-ionic surfactants such as Polysorbate 80™ and HCO-50.

Oils include sesame oils and soybean oils, and can be combined with solubilizers such as benzyl benzoate or benzyl alcohol. These may also be formulated with buffers, for example, phosphate buffers or sodium acetate buffers; analgesics, for example, procaine hydrochloride; stabilizers, for example, benzyl alcohol or phenol; or antioxidants. The prepared injections are typically aliquoted into appropriate ampules.

The administration is preferably carried out parenterally, and specifically includes injection, intranasal administration, intrapulmonary administration, and percutaneous administration. For example, injections can be administered systemically or locally by intravenous injection, intramuscular injection, intraperitoneal injection, or subcutaneous injection.

Furthermore, the method of administration can be appropriately selected according to the age and symptoms of the patient. A single dosage of the pharmaceutical composition containing an antibody or a polynucleotide encoding an antibody can be selected, for example, from the range of 0.0001 to 1,000 mg per kg of body weight. Alternatively, the dosage may be, for example, in the range of 0.001 to 100,000 mg/patient. However, the dosage is not limited to these values. The dosage and method of administration vary depending on the patient's body weight, age, and symptoms, and can be appropriately selected by those skilled in the art.

In the present invention, pharmaceutical compositions containing a polypeptide of the present invention mentioned above are useful as an active ingredient of therapeutic agents or preventive agents for immunological inflammatory diseases, cancer, and such. Without being limited thereto, the term "immunological inflammatory diseases" includes rheumatoid arthritis, autoimmune hepatitis, autoimmune thyroiditis, autoimmune blistering diseases, autoimmune adrenocortical disease, 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 mycloma, 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,

lens-induced uveitis, systemic lupus erythematosus, allergic rhinitis, allergic dermatitis, ulcerative colitis, hypersensitivity, asthma, muscle degeneration, cachexia, systemic scleroderma, localized scleroderma, Sjogren's syndrome, Behchet's disease, Reiter's syndrome, type I and type II diabetes, bone resorption disorder, 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, idiopathic thrombocytopenia, Goodpasture's syndrome, Guillain-Barre syndrome, Hashimoto's thyroiditis, pemphigus, IgA nephropathy, pollinosis, antiphospholipid antibody syndrome, polymyositis, Wegener's granulomatosis, arteritis nodosa, mixed connective tissue disease, and fibromyalgia.

In the present invention, "cancer" means a physiological state in mammals that is typically characterized by uncontrolled cell growth, or refers to such a physiological state. In the present invention, the type of cancer is not particularly limited, but includes the following. Carcinoma (epithelial cancer) includes 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 cancer, renal cancer, and other glandular tissue cancers. Sarcoma (non-epithelial cancer) includes liposarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, angiosarcoma, fibrosarcoma, malignant peripheral nerve tumor, gastrointestinal stromal tumor, desmoid tumor, Ewing's sarcoma, osteosarcoma, chondrosarcoma, leukemia, lymphoma, myeloma, and other solid organ tumors such as melanoma and brain tumor.

As used herein, the three-letter and single-letter codes for respective amino acids are as follows:

Alanine: Ala (A)
Arginine: Arg (R)
Asparagine: Asn (N)
Aspartic acid: Asp (D)
Cysteine: Cys (C)
Glutamine: Gln (Q)
Glutamic acid: Glu (E)
Glycine: Gly (G)
Histidine: His (H)
Isoleucine: Ile (I)
Leucine: Leu (L)
Lysine: Lys (K)
Methionine: Met (M)
Phenylalanine: Phe (F)

Proline: Pro (P)
Serine: Ser (S)
Threonine: Thr (T)
Tryptophan: Trp (W)
Tyrosine: Tyr (Y)
Valine: Val (V)

All prior art documents cited herein are incorporated by reference in their entirety.

Examples

Herein below, the present invention will be specifically described with reference to the Examples, but it is not to be construed as being limited thereto. In the present Examples, the sites of amino acids modified in the Fc region were numbered according to the EU numbering system (see, Sequences of proteins of immunological interest, NIH Publication No. 91-3242).

[Example 1] Improvement of thermal stability through modification of the CH2 domain loop region

Generally, β sheet structure is known to readily undergo structural changes and reduction in thermal stability by amino acid mutations (Biochemistry 1994; 33:5510-5517; and Nature 1994; 367:660-663). Therefore, in the present invention, the loop regions of the Fc region were selected for mutagenesis to improve the thermal stability.

The amino acids of L234-S239, D265-P271, Q295, Y296, S298, Y300, S324-S337 in the loop region of the CH2 domain of Fc region B3 (SEQ ID NO: 16) were substituted with each of 18 amino acids not including the original amino acid and cysteine, to produce Fc mutants (Fig. 4). These are called Fc variants. Anti-GPC3 antibodies were produced using these Fc variants. Antibodies composed of an H chain which consists of variable region GpH7 (SEQ ID NO: 17) and an Fc variant as the Fc region and an L chain which consists of variable region GpL16 (SEQ ID NO: 18) and constant region k0 (SEQ ID NO: 19) (hereinafter denoted as GpH7-Fc variant/GpL16-k0) were produced according to the method of Reference Example 1.

The melting temperature (Tm) of the produced antibodies was evaluated according to the method of Reference Example 2. In the following, unless otherwise noted, "Tm" refers to the Tm of the CH2 domain when a sample in the form of IgG was subjected to measurement. The obtained Tm data are shown in Fig. 1.

The Tm of B3, which did not contain mutations (GpH7-B3/GpL16-k0: GpH7(SEQ ID NO: 17), B3 (SEQ ID NO: 16), GpL16(SEQ ID NO: 18), k0(SEQ ID NO: 19)), was approximately 68°C, and mutants showing a higher Tm than this value are shown in Tables 1-1 and 1-2.

Table 1-1

Mutated residue	Amino acid after mutation	Tm (°C)
L234	G	69.5
	A	68.8
	V	69.7
	F	68.5
	P	68.9
	M	68.9
	I	69.1
	K	70.8
	R	70.3
	S	69.3
	T	69.2
	Y	69.0
	H	69.0
	N	69.1
	Q	69.4
	W	68.9
L235	G	69.0
	A	68.8
	V	69.2
	F	68.9
	P	68.9
	M	69.0
	I	69.1
	K	70.7
	R	70.6
	S	68.9
	T	68.4
	Y	68.8
	N	68.1
G236	A	68.4
	P	68.9
	L	68.4
	K	69.3
	R	68.6
	T	68.9
	H	68.2
	N	68.1

Mutated residue	Amino acid after mutation	Tm (°C)
G237	R	70.1
P238	I	68.1
S239	M	68.4
	K	73.2
	R	72.2
	T	68.2
	H	68.2
	Q	71.2
D265	G	69.0
V266	I	69.1
	L	69.7
S267	P	70.4
	K	68.5
H268	A	68.5
	V	68.1
	F	69.6
	P	69.9
	M	70.0
	I	69.6
	L	69.9
	K	70.4
	R	69.2
	T	68.1
	Y	68.5
	Q	68.7
	W	68.5
E269	A	68.6
	V	68.2
	D	68.6
	K	68.3
	R	68.9
	S	68.7
	T	68.1
	H	68.6

Table 1-2 is a continuation of Table 1-1.

Table 1-2

Mutated residue	Amino acid after mutation	Tm (°C)
D270	A	70.0
	F	71.4
	M	69.2
	E	69.3
	T	68.6
	Y	71.2
	H	71.4
	N	70.2
	Q	68.4
	W	70.4
P271	D	68.4
Q295	M	70.8
	L	69.8
Y296	G	70.9
	F	69
	D	69.6
	E	69
	S	70.6
	T	68.3
	N	69.9
	Q	70.8
S298	G	72
	A	68.1
	F	68.7
	M	69.7
Y300	G	68.5
	P	69.9
	D	68.4
	E	68.6
S324	F	69
	I	68.4
	K	68.2
	R	68.8
	Y	68.6
	H	69.3
	N	69.7

Mutated residue	Amino acid after mutation	Tm (°C)
N325	G	71.4
	A	69.9
	V	70.1
	F	68.7
	M	71.2
	I	70.3
	L	70.4
	S	71
	T	70.9
	H	71.3
K326	G	69.6
	A	69.2
	P	68.4
	R	68.8
	S	69.8
	N	68.9
A327	F	68.6
	M	69
	L	69.4
	K	68.4
	R	69.1
	N	68.2
P329	A	68.7
A330	V	68.5
	M	68.2
	I	68.2
	K	68.2
	Y	69
	H	69.5
	N	68.2
E333	V	68.4
	Q	68.4
T335	V	68.4
S337	R	68.1

[Example 2] Preparation and evaluation of IgG1 with novel Fc regions that improve thermal stability

Based on the data from Example 1 and structural information (Nature 2000; 406: 267-273), several mutations presumed to be particularly effective for improving thermal stability were selected. One or more of the selected mutations were introduced into the H chains of the anti-GPC3 antibody (GpH7-G1d/GpL16-k0:GpH7 (SEQ ID NO: 17), G1d (SEQ ID NO: 15), GpL16 (SEQ ID NO: 18), k0 (SEQ ID NO: 19)) and the anti-IL6R antibody (MH0-G1d/ML0-k0:GpH7 (SEQ ID NO: 17), G1d (SEQ ID NO: 15), ML0 (SEQ ID NO: 21), k0 (SEQ ID NO: 19)) to produce TS1 to TS19 (SEQ ID NOs: 26-44) shown in Table 2. At the same time, to evaluate effects on improvement of thermal stability by introduction of disulfide bond(s) in IgG form, the mutations of m01 and m02 reported in a prior document (J Biol. Chem. 2009; 284: 14203-14210) were introduced to the H chain of anti-IL6R to produce the TSm01 and TSm02 variants (SEQ ID NOs: 24 and 25). Each antibody was expressed and purified by the method of Reference Example 1.

Table 2

Variant name	Alteration sites	SEQ ID NO:
G1d	WT	15
TS01	L234I	26
TS02	V266I/H268Q/E269D/D270E	27
TS03	Q295M	28
TS04	Q295M/Y300E	29
TS05	Q295L	30
TS06	K326S/A330H	31
TS07	K326S/S324H/A330H	32
TS08	K326A/A330Y	33
TS09	L234K/L235K	34
TS10	L234K/L235R	35
TS11	L234R/L235K	36
TS12	L234R/L235R	37
TS13	S267P/H268M/D270F	38
TS14	H268M/D270F	39
TS15	H268K/D270F	40
TS16	Q295M/Y296G/S298G	41
TS17	S239K/N325G	42
TS18	S239K/N325M	43
TS19	S239K/N325H	44
TSm01	L242C/K334C	24
TSm02	V240C/K334C	25

Using the prepared antibodies, Tm values were compared by the method described in Reference Example 2. The results of Tm measurements are shown in Table 3.

Table 3

	Tm(°C)	
Constant region name	anti-GPC3	anti-IL6R
TS1	69.5	70.5
TS2	69.8	70.7
TS3	71.1	72.4
TS4	62.8	63.1
TS5	70.1	71.4
TS6	70.4	71.6
TS7	69.8	70.8
TS8	70.0	71.0
TS9	n.t.	73.4
TS10	71.6	73.8
TS11	71.8	73.7
TS12	71.9	73.9
TS13	73.7	78.4
TS14	72.3	74.2
TS15	72.5	75.3
TS16	73.5	80.0
TS17	74.2	78.9
TS18	73.6	77.9
TS19	73.7	78.6
B3	69.1	n.t.
TSm01	n.t.	n.d.
TSm02	n.t.	74.5
G1	69.4	70.4

In the results, the samples that were not evaluated are indicated as "n.t." (not tested), and the samples for which Tm was difficult to detect are indicated as "n.d." (not detected).

From the variants of TS1-TS19, the variants of TS1-3 and TS5-19 showed improvement of Tm when both the H chain sequence of anti-GPC3 and that of anti-IL6R were used. On the

other hand, TS4 showed a decrease in Tm for both H chain sequences. The alteration of Q295M, which was introduced into TS4, improved Tm by approximately 2°C by itself alone (TS3), but was found to result in decreased Tm when the Y300E alteration was simultaneously introduced. According to the structural information, Q295 and Y300 are located opposite to each other on the same loop. The Q295M substitution may enhance the amino acid side chain interaction with Y300. However, it is speculated that simultaneous introduction of the Q295M and Y300E substitutions eliminated the interaction between the amino acid side chains.

As shown above, it was demonstrated that a combination of mutations improving Tm further improves Tm except for mutations having bad influence on structure. As such, in addition to TS1-3 and TS5-19 disclosed herein, it is possible to produce more combinations of Tm-improving alterations based on structural information.

With regard to TSm01 and TSm02, which were evaluated at the same time, the prior document (J Biol. Chem. 2009; 284:14203-14210) demonstrated that they increased Tm about 10°C to 20°C when the CH2 domain alone was expressed and evaluated for Tm. However, in the present examination where they were evaluated for Tm in the IgG form, multiple denaturation points were detected for TSm01, and it was difficult to clearly determine the thermal denaturation of the CH2 domain. This suggests a high possibility that TSm01 is structurally heterogeneous.

Furthermore, the Tm of TSm02 increased only by approximately 4°C as compared to that of IgG1. This demonstrates that the introduction of disulfide bonds is less effective in improving Tm in the IgG form, and the mutations found by the present inventors are more effective for improving Tm.

Tm of Fab of the anti-GPC3 antibody used in this examination is 74.7°C. Therefore, with regard to TS13 to TS19, in which mutations have been introduced into the H chain of anti-GPC3, it was presumed that the fluorescence transition curves of CH2 and Fab would overlap, making accurate calculation of Tm difficult. Accordingly, as it was considered inappropriate to use the H chain of anti-GPC3 to test combinations effect on Tm, subsequent examinations were carried out using the H chain of anti-IL6R.

[Example 3] Assessment of binding of novel Fc regions to human Fcγ receptors

Regarding modification of antibody Fc regions, there are reports of Fc regions with enhanced or reduced effector functions such as ADCC activity (reference: current opinion, 2009, 20, 685-691). Antibodies with enhanced effector functions may be useful mainly as antibodies for cancer therapy, and antibodies with reduced effector functions may be useful as, for example, neutralizing antibodies or receptor-Fc fusions such as Enbrel and Orencis. It is important that they are used appropriately depending on their respective purposes.

The CH2 domain, which was modified in this examination, is known to be involved in interaction with several human Fcγ receptors (hereinafter denoted as hFcgRs) which affect effector functions. Therefore, the binding of TS1 and TS19 prepared by using the H chain of anti-IL6R produced in Example 2 to hFcgRs was measured, according to the method described in Reference Example 3. The measurement results are summarized in Table 4, where the binding of each antibody to each hFcgR relative to the binding of G1 to each hFcgR, which was taken as 100, was calculated.

Table 4

Variant name	hFcgRIa	hFcgRIIa(R)	hFcgRIIa(H)	hFcgRIIb	hFcgRIIIa(F)	hFcgRIIIa(V)
TS1	96.5	67.0	76.8	61.5	62.4	83.5
TS2	98.3	67.3	123.0	61.6	159.0	130.0
TS3	97.5	89.6	115.3	84.2	63.8	90.1
TS4	99.3	148.4	105.9	219.9	73.9	99.2
TS5	97.3	128.8	142.1	157.5	86.6	106.1
TS6	100.8	122.7	120.3	142.2	103.0	90.6
TS7	99.8	116.6	118.1	125.9	98.8	86.2
TS8	102.3	119.9	100.6	132.3	164.6	124.4
TS9	-1.9	1.3	0.5	1.4	1.1	0.5
TS10	0.2	1.4	0.7	3.0	2.2	1.1
TS11	-0.2	1.5	1.3	3.4	2.6	1.4
TS12	-1.0	0.6	0.9	2.8	1.6	1.1
TS13	63.0	1.2	1.2	3.4	1.8	1.4
TS14	87.1	3.4	29.4	7.1	5.5	10.1
TS15	80.8	4.5	30.6	9.1	5.9	10.1
TS16	96.8	25.3	15.9	21.7	13.8	28.9
TS17	9.0	2.7	1.0	6.0	4.4	1.9
TS18	11.5	7.9	2.3	10.9	3.9	1.8
TS19	10.7	3.5	2.3	8.1	3.8	4.2

The results showed that while the binding of TS1 to TS8 to hFcgRs was equivalent to that of G1, the binding of TS9-19 to hFcgRs was weaker than that of G1.

[Example 4] Production and evaluation of novel Fc regions with combined mutations that maintain binding ability to hFcgRs

When mutations with improving stability are introduced, it is important that antibodies for cancer therapy, whose effector functions are important, retain binding ability to hFcgRs. The mutations of TS1 to TS8, which were found to maintain binding ability to hFcgRs in Example 3, were combined to produce new variants TS20 to TS27 as shown in Table 5 (SEQ ID NOs: 45 to

52). Each antibody was expressed and purified by the method described in Reference Example 1. The prepared antibodies were subjected to Tm assessment by the method of Reference Example 2, and the results are shown in Table 6.

Table 5

Variant name	Alteration sites	SEQ ID NO:
TS20	Q295M/K326S/A330H	45
TS21	Q295M/K326A/A330Y	46
TS22	Q295L/K326S/A330H	47
TS23	Q295L/K326A/A330Y	48
TS24	Q295M/K326S/A330Y	49
TS25	Q295M/K326A/A330H	50
TS26	Q295L/K326S/A330Y	51
TS27	Q295L/K326A/A330H	52

Table 6

Variant name	Tm (°C)
TS20	73.4
TS21	72.8
TS22	72.3
TS23	71.7
TS24	73.4
TS25	72.8
TS26	72.2
TS27	71.7
G1	70.4

Furthermore, binding ability to hFcgRs was measured by the method described in Reference Example 3. Binding of each antibody to each hFcgR was calculated relative to the binding of G1 to each hFcgR, which was taken as 100, and the results are shown in Table 7.

Table 7

Variant name	hFcgRIa	hFcgRIIa(R)	hFcgRIIa(H)	hFcgRIIb	hFcgRIIIa(F)	hFcgRIIIa(V)
TS20	105.8	116.5	132.1	130.9	105.0	91.2
TS21	107.2	113.1	114.0	121.2	164.2	124.3
TS22	107.7	152.7	157.2	231.9	138.2	107.4
TS23	109.0	152.9	144.7	226.2	219.6	136.7
TS24	106.9	106.9	122.3	113.5	155.1	121.4
TS25	104.8	122.9	124.7	137.0	113.5	92.8
TS26	106.8	145.3	151.5	208.4	204.4	134.0
TS27	106.3	157.8	151.1	241.5	147.6	108.7

For all variants of TS20 to TS27, combining the mutations resulted in improved Tm while maintaining the binding ability to hFcgRs. The variants which were the most effective to improve Tm were TS20 and TS24, and they increase Tm approximately 3°C as compared to G1.

[Example 5] Production and evaluation of novel Fc regions with combined mutations that reduce binding ability to hFcgRs

When mutations for improving stability are introduced into neutralizing antibodies, it is preferred to have as low effector functions as possible. The mutations of TS9 to TS19, which were found out to reduce binding affinity to hFcgRs in Example 3, were combined to produce new variants TS28 to TS43 as shown in Table 8 (SEQ ID NOs: 53 to 68). Each antibody was expressed and purified by the method described in Reference Example 1. The prepared antibodies were subjected to Tm assessment by the method of Reference Example 2, and the results are shown in Table 9.

Table 8

Variant name	Alteration sites	SEQ ID NO:
TS28	L234K/L235K/S239K/H268K/D270F/Q295M/Y296G/S298G/N325G	53
TS29	L234K/L235K/S239K/H268K/D270F/Q295M/Y296G/S298G/N325H	54
TS30	L234K/L235K/S239K/Q295M/Y296G/S298G/N325G	55
TS31	L234K/L235K/S239K/Q295M/Y296G/S298G/N325H	56
TS32	L234K/L235K/H268K/D270F/Q295M/Y296G/S298G/N325G	57
TS33	L234K/L235K/H268K/D270F/Q295M/Y296G/S298G/N325H	58
TS34	L234K/L235K/Q295M/Y296G/S298G/N325G	59
TS35	L234K/L235K/Q295M/Y296G/S298G/N325H	60
TS36	L234K/L235R/S239K/H268K/D270F/Q295M/Y296G/S298G/N325G	61
TS37	L234K/L235R/S239K/H268K/D270F/Q295M/Y296G/S298G/N325H	62
TS38	L234K/L235R/S239K/Q295M/Y296G/S298G/N325G	63
TS39	L234K/L235R/S239K/Q295M/Y296G/S298G/N325H	64
TS40	L234K/L235R/H268K/D270F/Q295M/Y296G/S298G/N325G	65
TS41	L234K/L235R/H268K/D270F/Q295M/Y296G/S298G/N325H	66
TS42	L234K/L235R/Q295M/Y296G/S298G/N325G	67
TS43	L234K/L235R/Q295M/Y296G/S298G/N325H	68

Table 9

Variant name	Tm (°C)
TS28	85.8
TS29	84.6
TS30	86.6
TS31	86.2
TS32	84.9
TS33	83.5
TS34	85.3
TS35	84.8
TS36	86.0
TS37	85.0
TS38	86.6
TS39	85.9
TS40	85.1
TS41	83.8
TS42	85.4
TS43	84.9
G1	70.4

Furthermore, binding ability to hFcgRs was measured by the method described in Reference Example 3. Binding of each antibody to each hFcgR was calculated relative to the binding of G1 to each hFcgR, which was taken as 100, and the results are shown in Table 10.

Table 10

Variant name	hFcgRIa	hFcgRIIa(R)	hFcgRIIa(H)	hFcgRIIb	hFcgRIIIa(F)	hFcgRIIIa(V)
TS28	5.8	1.9	1.7	7.2	3.8	1.7
TS29	5.1	2.1	0.7	7.2	4.2	1.6
TS30	0.1	1.2	0.2	3.8	0.7	1.1
TS31	0.2	1.3	−0.5	3.6	1.9	1.2
TS32	−0.5	0.9	1.0	1.5	0.8	0.9
TS33	−0.9	1.2	0.7	4.6	0.7	1.0
TS34	−0.9	0.9	1.4	4.2	1.8	1.5
TS35	0.5	1.1	1.7	6.2	2.0	1.5
TS36	−0.4	1.0	0.7	4.1	0.7	1.1
TS37	0.6	0.9	0.7	4.5	1.4	0.6
TS38	0.3	2.3	1.7	5.8	2.9	0.9
TS39	0.0	1.5	1.0	2.5	2.4	0.8
TS40	−1.8	1.2	0.7	0.3	0.5	1.0
TS41	0.2	1.2	1.4	4.2	2.4	1.0
TS42	−0.2	1.3	1.6	6.9	2.5	1.3
TS43	−0.9	1.7	−0.1	6.2	2.7	1.1

For all the variants of TS28 to TS43, combining the mutations increased Tm by 13°C or more. Furthermore, combining the mutations greatly reduced the binding ability to FcgRs.

[Example 6] Assessment of aggregate content of IgG1 with novel Fc regions having improved thermal stability

Since aggregates affect storage stability and immunogenicity, it is preferred that mutations for improving thermal stability should not increase the content of aggregate . Accordingly, TS20 to TS43, which combine multiple mutations, and TSm01, and TSm02 were assessed for aggregate content by the method of Reference Example 4. The chromatograms for the measurement are shown in Fig. 2, and the aggregate contents are shown in Table 11.

Table 11

Variant name	Aggregate content (%)
TS20	1.73
TS21	1.70
TS22	1.84
TS23	1.71
TS24	1.66
TS25	1.45
TS26	1.82
TS27	1.96
TS28	2.00
TS29	3.03
TS30	2.72
TS31	2.67
TS32	2.08
TS33	3.77
TS34	2.31
TS35	2.90
TS36	1.86
TS37	1.69
TS38	2.22
TS39	2.19
TS40	1.53
TS41	2.49
TS42	2.04
TS43	1.95
TSm01	7.44
TSm02	4.11
G1	1.49

TS20 to TS27, which maintain the binding ability to hFcgRs, showed comparable aggregation content to G1, demonstrating that these thermal stability-improving mutations were found not to have a large effect on aggregate content. On the other hand, for TS28 to TS43, which greatly reduced the binding ability to hFcgRs, while the amount of aggregates was slightly increased in TS29, 33, and 35, the other variants showed almost the same aggregate amount as that of G1. In contrast, the disulfide bond-introduced variants TSm01 and TSm02 showed a significant increase in the aggregate content, that is, about 5 times and 3 times that of G1, respectively.

The above-mentioned results demonstrate that the mutations discovered in this examination by the present inventors are first-ever mutations that improved the thermal stability while maintaining the physicochemical properties.

[Example 7] Production and evaluation of IgG1 with novel Fc regions that improve thermal stability

The above-mentioned result showed that introducing mutations to the CH2 domain improves the Tm. Therefore, regions that had not been examined for introduction of mutations in Example 1 were examined for whether there were any mutations to improve the Tm, and new variants TS44 to TS67 as shown in Table 12 were produced (SEQ ID NOs: 69-92). Each antibody was expressed and purified by the method described in Reference Example 1 and the results are shown in Table 13. Furthermore, binding ability to hFcgRs was measured by the method described in Reference Example 3. Binding of each antibody to each hFcgR was calculated relative to the binding of G1 to each hFcgR, which was taken as 100, and the results are shown in Table 14.

Table 12

Variant name	Alteration sites	SEQ ID NO:
TS44	P247V	69
TS45	T250F	70
TS46	T250I	71
TS47	T250M	72
TS48	T250V	73
TS49	T250W	74
TS50	T250Y	75
TS51	S298G	76
TS52	T307A	77
TS53	T307Q	78
TS54	T307P	79
TS55	L309A	80
TS56	L309D	81
TS57	L309R	82
TS58	L309P	83
TS59	N315A	84
TS60	K360H	85
TS61	G385D/Q386P/N389S	86
TS62	P387E	87
TS63	M428H	88
TS64	M428W	89
TS65	M428Y	90
TS66	M428F	91
TS67	H433K	92

Table 13

Variant name	Tm(°C)
TS44	72.0
TS45	74.1
TS46	73.9
TS47	69.3
TS48	75.5
TS49	71.5
TS50	75.1
TS51	73.5
TS52	70.8
TS53	71.2
TS54	74.1
TS55	71.4
TS56	72.5
TS57	72.6
TS58	68.3
TS59	71.8
TS60	70.2
TS61	70.1
TS62	72.0
TS63	69.3
TS64	74.7
TS65	73.3
TS66	72.8
TS67	70.3
G1	70.4

Table 14

Variant name	hFcgRIa	hFcgRIIa(R)	hFcgRIIa(H)	hFcgRIIb	hFcgRIIIa(F)	hFcgRIIIa(V)
TS44	101.3	103.4	110.2	112.6	92.0	102.9
TS45	104.9	125.1	119.3	150.2	62.8	84.7
TS46	99.2	102.3	104.6	104.6	66.1	89.6
TS47	100.7	126.6	114.4	162.9	49.8	72.0
TS48	101.5	111.3	108.4	113.2	66.0	89.4
TS49	99.6	123.7	126.6	148.3	82.0	96.9
TS50	101.5	136.6	129.3	169.4	83.5	98.9
TS51	99.2	55.8	27.4	40.8	36.0	58.9
TS52	98.8	98.3	101.8	97.2	64.6	89.0
TS53	101.2	99.0	102.8	95.9	66.4	90.8
TS54	102.7	103.3	103.5	102.3	66.8	90.6
TS55	99.2	101.4	104.1	106.4	70.2	90.5
TS56	67.0	76.7	79.2	74.3	47.2	69.1
TS57	101.1	97.0	98.1	97.8	61.4	86.2
TS58	96.4	68.7	82.2	70.4	41.5	61.2
TS59	101.8	99.1	100.0	99.0	73.4	96.1
TS60	104.7	102.7	104.8	99.7	70.3	94.2
TS61	100.9	106.2	106.4	112.4	73.4	96.6
TS62	101.3	99.7	101.8	95.6	68.9	91.7
TS63	98.6	102.1	102.2	108.5	71.7	90.3
TS64	99.4	114.9	110.8	124.4	89.2	104.7
TS65	100.8	108.9	110.8	111.4	76.3	96.8
TS66	103.2	111.5	112.9	114.6	78.8	99.2
TS67	99.0	99.7	103.1	97.7	66.0	91.7

The variant with the highest Tm in this examination was TS48, and increased Tm approximately 5°C. The other variants also showed improvement in the Tm. The binding ability of TS51 and TS56 to hFcgRs was slightly decreased, and the others maintained their hFcgRs-binding ability.

[Reference Example 1] Production of antibody expression vectors and expression and purification of antibodies

Amino acid substitutions were introduced by methods known to those skilled in the art using the QuikChange Site-Directed Mutagenesis Kit (Stratagene), PCR, and such, or the In fusion Advantage PCR cloning kit (TAKARA), and then expression vectors were constructed. The nucleotide sequences of the obtained expression vectors were determined by methods known to those skilled in the art. The produced plasmids were transiently introduced into human embryonic kidney cancer-derived cell line HEK293H (Invitrogen) or FreeStyle293 (Invitrogen) to express antibodies. From the resulting culture supernatant, antibodies were purified by

methods known to those skilled in the art using the rProtein A SepharoseTM Fast Flow (GE Healthcare). The concentrations of the purified antibodies were determined by measuring absorbance at 280 nm using a spectrophotometer, and calculating from the measured values using an extinction coefficient determined by the PACE method (Protein Science 1995; 4: 2411-2423).

[Reference Example 2] Assessment of melting temperature (Tm) of the modified antibodies by differential scanning fluorimetry

In this examination, thermal stability was assessed by measuring the melting temperature (Tm) of antibodies by differential scanning fluorimetry using Rotor-Gene Q (QIAGEN). It has been reported that this method shows a good correlation with Tm assessment that uses differential scanning calorimetry, which is a widely known method for evaluating thermal stability of antibodies (Journal of Pharmaceutical Science 2010; 4: 1707-1720).

The 5000 times concentrated SYPRO orange (Molecular Probes) was diluted with PBS (Sigma), and then added to the antibody solutions to prepare measurement samples. A 20 μL aliquot of each sample was placed into a measurement tube, and the temperature was increased from 30°C to 99°C at 0.4°C increments with an equilibration time of approximately six seconds before measurement of fluorescence intensity at 470 nm (excitation wavelength) / 555 nm (fluorescence wavelength).

The data were analyzed using Rotor-Gene Q Series Software (QIAGEN) to calculate the temperature at which fluorescence transition was observed, and this temperature was defined as Tm.

[Reference Example 3] Assessment of binding ability to hFcgRs

Interactions between antibodies and hFcgRs (hFcgRIa, hFcgRIIa(R), hFcgRIIa(H), hFcgRIIb, hFcgRIIIa(F), and hFcgRIIIa(V)) were analyzed using Biacore T100 (GE Healthcare). HBS-EP+ (GE Healthcare) was used for the running buffer, and the measurement temperature was set at 25°C. Protein A (Invitrogen) was immobilized by the amino coupling method, and an antibody of interest was captured thereon. Then, hFcγR solutions diluted using the running buffer were injected to allow interaction with the captured antibody at a flow rate of 30 μL/min for five minutes for hFcγRIa, and at a flow rate of 5 μL/min for one minute for the other hFcγRs. The level of binding ability to the antibody was determined, and the results were compared among the antibodies. Since the hFcγR binding level depends on the amount of captured antibodies, the FcgR-binding levels were corrected so that the capture level of each antibody would be 200 RU (resonance unit) for hFcgRIa and 1000 RU (resonance unit) for the other

hFcgRs. The captured antibodies were washed by allowing 10 mM glycine-HCl (pH 1.5) to react for 30 seconds at a flow rate of 30 μL/min to recycle the chip for reuse.

[Reference Example 4] Evaluation of aggregate content

The aggregate content in the purified antibody was evaluated by SEC analysis using the Alliance system (Waters). The mobile phase was 50 mM phosphate buffer containing 300 mM sodium chloride (pH7.0, Isekyu), the analytical column was G3000SW$_{XL}$ (TOSOH), and measurements were taken at a wavelength of 215 nm. The data were analyzed using Empower2 (Waters). Components that eluted as higher molecular weight species than the monomer were collectively taken as aggregates, and their content was calculated.

Industrial Applicability

In the reported antibody Fc region variants, the stability of the Fc region is reduced in most cases. In addition, it is important that an antibody Fc region has effector functions, that is, binds to FcγRs. By the present invention, it is possible to provide highly stable Fc region variants maintaining FcγR-binding, or highly stable Fc region variants with reduced FcγR-binding.

CLAIMS

1. A polypeptide comprising a modified antibody Fc region, wherein the modified antibody 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 or His.

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 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 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).

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

6. The polypeptide of any one of claims 1 to 5, wherein the modified antibody Fc region comprises a further amino acid modification at position 236 (EU numbering).

7. The polypeptide of any one of claims 1 to 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 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).

8. The polypeptide of any one of claims 1 to 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 234 (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 5, wherein the modified antibody Fc region comprises further one or more amino acid modification(s) at amino acid position(s) is position 325 (EU numbering).

10. The polypeptide of any one of claims 4, 5 and 7 wherein the 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), position 325 (EU numbering) is selected from the group consisting of

a) at position 234 (EU numbering) is a substitution with Lys;
b) at position 268 (EU numbering) is a substitution with Lys or His;
c) at position 270 (EU numbering) is a substitution with Phe or Asp;
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 His or Gly.

11. The polypeptide of any one of claims 4, 5 and 8, wherein the 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) is selected from the group consisting of

a) at position 234 (EU numbering) is a substitution with Lys;
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 His or Gly.

12. The polypeptide of any one of claims 4, 5 and 9, wherein the one or more amino acid modification(s) is a substitution of the amino acid at position 325 (EU numbering) with Gly, Met or His.

13. A method for improving stability of a polypeptide comprising a modified antibody Fc region as compared to that of a parent polypeptide by introducing an amino acid modification comprising at 239 (EU numbering).

14. The method of claim 13, wherein the amino acid modification at position 239 (EU numbering) is a substitution with Met, Lys, Arg, Thr, His or Glu.

15. The method of claim 13 or 14, 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 235 (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).

16. The method of any one of claims 13 to 15, wherein the stability is assessed or determined using melting temperature (Tm) as an index.

17. The method of any one of claims 13 to 15, 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.

18. The method of any one of claims 13 to 15, 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.

19. The method of any one of claims 13 to 18, which further comprises the step of introducing a modification to maintain or enhance FcγR-binding activity as compared to that of the parent polypeptide.

20. The method of any one of claims 13 to 18, which further comprises the step of introducing a modification to reduce FcγR-binding activity as compared to that of the parent polypeptide.

21. The method of any one of claims 13 to 18 and 20, comprises intorducing further one or more amino acid modification(s) 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).

22. The method of any one of claims 13 to 18 and 20, comprises intorducing 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).

23. The method of any one of claims 13 to 18 and 20, comprises introducing further amino acid modification at position 325 (EU numbering).

24. The method of claim 23, which comprises introducing further amino acid modification at position 326 (EU numbering).

25. The method of any one of claims 13 to 18, 20 and 21, wherein the one or more amino acid modification(s) 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), position 325 (EU numbering) is selected from the group consisting of
a) at position 234 (EU numbering) is a substitution with Lys;
b) at position 235 (EU numbering) is a substitution with Lys or Arg;

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.

26. The method of any one of claims 13 to 18, 20 and 22, wherein the one or more amino acid modification(s) 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) is selected from the group consisting of
a) at position 234 (EU numbering) is a substitution with Lys;
b) at position 235 (EU numbering) is a substitution with Lys or Arg;
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.

27. The method of any one of claims 13 to 18, 20 and 23, wherein the one or more amino acid modification(s) is a substitution of the amino acid at position 325 (EU numbering) with Gly, Met or His.

28. The method of any one of claims 13 to 27, wherein the amino acid modification is modification in a polypeptide comprising an Fc region of human IgG.

29. A nucleic acid encoding a polypeptide comprising a modified antibody Fc region, which comprises an amino acid modification at position 239 (EU numbering), and has improved stability as compared to that of a parent polypeptide.

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

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

32. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 12, or a polypeptide produced by the method of any one of claims 13 to 28.

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

34. The agent of claim 33, 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.

35. The agent of claim 33, 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.

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Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
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            100                 105                 110

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
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ttgttgggag taaaaatgtg tcttcagaga ctgtgaacat caccatcact caaggtttgg 600

cagtgtcaac catctcatca ttctctccac ctgggtacca agtctctttc tgcttggtga 660

tggtactcct ttttgcagtg gacacaggac tatatttctc tgtgaagaca aacatttgaa 720

gctcaacaag agactggaag gaccataaac ttaaatggag aaaggaccct caagacaaat 780

gacccccatc ccatgggagt aataagagca gtggcagcag 820

<210> 10
<211> 233
<212> PRT
<213> Homo sapiens

<400> 10

```
Met Trp Gln Leu Leu Leu Pro Thr Ala Leu Leu Leu Leu Val Ser Ala
1               5                  10                  15

Gly Met Arg Thr Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro
            20                  25                  30

Gln Trp Tyr Ser Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
        35                  40                  45

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
    50                  55                  60

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
65                  70                  75                  80

Val Asn Asp Ser Gly Glu Tyr Arg Cys Gln Thr Asn Leu Ser Thr Leu
                85                  90                  95

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
            100                 105                 110

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
        115                 120                 125

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
    130                 135                 140

Gly Lys Asp Arg Lys Tyr Phe His His Asn Ser Asp Phe His Ile Pro
145                 150                 155                 160

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Val
                165                 170                 175

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
```

180 185 190

Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Ser Pro Pro Gly Tyr Gln
195 200 205

Val Ser Phe Cys Leu Val Met Val Leu Leu Phe Ala Val Asp Thr Gly
210 215 220

Leu Tyr Phe Ser Val Lys Thr Asn Ile
225 230

<210> 11
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 11

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
```

260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 12
<211> 326
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 12

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        115                 120                 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    210                 215                 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225                 230                 235                 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
```

245 250 255

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly Lys
325

<210> 13
<211> 377
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 13

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro
            100                 105                 110

Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
        115                 120                 125

Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys
    130                 135                 140

Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
145                 150                 155                 160

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
                165                 170                 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            180                 185                 190

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
        195                 200                 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    210                 215                 220

Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
```

225 230 235 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
245 250 255

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
260 265 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
275 280 285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
290 295 300

Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn
305 310 315 320

Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
325 330 335

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile
340 345 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln
355 360 365

Lys Ser Leu Ser Leu Ser Pro Gly Lys
370 375

<210> 14
<211> 327
<212> PRT
<213> Artificial Sequence

<220>

<223> an artificially synthesized sequence

<400> 14

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                  10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
```

165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> 15
<211> 328

<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 15

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
```

145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 16
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 16

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
```

```
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Glu Ser Leu Ser Leu Ser Pro
325

<210> 17
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 17

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Lys Thr Gly Asp Thr Ala Tyr Ser Glu Ser Phe
50 55 60

Gln Asp Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser

115

<210> 18
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 18

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

<210> 19
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 19

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 20
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 20

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln

1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
20 25 30

His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Ser Leu Val Thr Val Ser Ser
115

<210> 21
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 21

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 22
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 22

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

```
Gly Ala Ile Asp Pro Lys Thr Gly Asp Thr Ala Tyr Ser Glu Ser Phe
    50                  55                  60

Gln Asp Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
        195                 200                 205

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
    210                 215                 220
```

```
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
225                 230                 235                 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                245                 250                 255

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
            260                 265                 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        275                 280                 285

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            340                 345                 350

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
```

405 410 415

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
420 425 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440

<210> 23
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 23

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
20 25 30

His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
```

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 24
<211> 328

<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 24

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Cys Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
```

145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Cys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 25
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 25

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Cys Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys

130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Cys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 26
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 26

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Ile Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro

115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 27
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 27

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Ile Ser Gln Asp Glu Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 28
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 28

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys

85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 29
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 29

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr

65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Tyr Asn Ser Thr Glu Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 30
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 30

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

```
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240
```

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 31
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 31

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser

35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Ser Ala Leu Pro His Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 32
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 32

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
```

```
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val His Asn
        195                 200                 205
```

Ser Ala Leu Pro His Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 33
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 33

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys

1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Ala Ala Leu Pro Tyr Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 34
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 34

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 35
<211> 328
<212> PRT

<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 35

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 36
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 36

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Arg Lys Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 37
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 37

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Arg Arg Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300
```

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 38
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 38

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Pro Met Glu Phe Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285
```

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 39
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 39

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser Met Glu Phe Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 40
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 40

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 41
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 41

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240
```

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 42
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 42

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 43
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 43

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Met
        195                 200                 205
```

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 44
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 44

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 45
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 45

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

```
Glu Met Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Ser Ala Leu Pro His Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 46
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 46

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Ala Ala Leu Pro Tyr Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 47
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 47

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Ser Ala Leu Pro His Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 48
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 48

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Ala Ala Leu Pro Tyr Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 49
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 49

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Ser Ala Leu Pro Tyr Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

```
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 50
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 50

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
```

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Ala Ala Leu Pro His Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 51
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 51

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Ser Ala Leu Pro Tyr Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 52
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 52

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Ala Ala Leu Pro His Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240
```

```
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 53
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 53

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
```

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 54
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 54

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
195 200 205

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 55
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 55

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15
```

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 56
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 56

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

```
Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 57
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 57

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

```
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 58

<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 58

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro

325

<210> 59
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 59

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Lys Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
```

305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 60
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 60

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

```
Pro Ala Pro Glu Lys Lys Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
```

290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 61
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 61

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe

275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 62
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 62

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn

260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 63
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 63

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
```

245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 64
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 64

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu

225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 65
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 65

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
```

210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 66
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 66

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser Lys Glu Phe Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His

195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 67
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 67

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
```

180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Gly
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 68
<211> 328
<212> PRT
<213> Artificial Sequence

<220>

<223> an artificially synthesized sequence

<400> 68

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Lys Arg Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
```

165 170 175

Glu Met Gly Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser His
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 69
<211> 328

<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 69

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Val Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
```

145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 70
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 70

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Phe Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
```

130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 71
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 71

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro

115 120 125

Lys Pro Lys Asp Ile Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 72
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 72

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Met Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 73
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 73

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys

85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

```
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 74
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 74

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
```

65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Trp Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 75
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 75

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Tyr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 76
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 76

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser

35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Gly Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 77
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 77

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
```

20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Ala Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 78
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 78

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys

1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Gln Val Leu
180 185 190

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 79
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 79

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 80
<211> 328
<212> PRT

<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 80

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

```
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Ala
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 81
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 81

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Asp
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 82
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 82

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Arg
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300
```

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 83
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 83

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Pro
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 84
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 84

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Ala Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 85
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 85

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr His Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 86
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 86

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240
```

```
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Asp Pro Pro Glu Ser
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 87
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 87

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
```

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Glu Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
```

<210> 88
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 88

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val His His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 89
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 89

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190
```

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Trp His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro
                325
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<210> 90
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 90

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Tyr His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 91
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<223> an artificially synthesized sequence

<400> 91

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Phe His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 92
<211> 328
<212> PRT
<213> Artificial Sequence

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<223> an artificially synthesized sequence

<400> 92

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu Lys Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325