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(54) Title: FC MUTANT WITH ALTERED BINDING TO FC RECEPTOR

(54) 发明名称: 与Fc受体结合改变的Fc突变体

(57) Abstract: The present invention relates to a modified immunoglobulin constant region (Fc) mutant molecule having reduced binding to FcγR or C1q. The molecule can significantly reduce undesired ADCC and/or ADCP and/or CDC effector function in vivo. In addition, the present invention relates to a use of the Fc mutant molecule, a fusion protein comprising the mutant molecule and a use thereof.

(57) 摘要: 涉及经过修饰的具有降低的与FcγR或C1q结合的免疫球蛋白恒定区(Fc)突变分子, 该分子可以在机体内显著降低不期望的ADCC和/或ADCP和/或CDC效应子功能。此外, 还涉及上述Fc突变分子的用途、包含所述突变分子的融合蛋白以及其用途。



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FC MUTANT WITH ALTERED BINDING TO FC RECEPTOR

TECHNICAL FIELD

The present invention generally relates to the field of immunology and antibody engineering. Specifically, the present invention relates to a variant of IgG immunoglobulins, a preparation method therefor, and use thereof.

BACKGROUND

With the development of therapeutic antibodies in recent years, in one aspect, researchers continue to search for new targets, and in another aspect, they continue to upgrade and engineer druggable antibodies in efforts to improve or enhance the beneficial effects. One of the focuses of research is on engineering of the Fc region of an antibody.

It is well known that although the Fc region of an antibody has no antigen-binding activity, it is the site of interaction of an antibody with cell surface Fc receptors and thus plays a critical role in the effector functions of an antibody. The Fc region allows the antibody to exert a variety of effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) by interacting with different Fc receptors. With respect to ADCC, ADCP, and CDC effector functions, effective or even enhanced ADCC, ADCP, and CDC effector functions are beneficial for the therapeutic effect of an antibody for recognizing an antigen expressed on a tumor cell or pathogen and targeting the elimination of malignant cells, whereas reduced or even eliminated ADCC, ADCP, and CDC effector functions are often required for antibodies targeting, for example, an antigen expressed on a T cell to block cell surface receptors/cytokines or immunomodulation, as antibodies targeting cell surface antigens may induce unnecessary immune stimulation to immune cells and associated effector functions and complement activation with negative consequences, which is particularly important for immune checkpoint inhibitor antibodies requiring low loss of the target cell.

Human IgG subclasses (IgG1, IgG2, IgG3, and IgG4) have different immune functions. For example, IgG antibodies of different subclasses have different ADCC activities, and IgG1 and IgG3 have stronger ADCC activities compared to other subclasses; IgG1, IgG2, IgG3, and IgG4 have antibody-dependent cellular phagocytosis (ADCP). Since a fusion construct of therapeutic antibodies with Fc often requires targeting and activation or neutralization of target ligand functional region, but can not destroy or damage the desired local cells or tissues, there is a continuing real need for Fc mutants with reduced or eliminated Fc effector functions (e.g., reduced or eliminated ADCC and/or ADCP activity, and reduced or eliminated CDC activity) in actual production and applications, and the present application satisfies the need.

It has been reported in the literature that mutation of a part of amino acids in the Fc region may reduce or eliminate ADCC and/or ADCP activity and reduce or eliminate CDC activity. For example, patent families US8734791B2, US10183999B2, US8883147B2 of XENCOR, patent family CN103476795B of Roche, and the like, mostly can reduce ADCC and CDC activity, however, mutations that can completely eliminate ADCC and CDC effects are rare. The present application obtains Fc mutant molecules that can completely eliminate ADCC and CDC effects by directional engineering of wild-type Fc amino acid sequences.

SUMMARY

The present invention provides a modified mutant molecule of an immunoglobulin constant region (Fc region) that can be used to engineer an antibody or antibody therapeutic agent.

By including the mutation and/or combination thereof disclosed herein in the Fc region, the binding of antibodies and antibody therapeutic agents comprising the mutant Fc region of the present application and other molecules comprising a mutant Fc region to FcγR or C1q is greatly reduced compared to molecules comprising a wild-type Fc region, thereby significantly reducing undesirable ADCC and/or ADCP and/or CDC effector functions *in vivo*. Further, the Fc mutation disclosed herein does not affect the binding ability of antibodies and antibody therapeutic agents comprising the mutant Fc region of the present application and other molecules comprising a mutant Fc region to FcRn, and thus does not affect the half-life of the corresponding molecule. Accordingly, the present application provides an Fc region polypeptide molecule carrying a specific mutation and an antibody molecule comprising the mutant Fc region described above that has a reduced or eliminated ADCC and/or ADCP and/or CDC effector function but still retains the ability to bind to FcRn, or a molecule having a similar structure.

In a first aspect, the present application provides an Fc mutant having a different modification that exhibit reduced affinity for an Fc receptor and/or C1q compared to a wild-type Fc region, thereby reducing or eliminating ADCC, CDC, and ADCP effector functions induced by the Fc mutant. In one embodiment, the ADCC, CDC, and ADCP effector functions induced by the Fc mutant are reduced to at least 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 2%, or 1% of the ADCC, CDC, and ADCP effector functions induced by a corresponding wild-type Fc, or completely eliminated.

In one embodiment, the Fc mutant provided herein comprises one or more amino acid deletions. In one specific embodiment, the Fc mutant provided herein comprises a deletion at amino acid position 329 (Δ329) according to EU index numbering as in Kabat. In one specific embodiment, the Fc mutant provided herein differs from the corresponding wild-type Fc by the deletion at position 329 (Δ329) according to EU index numbering as in Kabat. In another specific embodiment, the Fc mutant provided herein comprises a deletion at amino acid positions 329 and 330 (Δ329 and Δ330) according to EU index numbering as in Kabat. In one specific embodiment, the Fc mutant provided herein differs from the corresponding wild-type Fc by the deletion at amino acid positions 329 and 330 (Δ329 and Δ330) according to EU index numbering as in Kabat.

In one embodiment, the Fc mutant provided herein comprises one or more amino acid substitutions. In one specific embodiment, the Fc mutant provided herein comprises a substitution at amino acid positions 234 and/or 235 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively. In one preferred embodiment, the Fc mutant comprises L234A + L235A, V234A, or F234A + L235A. In one specific embodiment, the Fc mutant provided herein differs from the corresponding wild-type Fc by L234A + L235A, V234A, or F234A + L235A.

In one embodiment, the Fc mutant provided herein comprises one or more amino acid deletions and one or more amino acid substitutions. In one specific embodiment, the Fc mutant provided herein comprises a deletion at

amino acid position 329 and a substitution at position 330 according to EU index numbering as in Kabat, wherein position 330 is substituted by G, D, or Q. In one preferred embodiment, the Fc mutant comprises $\Delta 329 + A330G$ or $\Delta 329 + S330G$. In one specific embodiment, the Fc mutant provided herein differs from the corresponding wild-type Fc by $\Delta 329 + A330G$ or $\Delta 329 + S330G$.

In one specific embodiment, the Fc mutant provided herein comprises a deletion at amino acid position 329 and a substitution at amino acid positions 234 and 235 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively. In one preferred embodiment, the Fc mutant comprises $L234A + L235A + \Delta 329$, $V234A + \Delta 329$, or $F234A + L235A + \Delta 329$. In one specific embodiment, the Fc mutant provided herein differs from the corresponding wild-type Fc by $L234A + L235A + \Delta 329$, $V234A + \Delta 329$, or $F234A + L235A + \Delta 329$.

In another specific embodiment, the Fc mutant provided herein comprises a deletion at amino acid positions 329 and 330 and a substitution at amino acid positions 234 and 235 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively. In one preferred embodiment, the Fc mutant comprises $L234A + L235A + \Delta 329 + \Delta 330$, $V234A + \Delta 329 + \Delta 330$, or $F234A + L235A + \Delta 329 + \Delta 330$. In one specific embodiment, the Fc mutant provided herein differs from the corresponding wild-type Fc by $L234A + L235A + \Delta 329 + \Delta 330$, $V234A + \Delta 329 + \Delta 330$, or $F234A + L235A + \Delta 329 + \Delta 330$.

In another specific embodiment, the Fc mutant provided herein comprises a deletion at amino acid position 329 and a substitution at amino acid positions 234, 235, and 330 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively, and position 330 is substituted by G, D, or Q. In one preferred embodiment, the Fc mutant comprises $L234A + L235A + A330G + \Delta 329$, $L234A + L235A + S330G + \Delta 329$, $V234A + L235A + A330G + \Delta 329$, $V234A + L235A + S330G + \Delta 329$, $F234A + L235A + S330G + \Delta 329$, or $F234A + L235A + A330G + \Delta 329$. In one specific embodiment, the Fc mutant provided herein differs from the corresponding wild-type Fc by $L234A + L235A + A330G + \Delta 329$, $L234A + L235A + S330G + \Delta 329$, $V234A + L235A + A330G + \Delta 329$, $V234A + L235A + S330G + \Delta 329$, $F234A + L235A + S330G + \Delta 329$, or $F234A + L235A + A330G + \Delta 329$.

In some embodiments, the Fc mutant provided herein is an IgG1 Fc mutant, and the mutant has reduced or even eliminated ability to bind to Fc γ R compared to the corresponding wild-type Fc region. In other embodiments, the Fc mutant provided herein is an IgG2, IgG3, or IgG4 Fc mutant, and the mutant has reduced or even eliminated ability to bind to Fc γ R compared to the corresponding wild-type Fc region. Preferably, the Fc mutant provided herein retains the ability to bind to FcRn.

The Fc mutant disclosed in the present application can be used as a platform component in any scenario where ADCC/ADCP/CDC effector function needs to be reduced or even eliminated, for example, in any type of antibody molecule where ADCC/ADCP/CDC effector function is desired to be reduced or even eliminated, or in molecules having similar antibody structures.

In one embodiment, the Fc mutant is substantially based on an IgG sequence. In one preferred embodiment, the Fc mutant is substantially based on a human IgG sequence. In another embodiment, the Fc mutant is substantially based on a human IgG1 sequence.

In another embodiment, the Fc mutant may also comprise other modifications, such as other modifications known in the art for reducing immunogenicity and improving stability, solubility, functions, and clinical benefits.

In one specific embodiment, the Fc mutant comprises the following sequence:

- 1) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 2, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 2) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 3, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 3) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 4, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 4) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 5, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 5) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 6, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 6) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 7, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 7) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 8, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 8) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 11, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 9) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 12, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 10) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 13, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 11) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 14, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 12) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 15, or an amino acid

- 25) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 30, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 26) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 31, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 27) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 32, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 28) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 33, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence.

In a second aspect, the present invention provides a polypeptide comprising the Fc mutant according to the first aspect. The polypeptide has reduced or eliminated ADCC and/or ADCP and/or CDC effector function compared to the polypeptide comprising a wild-type Fc region. Preferably, the polypeptide does not cause ADCC and/or ADCP and/or CDC effect. In one specific embodiment, the polypeptide simultaneously has a prolonged half-life. In one embodiment, the ADCC, CDC, and ADCP effector functions induced by the polypeptide comprising the Fc mutant according to the first aspect are reduced to at least 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 2%, or 1% of the ADCC, CDC, and ADCP effector functions induced by the polypeptide comprising the corresponding wild-type Fc, or completely eliminated.

In some embodiments, the polypeptide is an antibody molecule; preferably, the antibody molecule is an IgG antibody molecule. In another embodiment, the antibody molecule is a multispecific antibody (e.g., bispecific antibody), a humanized antibody, a chimeric antibody, or an antibody fusion. The antibody molecule comprising the Fc mutant obtained according to the present application has a reduced or even eliminated ability to bind to FcγR compared to the corresponding wild-type antibody molecule, and thus has reduced or eliminated ADCC and/or ADCP and/or CDC effector function.

In some embodiments, the polypeptide is a fusion protein comprising one or more fusion partners operably linked to the Fc mutant. The fusion partner can generally be any protein or small molecule, such as the variable region of any antibody, the target-binding region of a receptor, an adhesion molecule, a ligand, an enzyme, a cytokine, a chemokine, or some other proteins or protein domains. In one embodiment, the fusion protein is, for example, an immunoadhesin.

In one embodiment, the present application provides an IgG antibody comprising the Fc mutant, which comprises a deletion at amino acid position 329 (Δ 329) according to EU index numbering as in Kabat. In another specific embodiment, the present application provides an IgG antibody comprising the Fc mutant, which comprises a deletion at amino acid positions 329 and 330 (Δ 329 and Δ 330) according to EU index numbering as in Kabat.

In one embodiment, the present application provides an IgG antibody comprising the Fc mutant, which

comprises a substitution at amino acid positions 234 and/or 235 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively. In one preferred embodiment, the IgG antibody comprises L234A + L235A, V234A, or F234A + L235A.

In one embodiment, the present application provides an IgG antibody comprising the Fc mutant, which comprises a deletion at amino acid position 329 and a substitution at position 330 according to EU index numbering as in Kabat, wherein position 330 is substituted by G, D, or Q. In one preferred embodiment, the IgG antibody comprises $\Delta 329 + A330G$ or $\Delta 329 + S330G$.

In one embodiment, the present application provides an IgG antibody comprising the Fc mutant, which comprises a deletion at amino acid position 329 and a substitution at amino acid positions 234 and 235 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively. In one preferred embodiment, the IgG antibody comprises L234A + L235A + $\Delta 329$, V234A + $\Delta 329$, or F234A + L235A + $\Delta 329$.

In one embodiment, the present application provides an IgG antibody comprising the Fc mutant, which comprises a deletion at amino acid positions 329 and 330 and a substitution at amino acid positions 234 and 235 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively. In one preferred embodiment, the IgG antibody comprises L234A + L235A + $\Delta 329 + \Delta 330$, V234A + $\Delta 329 + \Delta 330$, or F234A + L235A + $\Delta 329 + \Delta 330$.

In one embodiment, the present application provides an IgG antibody comprising the Fc mutant, which comprises a deletion at amino acid position 329 and a substitution at amino acid positions 234, 235, and 330 according to EU index numbering as in Kabat, wherein L, V, and F at position 234 and/or L at position 235 are substituted by A, V, L, and I, respectively, and position 330 is substituted by G, D, or Q. In one preferred embodiment, the IgG antibody comprises L234A + L235A + A330G + $\Delta 329$, L234A + L235A + S330G + $\Delta 329$, V234A + L235A + A330G + $\Delta 329$, V234A + L235A + S330G + $\Delta 329$, F234A + L235A + S330G + $\Delta 329$, or F234A + L235A + A330G + $\Delta 329$.

In some embodiments, the IgG antibody provided herein is an IgG1 antibody, and the antibody has reduced or even eliminated ability to bind to Fc γ R compared to the corresponding wild-type antibody. In other embodiments, the IgG antibody provided herein is an IgG2, IgG3, or IgG4 antibody, and the antibody has reduced or even eliminated ability to bind to Fc γ R compared to the corresponding wild-type antibody. Preferably, the antibody provided herein retains the ability to bind to FcRn.

In some embodiments, the antibody molecule is an IgG antibody against claudin18.2.

In one specific embodiment, the IgG antibody comprising the Fc mutant provided herein comprises the following heavy chain and light chain:

- 1) comprising a heavy chain set forth in SEQ ID NO: 2 and a light chain set forth in SEQ ID NO: 9; or
- 2) comprising a heavy chain set forth in SEQ ID NO: 3 and a light chain set forth in SEQ ID NO: 9; or
- 3) comprising a heavy chain set forth in SEQ ID NO: 4 and a light chain set forth in SEQ ID NO: 9; or
- 4) comprising a heavy chain set forth in SEQ ID NO: 5 and a light chain set forth in SEQ ID NO: 9; or
- 5) comprising a heavy chain set forth in SEQ ID NO: 6 and a light chain set forth in SEQ ID NO: 9; or
- 6) comprising a heavy chain set forth in SEQ ID NO: 7 and a light chain set forth in SEQ ID NO: 9; or

- 7) comprising a heavy chain set forth in SEQ ID NO: 8 and a light chain set forth in SEQ ID NO: 9; or
- 8) comprising a heavy chain set forth in SEQ ID NO: 11 and a light chain set forth in SEQ ID NO: 9; or
- 9) comprising a heavy chain set forth in SEQ ID NO: 12 and a light chain set forth in SEQ ID NO: 9; or
- 10) comprising a heavy chain set forth in SEQ ID NO: 13 and a light chain set forth in SEQ ID NO: 9; or
- 11) comprising a heavy chain set forth in SEQ ID NO: 14 and a light chain set forth in SEQ ID NO: 9; or
- 12) comprising a heavy chain set forth in SEQ ID NO: 15 and a light chain set forth in SEQ ID NO: 9; or
- 13) comprising a heavy chain set forth in SEQ ID NO: 16 and a light chain set forth in SEQ ID NO: 9; or
- 14) comprising a heavy chain set forth in SEQ ID NO: 17 and a light chain set forth in SEQ ID NO: 9; or
- 15) comprising a heavy chain set forth in SEQ ID NO: 19 and a light chain set forth in SEQ ID NO: 9; or
- 16) comprising a heavy chain set forth in SEQ ID NO: 20 and a light chain set forth in SEQ ID NO: 9; or
- 17) comprising a heavy chain set forth in SEQ ID NO: 21 and a light chain set forth in SEQ ID NO: 9; or
- 18) comprising a heavy chain set forth in SEQ ID NO: 22 and a light chain set forth in SEQ ID NO: 9; or
- 19) comprising a heavy chain set forth in SEQ ID NO: 23 and a light chain set forth in SEQ ID NO: 9; or
- 20) comprising a heavy chain set forth in SEQ ID NO: 24 and a light chain set forth in SEQ ID NO: 9; or
- 21) comprising a heavy chain set forth in SEQ ID NO: 25 and a light chain set forth in SEQ ID NO: 9; or
- 22) comprising a heavy chain set forth in SEQ ID NO: 27 and a light chain set forth in SEQ ID NO: 34; or
- 23) comprising a heavy chain set forth in SEQ ID NO: 28 and a light chain set forth in SEQ ID NO: 34; or
- 24) comprising a heavy chain set forth in SEQ ID NO: 29 and a light chain set forth in SEQ ID NO: 34; or
- 25) comprising a heavy chain set forth in SEQ ID NO: 30 and a light chain set forth in SEQ ID NO: 34; or
- 26) comprising a heavy chain set forth in SEQ ID NO: 31 and a light chain set forth in SEQ ID NO: 34; or
- 27) comprising a heavy chain set forth in SEQ ID NO: 32 and a light chain set forth in SEQ ID NO: 34; or
- 28) comprising a heavy chain set forth in SEQ ID NO: 33 and a light chain set forth in SEQ ID NO: 34.

In another embodiment, the polypeptide (e.g., antibody) comprising the Fc mutant provided herein may also comprise other modifications in the Fc region, such as other modifications known in the art for reducing immunogenicity of a polypeptide (e.g., antibody), increasing half-life, and improving stability, solubility, functions, and clinical benefits.

In another embodiment, the antibody comprising the Fc mutant provided herein has a heavy chain variable region and a light chain variable region known in the art for different target antigens. Those skilled in the art can readily graft the heavy chain variable region and the light chain variable region known in the art onto the Fc mutant disclosed herein to obtain an antibody variant having desired properties (e.g., reduced or eliminated ADCC and/or ADCP and/or CDC effector function).

In a third aspect, the present invention provides a pharmaceutical composition comprising the polypeptide according to the second aspect and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition comprises an antibody molecule carrying the Fc mutant described in the present invention. In one embodiment, the pharmaceutical composition comprises an IgG antibody carrying the Fc mutant described in the present invention. In another embodiment, the pharmaceutical composition comprises

an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, or an IgG4 antibody carrying the Fc mutant described in the present invention.

In a fourth aspect, the present invention provides a method for reducing or eliminating ADCC/ADCP/CDC effector function of an antibody, and retaining or even increasing half-life, according to the Fc region modification described in the present application. In one embodiment, ADCC/ADCP/CDC effector function of an antibody is reduced or eliminated by one or more modifications disclosed herein to the antibody Fc region in need of reducing or eliminating ADCC/ADCP/CDC effector function.

In a fifth aspect, the present invention provides use of the Fc mutant in preparing a drug. In one embodiment, the drug is for immunotherapy or adjuvant immunotherapy. In one embodiment, the drug has reduced or eliminated ADCC/ADCP/CDC effector function. In one specific embodiment, for example, the drug is a fusion protein comprising the Fc mutant of the present application, for example, an IL-2 Fc fusion protein. In another specific embodiment, for example, the drug is an antibody targeting an immune cell surface molecule comprising the Fc mutant of the present application, which has reduced or eliminated ADCC/ADCP/CDC effector function. In another embodiment, the drug is for treating a tumor in a subject. For example, in one embodiment, the drug activates immune cells of the patient without activating ADCC/ADCP/CDC effect and with a prolonged half-life, thereby achieving an anti-tumor effect.

In a sixth aspect, the present invention provides a method for treating a disease in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition for the corresponding disease comprising the Fc mutant of the present application. In one embodiment, the disease is a disease requiring immunotherapy or adjuvant immunotherapy. For antibodies that target cell surface molecules, particularly antibodies on immune cells, it is advantageous to eliminate effector functions. In one embodiment, the present invention provides a method for treating a disease in a subject, comprising administering to the subject an effective amount of an antibody against an antigen on a corresponding immune cell comprising the Fc mutant of the present application.

In a seventh aspect, the present invention provides a kit comprising the Fc mutant disclosed herein, the polypeptide comprising the Fc mutant, or an immunoglobulin molecule comprising the Fc mutant. In one embodiment, the present invention provides a detection kit, which, by fusing functional molecules (such as enzymes, antigens, receptors, ligands, cytokines, and the like) with Fc, can improve the stability of fusion protein, and can also be applied to non-clinical fields such as flow cytometry, immunohistochemistry, *in vitro* activity detection, protein microarray detection, and the like.

The antibody molecule carrying a specific Fc mutation provided herein has reduced or eliminated ADCC, ADCP, and CDC effector functions, but still retains the ability to bind to FcRn, so that the antibody molecule can be used as an improved antibody mutant, which not only improves the curative effect of the antibody, but also ensures the safety, the stability and the low immunogenicity of the antibody. It has been surprisingly found

that deletion of the proline residue at position 329 of the Fc region significantly reduces the binding of the Fc region to receptors FcγRIII, FcγRII, FcγRI, and C1q, thereby significantly reducing or eliminating ADCC, ADCP, and CDC activity. Furthermore, Pro329 of the Fc region and a combinatorial mutation, for example, selected from one or more of A330 deletion, A330G, L234A, and L235A result in a significant reduction of binding to the receptors FcγRIII, FcγRII, FcγRI, and C1q, thereby significantly reducing or eliminating ADCC, ADCP, and CDC activity.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: crystal structure of human IgG1 Fc and human CD16A (PDB: 3SGJ).

FIG. 2 shows the binding of the Fc mutants of the present invention to various FcγRs. FIG. 2a: binding curves of the Fc mutants to CD16A (F176) (pH 7.4). FIG. 2b: binding curves of the Fc mutants to CD16A (V176) (pH 7.4). FIG. 2c: binding curves of the Fc mutants to CD16B (NA1) (pH 7.4). FIG. 2d: binding curves of the Fc mutants to CD16B (NA2) (pH 7.4). FIG. 2e: binding curves of the Fc mutants to CD32A (H167) (pH 7.4). FIG. 2f: binding curves of the Fc mutants to CD32A (R167) (pH 7.4). FIG. 2g: binding curves of the Fc mutants to CD32B (pH 7.4). FIG. 2h: binding curves of the Fc mutants to CD64 (pH 7.4). FIG. 2i: binding curves of the Fc mutants to FcRn at pH 6.0. FIG. 2j: binding curves of the Fc mutants to FcRn at pH 7.0. FIG. 2k: binding and dissociation curves of the Fc mutants to C1q.

FIG. 3 shows the binding of the Fc mutants to various FcγRs as determined by bio-layer interferometry, wherein the solution comprises 200 nM of the antibody. FIG. 3a: binding curves of the Fc mutants to CD16A (V176) (pH 7.4). FIG. 3b: binding curves of the Fc mutants to CD16A (F176) (pH 7.4). FIG. 3c: binding curves of the Fc mutants to CD16B (NA1) (pH 7.4). FIG. 3d: binding curves of the Fc mutants to CD16B (NA2) (pH 7.4). FIG. 3e: binding curves of the Fc mutants to CD32A (H167) (pH 7.4). FIG. 3f: binding curves of the Fc mutants to CD32A (R167) (pH 7.4). FIG. 3g: binding curves of the Fc mutants to CD32B (pH 7.4). FIG. 3h: binding curves of the Fc mutants to CD64 (pH 7.4). FIG. 3i: binding curves of the Fc mutants to FcRn at pH 6.0.

FIG. 4 shows the ADCC activity of the antibodies.

DETAILED DESCRIPTION

Unless otherwise indicated, conventional methods of chemistry, biochemistry, organic chemistry, molecular biology, microbiology, recombinant DNA techniques, genetics, immunology and cell biology that are known in the art will be employed for the implementation of the present invention. Descriptions of such methods can be found, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual* (3rd edition, 2001); Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2nd edition, 1989); Maniatis et al., *Molecular Cloning: A Laboratory Manual* (1982); Ausubel et. al., *Current Protocols in Molecular Biology* (John Wiley and Sons, updated in July 2008); *Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology*, Greene Pub. Associates and Wiley-Interscience; Glover, *DNA Cloning: A Practical Approach*, vol. I&II (IRL Press, Oxford, 1985); Anand, *Techniques for the Analysis of Complex Genomes*, (Academic Press, New York, 1992); *Transcription and Translation* (B. Hames & S. Higgins, Eds., 1984); Perbal, *A Practical Guide to Molecular Cloning* (1984); Harlow and Lane, *Antibodies* (Cold Spring

Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1998) *Current Protocols in Immunology* (Q. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, eds., 1991); *Annual Review of Immunology*; and journals and monographs such as *Advances in Immunology*.

Definitions

Before the present invention is described in detail below, it should be understood that the present invention is not limited to the particular methodology, protocols, and reagents described herein, as these may vary. It should also be understood that the terminology used herein is only intended to describe specific embodiments rather than limit the scope of the present invention, which will be limited only by the appended claims. Unless otherwise defined, any technical and scientific term used herein has the same meaning as commonly understood by those of ordinary skill in the art to which the present invention belongs.

For the purpose of explaining this specification, the following definitions will be used, and wherever appropriate, terms used in the singular form may also include the plural form, and vice versa. It should be understood that the terms used herein are for the purpose of describing specific embodiments only, and are not intended to be limiting.

The term “about” used in combination with a numerical value is intended to encompass the numerical values in a range from a lower limit less than the specified numerical value by 5% to an upper limit greater than the specified numerical value by 5%.

The term “and/or” means that when used to connect two or more options, it should be understood to refer to any one of the options or any two or more of the options.

The term “comprise” or “include” means that the described elements, integers or steps are included, but not to the exclusion of any other elements, integers or steps. The term “comprise” or “include” used herein, unless otherwise specified, also encompasses the situation where the entirety consists of the described elements, integers or steps. For example, when referring to an antibody variable region “comprising” a specific sequence, it is also intended to encompass an antibody variable region consisting of the specific sequence.

The term “antibody” is used herein in the broadest sense and encompasses a variety of antibody structures, including but not limited to, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a chimeric antibody, a multispecific antibody (e.g., a bispecific antibody), a single-chain antibody, an intact antibody, or an antibody fragment thereof that exhibits the desired antigen-binding activity. An intact antibody will generally comprise at least two full-length heavy chains and two full-length light chains, but may comprise less chains in some cases, for example, natural antibodies in a camel may only comprise heavy chains. As used herein, the term “binding” and “specific binding” mean that the binding effect of an antibody is selective for antigens and can be distinguished from unwanted or non-specific interactions. The ability of an antibody to bind to a particular antigen can be determined by an enzyme-linked immunosorbent assay (ELISA), surface plasmon resonance (SPR), or bio-layer interferometry (ForteBio), or a conventional binding assay known in the art. For example, if an antibody binds to BCMA or CD3 with a KD of about 1×10^{-7} or less, a KD of about 1×10^{-8} or less, a KD of about 1×10^{-9} or less, a KD of about 1×10^{-10} or less, or a KD of about 1×10^{-11} or less in SPR, it is the antibody that “specifically binds to BCMA or CD3”. However, the antibody that specifically binds to

human BCMA or CD3 may have cross-reactivity with a BCMA or CD3 protein from other species. For example, an antibody specific to human BCMA or CD3, in some embodiments, can cross-react with cynomolgus monkey BCMA or CD3. A method for determining cross-reactivity includes the method described in examples and standard assays known in the art, such as biological optical interferometry or flow cytometry.

The terms “variable domain residue numbering of Kabat”, “Kabat numbering system”, or “amino acid position numbering according to Kabat” and variations thereof refer to the numbering system for antibody heavy chain variable domain or light chain variable domain editing according to Kabat et al. (see Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th edition, Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The Kabat numbering system is generally applicable to residues in the variable domain of antibodies (approximately the light chain residues at positions 1-107 and the heavy chain residues at positions 1-113).

The terms “EU numbering system”, “EU index as in Kabat”, or “EU index” generally apply to residues in an immunoglobulin heavy chain constant region (see, e.g., Kabat et al. above). Unless otherwise indicated herein, residue numbering in antibody variable domains herein is according to the Kabat numbering system; residue numbering in antibody constant domains is according to the residue numbering of the EU numbering system.

Antibody “effector function” refers to the biological activity attributed to the Fc region of an antibody (either the native sequence Fc region or the amino acid sequence variant Fc region) and varying with the antibody isotype. Examples of antibody effector functions include: complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), cell surface receptor (such as B cell receptors) down-regulation, B-cell activation, and the like.

The term “effector cell” refers to a cell that expresses one or more FcRs and executes effector functions, such as a cell that expresses FcγRIIIA and executes effector function of ADCC. In one embodiment, a cell that mediates ADCC function is, for example, NK cells, peripheral blood mononuclear cells, monocytes, cytotoxic T cells, and neutrophils. Effector cells may be derived from natural environment, such as blood.

The term “antibody-dependent cell-mediated cytotoxicity” or “ADCC” refers to a cell-mediated immune response in which Fc receptors present on the surface of certain cytotoxic cells recognize bound antibodies on target cells, such that the cytotoxic cells can specifically bind to antigen-bearing target cells, and activate effector cells of the immune system to lyse the target cells. The classical ADCC effect is mediated by natural killer cells (NK). Macrophages, neutrophils, and eosinophils can also mediate the ADCC effect. For example, eosinophils can kill certain parasites through the ADCC effect.

The term “antibody-dependent cellular phagocytosis” or “ADCP” refers to a cellular response in which activation of macrophages is induced by binding of a target cell-binding antibody to FcγRIIIa on the macrophage surface, thereby internalizing the target cell and acidifying and degrading the target cell by a phagosome. ADCP may also be mediated by FcγRIIa and FcγRI, but the proportion is relatively small.

The complement system is part of the innate immune system that is composed of a series of proteins. The proteins of the complement system, called “complement”, are represented by the abbreviations C1, C2, C3, and the like, and are a group of thermolabile proteins present in human or vertebrate serum and tissue fluids, which have enzymatic activity after activation. C1q is the first component of the complement-dependent cytotoxicity

(CDC) pathway that is capable of binding to six antibodies, but binding to two IgG is sufficient to activate the complement cascade.

The term “complement-dependent cytotoxicity” or “CDC” refers to complement-involved cytotoxicity in which the Fc effector domain of an antibody that binds to a target activates a series of complement cascades, forming pores in the target cell membrane, and resulting in target cell death.

The term “Fc region” refers to the C-terminal region of an immunoglobulin heavy chain, including Fc regions of native sequences and variant Fc regions. The human IgG heavy chain Fc region is generally defined as the segment from the amino acid residue at position Cys226 or Pro230 to the carboxy terminus, and the C-terminus lysine residue at position 447 of the Fc region (according to the EU numbering system) may be present or absent. Thus, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, or antibody populations in which antibodies with K447 residues and antibodies without K447 residues are mixed.

In certain embodiments, the Fc region of an immunoglobulin comprises two constant domains, i.e., CH2 and CH3, and in other embodiments, the Fc region of an immunoglobulin comprises three constant domains, i.e., CH2, CH3, and CH4.

The binding of IgG to Fcγ receptors or C1q is dependent on residues located in the hinge region and CH2 domains. Two regions of the CH2 domain are critical for the binding of FcγR to complement C1q, and have a unique sequence in IgG2 and IgG4. It has been shown that substitution of residues at positions 233-236 of human IgG1 and IgG2 and substitution of residues at positions 327, 330, and 331 of human IgG4 can significantly reduce ADCC and CDC activities (Armour et al., *Eur. J. Immunol.* 29(8), 1999, 2613-2624; Shields et al., *J. biol. chem.* 276(9), 2001, 6591-6604). Furthermore, Idusogie et al. show that alanine substitutions at various positions including K322 significantly reduce complement activation (Idusogie EE et al., *J. Immunol* 164(8), 2000, 4178-84).

“Functional Fc region” and similar terms are used interchangeably to refer to an Fc region having effector functions of a wild-type Fc region.

“Variant Fc region”, “Fc mutant”, “Fc region carrying a mutation”, “mutant Fc region”, “Fc region variant”, “Fc variant”, “mutated Fc region” and similar terms are used interchangeably to refer to an Fc region that comprises at least one amino acid modification and thus differs from the Fc region of the native sequence Fc region/wild-type Fc region.

In some embodiments, the variant Fc region comprises an amino acid sequence that differs from the amino acid sequence of the native sequence Fc region by one or more amino acid substitutions, deletions, or additions. In some embodiments, the variant Fc region has at least one amino acid deletion compared to the Fc region of a wild-type IgG. In some embodiments, the variant Fc region has at least one amino acid substitution compared to the Fc region of a wild-type IgG. In some embodiments, the variant Fc region has one or more amino acid substitutions and one or more amino acid deletions in the Fc region of the wild-type antibody. In some embodiments, the variant Fc region has at least one or two amino acid deletions in the Fc region described herein. In some embodiments, the variant Fc region has at least one, two, three, or more amino acid substitutions

in the Fc region described herein. In some embodiments, the variant Fc region has at least one, two, three or more amino acid substitutions in the Fc region described herein and at least one or two deletions in the Fc region described herein. In some embodiments, the variant Fc region has at least about 80%, 90%, 95%, 96%, 97%, 98%, 99%, or more homology to a wild-type Fc region and/or a parent Fc region.

“Fc receptor” or “FcR” refers to a molecule that binds to the Fc region of an antibody. In some embodiments, the FcR is a native human FcR. In some embodiments, the FcR is a receptor that binds to an IgG antibody, i.e., FcγR, including three receptors, FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16), as well as allelic variants and alternative splice forms of the receptors. The FcγRII receptors include FcγRIIA and FcγRIIB, and the FcγRIII receptors include FcγRIIIA and FcγRIIIB.

The FcγR can be classified into activating receptors (FcγRI, FcγRIIA, FcγRIIC, FcγRIIIA, and FcγRIIIB, also known as CD64, CD32A, CD32C, CD16A, and CD16B) and inhibitory receptors (FcγRIIB, also known as CD32B) based on receptor function. The activating receptor comprises an immunoreceptor tyrosine-based activation motif (or ITAM) in the cytoplasmic domain thereof, which functions to transmit an activation signal and facilitate cell activation. The inhibitory receptor comprises an immunoreceptor tyrosine-based inhibitory motif (or ITIM) in the cytoplasmic domain thereof, which functions to inhibit cell activation. The effector functions of the activating FcγR are mainly ADCC, ADCP, and antigen presentation; the effector functions of the inhibitory FcγR are mainly inhibiting, cleaning, and the like. FcγRIIB is the only inhibitory FcγR expressed in humans and mice, and expression of FcγRIIB is associated with the decreased antibody curative effect in antibodies directly targeting tumors.

Different FcγRs have different cell expression profiles. For example, FcγRIIIA (CD16A) is expressed on macrophages, monocytes, natural killer cells (NK cells), and the like. The FcγRIIIA receptor is the only receptor expressed on NK cells, which can mediate ADCC function.

The term “FcR” also includes the neonatal receptor (FcRn). FcRn is an IgG antibody receptor located on the surface of cell membranes. FcRn is responsible for the transfer of maternal IgGs to the fetus and regulates the homeostasis of immunoglobulins *in vivo*. The FcRn can be combined with the Fc part of the IgG, prevents the IgG molecule from being cracked by lysosomes, can increase the half-life of the IgG *in vivo*, and participates in the *in vivo* transportation, maintenance, distribution, and metabolism processes of the IgG.

The IgG1-IgG4 subclasses have different abilities to bind to Fc receptors. IgG1 and IgG3 are universal ligands for different FcγRs, which bind to all FcγRs and have a strong ADCC effect. IgG2 or IgG4, also commonly referred to as the “inert” IgG subclass, is used to avoid immune activation effects. Indeed, many mAbs select IgG4 as the stem of the antibody to avoid ADCC effects. However, IgG2 and IgG4 are not completely “inert” and can bind to the activating forms of FcγRIIA-H131 and FcγRI, respectively, thereby initiating neutrophil activation.

Furthermore, in actual circumstances, there is a need to reduce ADCC effects caused by the IgG1 subclass, and in the prior art, “LALA” (L234A + L235A) mutation of IgG1, which can reduce the binding affinity of the Fc region of an antibody to FcγR by 100 times, has been widely used. The Fc mutant obtained by the present application, however, has lower binding affinity to FcγR compared to the “LALA” mutation, and thus more strongly reduces ADCC effects.

In the context of ADCC/ADCP/CDC, the expression “reduced ADCC and/or ADCP and/or CDC effector function” or “reduced ADCC/ADCP/CDC effector function” and similar expressions refer to a sufficiently high reduction in the value of ADCC and/or ADCP and/or CDC effector function caused by the Fc mutant of the present application, the polypeptide comprising the Fc mutant, or the like, as compared to the value of ADCC and/or ADCP and/or CDC effector function caused by the corresponding wild-type molecule, such that those skilled in the art will consider the reduction to be statistically significant within the corresponding biological context. For example, in certain embodiments, the reduction in the two values is, for example, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, or greater than about 100%, or even greater.

“Amino acid substitution” refers to the replacement of at least one amino acid residue present in a predetermined amino acid sequence by another, different “substituted” amino acid residue.

The term “conservative substitution” refers to a substitution of an amino acid by another amino acid of the same class, for example, the substitution of an acidic amino acid by another acidic amino acid, the substitution of a basic amino acid by another basic amino acid, or the substitution of a neutral amino acid by another neutral amino acid. Exemplary substitutions are shown in the table below:

Original residue	Exemplary substitution	Preferred conservative substitution
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Nle	Leu
Leu (L)	Nle; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr

Original residue	Exemplary substitution	Preferred conservative substitution
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Nle	Leu

Amino acids can be grouped by common side chain properties: (1) hydrophobicity: Ile, Met, Ala, Val, Leu, and Ile; (2) neutral hydrophilicity: Cys, Ser, Thr, Asn, and Gln; (3) acidity: Asp and Glu; (4) alkalinity: His, Lys, and Arg; (5) residues affecting chain orientation: Gly and Pro; and (6) aromaticity: Trp, Tyr, and Phe. Non-conservative substitutions require the exchange of a member of one of these classes for another class.

“Amino acid deletion” refers to the removal of at least one amino acid residue from a predetermined amino acid sequence.

The terms “host cell”, “host cell line” and “host cell culture” are used interchangeably and refer to cells into which exogenous nucleic acids are introduced, including progenies of such cells. Host cells include “transformants” and “transformed cells”, which include original primary transformed cells and progenies derived therefrom, regardless of the number of passages. Progeny may not be exactly the same as parent cells in terms of nucleic acid content, and may comprise mutations. Mutant progenies having the same function or biological activities that are screened or selected from the initially transformed cells are included herein.

The calculation of sequence identity between sequences is performed as follows.

To determine the percent identity of two amino acid sequences or two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., for optimal alignment, gaps can be introduced in one or both of the first and second amino acid sequences or nucleic acid sequences, or non-homologous sequences can be discarded for comparison). In one preferred embodiment, for comparison purposes, the length of the aligned reference sequence is at least 30%, preferably at least 40%, more preferably at least 50% or 60%, and even more preferably at least 70%, 80%, 90%, or 100% of the length of the reference sequence. Amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, the molecules are identical at this position.

A mathematical algorithm can be used to compare two sequences and calculate percent identity between the sequences. In one preferred embodiment, the percent identity between two amino acid sequences is determined with the Needleman and Wunsch algorithm ((1970) *J. Mol. Biol.*, 48:444-453; available at <http://www.gcg.com>) which has been integrated into the GAP program of the GCG software package, using the Blossum 62 matrix or PAM250 matrix and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In another preferred embodiment, the percent identity between two nucleotide acid sequences is determined with the GAP program of the GCG software package (available at <http://www.gcg.com>), using the NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred

parameter set (and one that should be used unless otherwise stated) is a Blossum 62 scoring matrix with a gap penalty of 12, a gap extension penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid sequences or nucleotide sequences can also be determined with PAM120 weighted remainder table, a gap length penalty of 12 and a gap penalty of 4, using the E. Meyers and W. Miller algorithm ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0).

Target antigen of antibody

The antibody comprising the Fc mutant provided herein can target any antigen, including but not limited to proteins, subunits, domains, motifs, and/or epitopes belonging to the following target antigens. The target antigens are, for example, cytokines, membrane binding factors, enzymes, receptors, ligands, pathogens and toxins thereof, virus particles, tumor-associated factors, signaling pathway member molecules, or the like. Suitable antigens depend on the desired application. For anti-cancer therapy, it is desirable to have targets whose expression is restricted within the cancer cells. Some targets that have proven particularly suitable for antibody therapy are those with signaling functions. Other therapeutic antibodies exert their effect by inhibiting the binding between the receptor and the conjugate ligand thereof to block the signaling of the receptor.

Many antibodies that have been approved for clinical trials or are under development may benefit from the Fc mutant of the present invention. Thus, the variable regions of the antibodies can be integrated with the Fc mutant disclosed herein to form products with improved superior properties. In one embodiment, the Fc mutant disclosed herein may be integrated into humanized antibodies, affinity-matured antibodies, and engineered antibodies, e.g., fused to the heavy chain variable regions thereof.

Additional modifications of Fc region

The Fc mutant provided herein, the fusion protein (e.g., antibody) comprising the Fc mutant, and the like can be further modified using a variety of methods already disclosed in the art, e.g., other modifications for reducing immunogenicity and improving stability, solubility, functions, and clinical benefits. Such modifications include, but are not limited to, for example, modifications at positions 252, 254, and 256, which can increase serum half-life.

EXAMPLE

The following examples further illustrate the present invention. However, it should be understood that the examples are described by way of illustration rather than limitation, and various modifications may be made by those skilled in the art.

Unless otherwise indicated, conventional methods of chemistry, biochemistry, organic chemistry, molecular biology, microbiology, recombinant DNA techniques, genetics, immunology and cell biology that are known in the art will be employed for the implementation of the present invention.

Example 1. Design of Fc Mutants

Given that the interaction of an antibody Fc region with an Fc receptor may have adverse effects, it is sometimes desirable in monoclonal antibody applications to eliminate effector functions of the Fc region (e.g., ADCC and CDC). For example, for the IgG1 subclass antibody, ADCC function is achieved primarily through the binding of the Fc region to FcγRIIIA. For the IgG1 subclass antibody requiring reduced ADCC and CDC functions, the Fc region thereof needs to be engineered to reduce binding to the Fcγ receptor. Therefore, this example explores the key sites for the interaction of human IgG1 Fc with FcγR based on the cocrystal structure of the human IgG1 Fc and FcγR, and designs the corresponding Fc mutant to reduce the interaction thereof with FcγR.

The crystal structure (PDB: 3SGJ) of the human IgG1 Fc and human CD16A (FcγRIII) is shown in FIG. 1, wherein two segments of the Fc, P232-V240 and N325-E333, form the binding site for the CD16A epitope, wherein the amino acid P329 of the Fc interacts with the π -bond formed between amino acids W90 and W113 of the CD16A, which is the key amino acid in their binding interface. Based on the key segment and the amino acids, the inventors designed the Fc mutants as shown in Table 1 based on the intermolecular interaction interface.

In this example, an IgG1 monoclonal antibody (Fcmut-01) against human claudin18.2 protein obtained by internal screening of Innovant Biologics was used as an example for the relevant design and study. That is, a series of mutants having different Fc mutations (Fcmut-02 to Fcmut-024) shown in Table 1 were obtained based on Fcmut-01 as a parent and a control. Fcmut-25 was Herceptin (Genentech), and Fcmut-26 to Fcmut 32 were different engineerings on the Fc of the Herceptin.

Table 1. Design of Fc Mutants

Molecule	Fc subtype	SEQ ID NO		Fc mutation site (according to EU index in Kabat)			
		Heavy chain	Light Chain	234	235	329	330
Fcmut-01	IgG1-WT	SEQ ID NO :1	SEQ ID NO :9	L	L	P	A
Fcmut-02	IgG1-mut	SEQ ID NO :2	SEQ ID NO :9	L	L	Deletion	A
Fcmut-03	IgG1-mut	SEQ ID NO :3	SEQ ID NO :9	L	L	Deletion	G
Fcmut-04	IgG1-mut	SEQ ID NO :4	SEQ ID NO :9	L	L	Deletion	Deletion
Fcmut-05	IgG1-mut	SEQ ID NO :5	SEQ ID NO :9	A	A	P	A
Fcmut-06	IgG1-mut	SEQ ID NO :6	SEQ ID NO :9	A	A	Deletion	A
Fcmut-07	IgG1-mut	SEQ ID NO :7	SEQ ID NO :9	A	A	Deletion	G
Fcmut-08	IgG1-mut	SEQ ID NO :8	SEQ ID NO :9	A	A	Deletion	Deletion
Fcmut-09	IgG2-WT	SEQ ID NO :10	SEQ ID NO :9	V	A	P	A
Fcmut-10	IgG2-mut	SEQ ID NO :11	SEQ ID NO :9	V	A	Deletion	A
Fcmut-11	IgG2-mut	SEQ ID NO :12	SEQ ID NO :9	V	A	Deletion	G
Fcmut-12	IgG2-mut	SEQ ID NO :13	SEQ ID NO :9	V	A	Deletion	Deletion
Fcmut-13	IgG2-mut	SEQ ID NO :14	SEQ ID NO :9	A	A	P	A
Fcmut-14	IgG2-mut	SEQ ID NO :15	SEQ ID NO :9	A	A	Deletion	A
Fcmut-15	IgG2-mut	SEQ ID NO :16	SEQ ID NO :9	A	A	Deletion	G

Fcmut-16	IgG2-mut	SEQ ID NO :17	SEQ ID NO :9	A	A	Deletion	Deletion
Fcmut-17	IgG4-S228P	SEQ ID NO :18	SEQ ID NO :9	F	L	P	S
Fcmut-18	IgG4-mut	SEQ ID NO :19	SEQ ID NO :9	F	L	Deletion	S
Fcmut-19	IgG4-mut	SEQ ID NO :20	SEQ ID NO :9	F	L	Deletion	G
Fcmut-20	IgG4-mut	SEQ ID NO :21	SEQ ID NO :9	F	L	Deletion	Deletion
Fcmut-21	IgG4-mut	SEQ ID NO :22	SEQ ID NO :9	A	A	P	S
Fcmut-22	IgG4-mut	SEQ ID NO :23	SEQ ID NO :9	A	A	Deletion	S
Fcmut-23	IgG4-mut	SEQ ID NO :24	SEQ ID NO :9	A	A	Deletion	G
Fcmut-24	IgG4-mut	SEQ ID NO :25	SEQ ID NO :9	A	A	Deletion	Deletion
Fcmut-25	IgG1-WT	SEQ ID NO :26	SEQ ID NO :34	L	L	P	A
Fcmut-26	IgG1-mut	SEQ ID NO :27	SEQ ID NO :34	L	L	Deletion	A
Fcmut-27	IgG1-mut	SEQ ID NO :28	SEQ ID NO :34	L	L	Deletion	G
Fcmut-28	IgG1-mut	SEQ ID NO :29	SEQ ID NO :34	L	L	Deletion	Deletion
Fcmut-29	IgG1-mut	SEQ ID NO :30	SEQ ID NO :34	A	A	P	A
Fcmut-30	IgG1-mut	SEQ ID NO :31	SEQ ID NO :34	A	A	Deletion	A
Fcmut-31	IgG1-mut	SEQ ID NO :32	SEQ ID NO :34	A	A	Deletion	G
Fcmut-32	IgG1-mut	SEQ ID NO :33	SEQ ID NO :34	A	A	Deletion	Deletion

Example 2. Expression and Purification of Antibodies Carrying Fc Mutation

Plasmid construction: The nucleotide sequences of the heavy chain Fc mutation described above and the light chain were obtained according to the conventional experimental methods and cloned into pcDNA3.1 vectors to obtain each plasmid.

Expression and purification of proteins

Preparation of transiently transfected plasmids: 1/10 (based on the transfection volume) of Opti-MEM™ reduced serum medium (Gibco, Catalog No. 31985-070) was added to the plasmid mixture (50 µg/50 mL, mass ratio of the heavy chain and light chain = 1:1). The Opti-MEM™ medium containing plasmids was filtered into a new 50-mL centrifuge tube, and filtered PEI (1 g/L, Polysciences) was added to the centrifugal tube (mass ratio of plasmid to PEI = 1:3). The mixture was mixed well and let stand for 20 min.

Cell transfection: The DNA/PEI mixture obtained above was poured gently to Expi293 cells (Gibco) and mixed

well. The cells were transfected at 37 °C/8% CO₂ for 14 h, then 0.1% valproic acid sodium salt (VPA) (2.2 M, Sigma), 2.5% glucose (200 g/L, Sigma), and 2.5% Feed solution (1 g/L Phytone peptone + 1 g/L Difco Select Phytone) were added according to the volume of transfected cells, and the cells were incubated at 37 °C/8% CO₂ for 7d.

Product purification: The obtained cell culture broth was centrifuged at 4000 rpm for 50 min, and the supernatant was collected and purified by a pre-packed column Hitrap Mabselect Sure (GE, 11-0034-95). The specific procedures are as follows: The packed column was equilibrated with 5 column volumes of equilibration buffer (20 mM Tris, 150 mM NaCl, pH 7.2) before purification; the collected supernatant was loaded on the column, and then the column was washed with 10 column volumes of equilibration buffer to remove non-specific binding proteins; the column was washed with 5 column volumes of eluent buffer (100 mM sodium citrate, pH 3.5), and the eluate was collected. The eluate was adjusted to pH 6.0 with 2 M Tris and the concentration was measured to give purified antibody products.

The collected antibody products were buffer-exchanged into PBS (Gibco, 70011-044) by ultrafiltration concentration, and further separated and purified using superdex200 increase (GE, 10/300GL, 10245605). The elution peak of the monomer was collected, and the equilibration buffer and elution buffer for the column were PBS (Gibco, 70011-044).

Example 3. Determination of Affinity of Fc Mutants for Fc Receptors

I. Determination of affinity of antibodies carrying Fc mutants by SPR

The binding of the antibody carrying the Fc mutant obtained in the present invention to human FcγR was determined using surface plasmon resonance (SPR), wherein the equilibrium dissociation constant (KD) for each antibody mutant to FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, and FcRn was specifically determined. Based on the principle of SPR, when a beam of polarized light entered the end face of a prism at a certain angle, surface plasma waves were generated at the interface between the prism and a gold film, causing free electrons in a metal film to generate resonance, namely surface plasmon resonance. When in analysis, a biomolecule recognition membrane was fixed on the surface of a sensing chip, then a sample to be detected flowed on the surface of the chip. If there were molecules capable of interacting with the biomolecule recognition membrane on the surface of the chip in the sample, the refractive index of the gold film surface was changed, finally causing changes in the SPR angle. The information such as the affinity and the kinetic constant of an analyte could be obtained by detecting the SPR angle changes.

In this example, the KD of the antibody carrying the Fc region mutation obtained in Example 2 and human FcγR was determined by Biacore (Cytiva, T200). The specific procedures were as follows: Each of FcγR and FcRn proteins (for information of each Fc receptor, see Table 2 below) containing a histidine tag was captured to the chip surface to which anti-histidine antibodies were coupled, and the binding and dissociation between the proteins on the chip surface and antibodies in the mobile phase were detected to obtain affinity and kinetic constants. The method comprises chip preparation and affinity detection. The assay procedure used 10×HBS-EP+ (BR-1006-69, Cytiva) diluted 10 times as an experimental buffer.

Table 2. Information about receptor for detection

Receptor name	Tag	Cat#	Manufacturer
Human FcγRIIIB/CD16B (NA1)	his	CDB-H5227	Acro
Human FcγRIIIB/CD16B (NA2)	his	CDB-H5222	Acro
Human FcRn/FCGRT & B2M heterodimeric protein	His, Strep II	FCM-H5286	Acro
Human FcγRIIIA/CD16A (V176) protein	his	CD8-H52H4	Acro
Human FcγRIIIA/CD16A (F176) protein	his	CDA-H5220	Acro
Human CD32A/FCGR2A protein (167his)	his	10374-H27H1	SINO
Human CD32A/FCGR2A protein (167Arg)	his	10374-H27H	SINO
Human CD32B/FCGR2B protein	his	10259-H08H	SINO
Human CD64/FCGR1A protein	his	10256-H08S-B	SINO

The specific procedures were as follows according to the manufacturer's instructions:

Chip preparation: The anti-histidine antibody in the histidine capture kit was coupled on the surface of a CM5 chip (29-1496-03, Cytiva) using the amino coupling kit (BR-1006-33, Cytiva) and the histidine capture kit (28995056, Cytiva), and the remaining activation sites were blocked by injection of 1 M ethanolamine after coupling.

Affinity assay: Each cycle included capture of the receptor, binding of a certain concentration of the antibody carrying the Fc region mutation of the present application, and regeneration of the chip. Each affinity assay cycle was performed on each antibody mutant solution after gradient dilution (0, 12.5, 25, 50, 100, 200, and 400 nM dilution gradient when binding to FcγRs; 0, 50, 100, 200, 400, 800, and 1600 nM dilution gradient when binding to FcRn) in an order from low to high concentrations. In each cycle, the antibody mutant solution flowed over the chip surface at a flow rate of 30 μL/min, with the binding time of 60 s and the dissociation time of 60 s. Finally, the chip was regenerated using 10 mM Glycine pH 1.5 (BR-1003-54, Cytiva). The obtained data were analyzed using Biacore T200 analysis software (version number 3.1) and using an analysis 1:1 binding or homeostasis analysis model to obtain the corresponding results.

Table 3 below shows the affinity data for each antibody mutant to each Fc receptor in the study, and FIG. 2 shows the fitted curve for the corresponding molecule.

From the results, it can be seen that: As a control antibody in the study, IgG1 wild-type Fcmut-01 antibody has high affinity for CD64 with the K_D value of $1.07\text{E-}09$, binds to the two subtypes H167 and R167 of CD32A with the K_D values of $2.01\text{E-}07$ and $4.60\text{E-}08$, respectively, has affinity for the two subtypes F176 and V176 of CD16A of $1.57\text{E-}07$ and $2.44\text{E-}08$, respectively, and has weak binding to CD16B (NA1), CD16B (NA2), and CD32B.

Antibody molecules carrying the Fc mutation do not bind to CD16A (F176), CD16A (V176), CD16B (NA1), CD16B (NA2), CD32A (H167), CD32A (R167), and CD32B except the mutant Fcmut-05 which has a relatively weak affinity for CD16A (V176) ($3.06\text{E-}07$). With respect to CD64 which strongly binds to wild-type IgG1, none of the mutant Fcmut-06/07/08 binds to CD64, while the binding of Fcmut-02/03/04/05 to CD64 is also greatly reduced by 8.7 times, 12.9 times, 14.02 times, and 50.75 times, respectively, as compared to the control Fcmut-01. Furthermore, Fcmut-26 to Fcmut-32 also show similar results. Compared to Fcmut-25, antibody

molecules carrying the Fc mutation do not bind to CD16A (F176), CD16A (V176), CD16B (NA1), CD16B (NA2), CD32A (H167), CD32A (R167), and CD32B except Fcmut-29.

F176 and V176 are the major genotypes of CD16A, and amino acid position 176 of CD16A is located in the binding region with Fc according to the crystal structure, thereby having an important effect on the affinity of CD16A for Fc. The Fc mutant obtained in the present application does not substantially interact with genotypes F176 and V176 of CD16A, so that it can be shown that the Fc mutant obtained in the present application will not substantially interact with all functional CD16A and thus will not cause ADCC effects. A protein molecule (e.g. an antibody) comprising the Fc mutant of the present application therefore has substantially no ADCC effector function.

The Fc region of an antibody is known to not bind to FcRn under neutral pH conditions but only under acidic conditions, which is the primary mechanism for a particularly long half-life of the antibody molecule. The control antibody Fcmut-01 is detected to have affinity for FcRn of 3.86E-07 at pH 6.0, but not to bind to FcRn at pH 7.0. The antibody molecule carrying the Fc mutation obtained in the study binds to FcRn in the same manner as the control antibody Fcmut-01 under the same conditions (FIGs. 2i and 2j), indicating that the Fc mutant obtained in the study does not affect the binding to FcRn.

FcRn is expressed on a variety of cells *in vivo*, and the binding of FcRn to the Fc region is pH dependent, the binding only around weak acidity pH 6.0, and no binding under neutral pH, thereby prolonging the half-life of the corresponding antibody. The experimental data of the present application show that the Fc region mutation carried by the antibody does not affect the binding of the antibody molecule to FcRn, so that the FcRn can still prolong the *in vivo* half-life of the antibody mutant of the present application.

The antibody mutant obtained in the present application does not bind to CD32B, which shows that the curative effect of the antibody can be enhanced by mutating the Fc region of the antibody.

The “LALA” mutation (Fcmut-05) widely used in the prior art reduces the binding affinity of the Fc region of an antibody to FcγR by 100 times. The Fc mutant obtained by the present application, however, has lower binding affinity to FcγR compared to the “LALA” mutation, and thus more strongly reduces ADCC effects.

Wild-type IgG2 and IgG4 have a weak ADCC effect or have no ADCC effect, and therefore many antibody molecules for which ADCC effects are desired to be avoided select for production an Fc region of the IgG2 subtype or the IgG4 subtype. However, in some cases, it is still desirable to further reduce the ADCC effector function of the IgG2 subtype or the IgG4 subtype. Therefore, the applicants further investigated the binding of the corresponding sites of Fc regions of the IgG2 and IgG4 subtypes (see Table 1) after corresponding mutations to various FcRs. The data show that the IgG2 subtype or IgG4 subtype Fc mutant comprising the corresponding mutation of the present application reduces the binding to FcγR relative to wild-type Fc.

Table 3. Binding constants of Fc mutants to Fc receptors

patent-ID	CD16A (F176)	CD16A (V176)	CD16B (NA1)	CD16B (NA2)	CD32A (H167)	CD32A (R167)	CD32B	CD64	FcRn (6.0)	FcRn (7.0)
Fcmut-01	1.57E-07	2.44E-08	weak	weak	2.01E-07	4.60E-08	weak	1.07E-09	3.86E-07	N.B.
Fcmut-02	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	9.31E-09	4.47E-07	N.B.

Fcmut-03	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	1.38E-08	3.17E-07	N.B.
Fcmut-04	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	1.50E-08	5.05E-07	N.B.
Fcmut-05	N.B.	3.06E-07	N.B.	N.B.	N.B.	N.B.	N.B.	5.43E-08	4.19E-07	N.B.
Fcmut-06	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	2.84E-07	N.B.
Fcmut-07	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	3.74E-07	N.B.
Fcmut-08	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	N.B.	4.02E-07	N.B.

N. B.: non-bound

II. The binding of the Fc mutant of the present invention to Fc receptor as determined by bio-layer interferometry
The affinity (KD) for binding of the Fc mutant of the present invention to human Fc receptors was determined by bio-layer interferometry (BLI).

Half an hour before the experiment, an appropriate number of HIS1K sensors (18-5120, Sartorius) were taken according to the number of samples and soaked in the SD buffer (1× PBS, 0.1% BSA, 0.05% Tween-20), and the buffer used in the experiment was changed to 10 mM HEPS, 150 mM NaCl, 3 mM EDTA, 0.05% P20, pH 6.0 when FcRn was bound. The antibody was diluted to 200 nM and the Fc receptor (for sample information, see Table 2) was diluted to 100 nM.

200 μL of SD buffer, 200 μL of a labeled antibody solution, and 200 μL of Fc receptors were added to 96-well black polystyrene microplates (Greiner, 655209), respectively. Detection was conducted using ForteBio Octet Red96e, and the sensors were arranged according to the positions of the samples. The instrument settings were as follows: The operation procedures were baseline equilibration 120 s, Fc receptor immobilization 100 s, baseline equilibration 120 s, antibody binding 60 s, and dissociation 60 s at 1000 rpm and 30 °C. After the experiment was completed, KD values were analyzed using ForteBio Octet analysis software.

The results are shown in Table 4 below and FIG. 3. Compared to Fcmut-25, antibody molecules carrying the Fc mutation do not bind to CD16A (F176), CD16A (V176), CD16B (NA1), and CD16B (NA2) except Fcmut-29. The mutant Fcmut-26/27/28/29/30/31/32 do not bind to CD32A H167, CD32A R167, and CD32B. The mutant Fcmut-30/31/32 do not bind to CD64, and the binding of Fcmut-/26/27/28/29 to CD64 is also greatly reduced. Fc-25 is an antibody that binds to HER2, the constant region of which is the wild-type IgG1 sequence. From the results, it can be seen that deletion of P329 reduces the binding of the molecule to the Fc gamma receptor, but the binding to FcRn (pH 6.0) is not affected.

Table 4a. Mutants binding to CD16A V176 on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.297	9.43E-08	1.64E+05	1.54E-02
Fc-26	0.0029	N.B		
Fc-27	0.007	N.B		
Fc-28	0.0156	N.B		
Fc-29	0.0909	1.55E-07	1.43E+05	2.22E-02
Fc-30	0.0211	N.B		
Fc-31	0.0241	N.B		

Fc-32	0.0141	N.B
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Table 4b. Mutants binding to CD16A F176 on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.1082	1.02E-07	1.98E+05	2.01E-02
Fc-26	0.0018	N.B		
Fc-27	0.0023	N.B		
Fc-28	0.0118	N.B		
Fc-29	0.0439	2.06E-07	1.72E+05	3.54E-02
Fc-30	0.0232	N.B		
Fc-31	0.0262	N.B		
Fc-32	0.0166	N.B		

Table 4c. Mutants binding to CD16B NA1 on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.0531	6.45E-07	7.74E+04	4.99E-02
Fc-26	-0.002	N.B		
Fc-27	0.0017	N.B		
Fc-28	0.0115	N.B		
Fc-29	0.0346	2.21E-07	2.35E+05	5.21E-02
Fc-30	0.0204	N.B		
Fc-31	0.028	N.B		
Fc-32	0.0184	N.B		

Table 4d. Mutants binding to CD16B NA2 on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.0801	1.05E-06	5.40E+04	5.68E-02
Fc-26	-0.0022	N.B		
Fc-27	0.0037	N.B		
Fc-28	0.0103	N.B		
Fc-29	0.0331	4.82E-07	1.50E+05	7.23E-02
Fc-30	0.024	N.B		
Fc-31	0.0269	N.B		

Fc-32	0.0172	N.B
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Table 4e. Mutants binding to CD32A H167 on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.2124	6.12E-06	1.11E+04	6.81E-02
Fc-26	0.0058	N.B		
Fc-27	0.0058	N.B		
Fc-28	0.0142	N.B		
Fc-29	0.0301	N.B		
Fc-30	0.0171	N.B		
Fc-31	0.0214	N.B		
Fc-32	0.0097	N.B		

Table 4f. Mutants binding to CD32A R167 on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.1615	4.28E-06	1.66E+04	7.13E-02
Fc-26	0.0044	N.B		
Fc-27	0.0028	N.B		
Fc-28	0.0089	N.B		
Fc-29	0.0293	N.B		
Fc-30	0.0181	N.B		
Fc-31	0.0199	N.B		
Fc-32	0.0099	N.B		

Table 4g. Mutants binding to CD32B on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.0799	2.57E-07	2.18E+05	5.61E-02
Fc-26	-0.003	N.B		
Fc-27	-0.0037	N.B		
Fc-28	0.0066	N.B		
Fc-29	0.0269	N.B		
Fc-30	0.0171	N.B		
Fc-31	0.0214	N.B		
Fc-32	0.0083	N.B		

Table 4h. Mutants binding to CD64 on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.8932	9.48E-09	2.92E+05	2.77E-03
Fc-26	0.6477	5.33E-08	2.63E+05	1.40E-02
Fc-27	0.4326	1.13E-07	3.15E+05	3.56E-02
Fc-28	0.5144	4.66E-08	2.37E+05	1.10E-02
Fc-29	0.2287	4.45E-08	3.61E+05	1.61E-02
Fc-30	0.0202	N.B		
Fc-31	0.0274	N.B		
Fc-32	0.0162	N.B		

Table 4i. Mutants binding to FcRn on HIS1K sensor

Sample ID	Response	KD (M)	kon(1/Ms)	kdis(1/s)
Fc-25	0.2392	2.84E-08	4.30E+05	1.22E-02
Fc-26	0.3488	5.09E-08	4.19E+05	2.13E-02
Fc-27	0.2855	6.23E-08	4.57E+05	2.84E-02
Fc-28	0.3545	4.55E-08	3.80E+05	1.73E-02
Fc-29	0.6114	3.28E-08	4.26E+05	1.40E-02
Fc-30	0.4914	2.21E-08	4.49E+05	9.93E-03
Fc-31	0.5716	2.58E-08	4.34E+05	1.12E-02
Fc-32	0.4803	2.39E-08	4.44E+05	1.06E-02

Experimental Example 4. Affinity of Fc Mutant of Present Invention for C1q as Determined by Bio-Layer

Interferometry

The strength of the affinity of the Fc antibody for C1q directly determines whether the antibody has CDC effector function, and therefore this example determines whether each Fc mutant has CDC effector function by detecting the affinity of the Fc mutant for C1q.

The affinity (KD) for binding of the antibodies of the present invention to human C1q was determined by bio-layer interferometry (BLI). A BLI affinity assay was conducted according to the existing method (Estep, P *et al.*, High throughput solution based measurement of antibody-antigen affinity and epitope binding, *MAbs*, 2013.5(2); p. 270-8).

First, the EZ-Link™ Sulfo-NHS-LC-Biotin (21327, Thermo Scientific) was mixed with the antibody in a molar ratio of 3:1, left to stand, and used for biotin labeling. The mixture was centrifuged to remove unlabeled biotin, and the antibody was exchanged into a PBS solution in equal volume.

Half an hour before the experiment, an appropriate number of SA sensors (Foretbio, 18-5019) were taken according to the number of samples and soaked in the SD buffer (1× PBS, 0.1% BSA, 0.05% Tween-20). The antibody was diluted to approximately 100 nM, and C1q (A099, Complement Technology) was diluted to 40 nM.

200 μL of SD buffer, 200 μL of the labeled antibody solution, and 200 μL of the C1q antigen were added to 96-well black polystyrene microplates (Greiner, 655209), respectively. Detection was conducted using Fortebio Octet Red96e, and the sensors were arranged according to the positions of the samples. The instrument settings were as follows: The operation procedures were Baseline, Loading -3 nm, Baseline, Association (Kon), and Dissociation (Kdis); the run time of each procedure was dependent on the rates of association and dissociation of samples; the rotation speed was 1000 rpm, and the temperature was 30 °C. After the experiment was completed, KD values were analyzed using ForteBio Octet analysis software, the coordinate axis data were derived, and Graphpad Prism 8 software was used for plotting.

The results are shown in Table 5 and FIG. 2k. Only Fcmut-01 can bind to C1q, the affinity is 2.02E-08, and none of Fcmut-2 to Fcmut-8 binds to C1q. The results show that the Fc mutant in the study can reduce or prevent the binding of Fc to C1q, and thus can reduce or eliminate CDC effector function of the antibody. Fcmut-10 to Fcmut-16 and Fcmut-18 to Fcmut-24 also do not bind to C1q, as compared with corresponding wild-type controls. Furthermore, Fcmut-26 to Fcmut-32 also do not bind to C1q, as compared with Fcmut-25.

Table 5. Affinity of Fc mutants for C1q

Sample	Antigen	Response (nm)	KD (M)	Kon (1/Ms)	Kdis (1/s)
Fcmut-01	C1q	0.1582	2.02E-08	3.67E+06	7.41E-02
Fcmut-02		0.0007	Non-bound		
Fcmut-03		0.0016	Non-bound		
Fcmut-04		-0.0027	Non-bound		
Fcmut-05		-0.0033	Non-bound		
Fcmut-06		-0.0035	Non-bound		
Fcmut-07		-0.0134	Non-bound		

Fcmut-08		0.0004	Non-bound
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Experimental Example 5. Affinity of Antibody of Present Invention for Antigen as Determined by Bio-Layer Interferometry

The affinity assay was performed using the same BLI method as described in Example 4, except the following. Half an hour before the experiment, an appropriate number of AHC sensors (Foretbio, 18-5060) were taken according to the number of samples and soaked in the SD buffer (1× PBS, 0.1% BSA, 0.05% Tween-20). The antibody and Claudin18.2 (cp0007, Genscript) were diluted to 100 nM, respectively.

200 μ L of SD buffer, 200 μ L of the antibody, and 200 μ L of the Claudin18.2 antigen were added to 96-well black polystyrene microplates (Greiner, 655209), respectively. Detection was conducted using Fortebio Octet Red96e, and the sensors were arranged according to the positions of the samples. The instrument settings were as follows: The operation procedures were Baseline, Loading, Baseline, Association (Kon), and Dissociation (Kdis); the run time of each procedure was dependent on the rates of association and dissociation of samples; the rotation speed was 1000 rpm, and the temperature was 30 °C. After the experiment was completed, KD values were analyzed using ForteBio Octet analysis software.

The results are shown in Table 6. The KD values of Fcmut-02 to 08 and the antigen are in the same order of magnitude as the KD value of Fcmut-01 and the antigen, so that the specific mutation in the Fc region disclosed herein does not affect the affinity of the corresponding antibody for the antigen, further indicating that the antibody containing the Fc mutant of the present invention will retain the self-owned antigen affinity.

Table 6. Affinity of antibodies for antigens

Sample	Antigen	Response (nm)	KD (M)	Kon (1/Ms)	Kdis (1/s)
Fcmut-01	Claudin18.2	0.1493	3.32E-09	6.02E+04	2.00E-04
Fcmut-02		0.138	2.73E-09	7.32E+04	2.00E-04
Fcmut-03		0.1496	2.90E-09	6.90E+04	2.00E-04
Fcmut-04		0.1462	2.83E-09	7.07E+04	2.00E-04
Fcmut-05		0.153	3.17E-09	6.32E+04	2.00E-04
Fcmut-06		0.1444	2.44E-09	8.19E+04	2.00E-04
Fcmut-07		0.1538	2.47E-09	8.09E+04	2.00E-04
Fcmut-08		0.1517	2.41E-09	8.29E+04	2.00E-04

Example 6. Antibody-Mediated ADCC Effect

One of the major effector functions mediated by Fc γ R is antibody-dependent cell-mediated cytotoxicity (ADCC), which is mediated by Fc γ RIIIA (CD16A) on NK cells and macrophages. After the affinity of the antibody carrying the Fc mutation obtained in the present application for Fc receptors is investigated in the previous example, this example continues to investigate the ADCC effector function of the antibody mutant.

In this example, the Jurkat-ADCCNF-AT luciferase effector cell line (hereinafter referred to as ADCC effector cells) from Promega was used. The ADCC activity of the antibodies was detected by detecting the activation of

NF-AT signal. The specific experimental process was as follows:

1) Preparation of cells

Cells DANG-18.2 (CLS Cell Lines Service) overexpressing human claudin18.2 on the surface and ADCC effector cells were counted: Supernatants of cells DANG-18.2 and ADCC effector cells were removed by centrifugation. The cells were washed twice with a PBS solution and then resuspended in a detection medium (1640 medium with 5% low IgG serum (Gibco)). The concentration of ADCC effector cells was adjusted to 6×10^6 cells/mL and the concentration of DANG-18.2 cells was adjusted to 1×10^6 cells/mL.

2) Plating: The target cells DANG-18.2 were plated onto a 96-well plate at 25 μ L/well.

3) Serial dilutions of the antibody of the present invention were added: The initial concentration of each antibody sample carrying the Fc region mutation and the control sample were as listed in Table 7, followed by three-fold dilution to obtain 10 dilution gradients, which were added to the well plates in sequence at 25 μ L/well.

Table 7. Initial concentration of antibody

Protein	Fcmut-01	Fcmut-02	Fcmut-03	Fcmut-04	Fcmut-05	Fcmut-06	Fcmut-07	Fcmut-08
Initial well protein concentration (μ g/mL)	30	300	300	300	300	300	300	300

4) The ADCC effector cells were added to each well plate at 25 μ L/well.

5) The cells were incubated in an incubator at 37 $^{\circ}$ C for 12 h.

6) The 96-well plate was taken out and stood at room temperature for 10 min, and 75 μ L of thawed Luciferase assay reagent (Bio-GloTM Luciferase assay reagent) was added to each well. The mixture was detected using a microplate reader, and the concentration-dependent curve was fitted with GraphPad software.

As shown in FIG. 4, the control antibody Fcmut-01 has the Fc region of the wild-type IgG1 monoclonal antibody, which can effectively activate the NF-AT signal of ADCC effector cells by binding to the antigen on the target cell (DANG-18.2), thereby initiating the downstream signaling pathway of ADCC, indicating that the antibody has excellent ADCC killing ability. However, other antibodies carrying the Fc region mutations obtained in the present application exhibit very weak or nearly no ADCC effects, in particular: The mutant Fcmut-05 (carrying the L234A and L235A mutations) shows a very weak ADCC activity at a concentration 10 times greater than that of the control Fcmut-01, whereas the other mutants show no ADCC activity even at a high concentration 10 times greater than that of the control Fcmut-01, indicating that the ADCC effector function of the antibody molecule carrying the Fc region mutation obtained in the present application is substantially removed, and the result is consistent with the affinity data of each of the antibody molecules in Example 3 for CD16A.

According to the prior art, the LALA mutation of the Fc region can significantly reduce the ADCC effect of the antibody. The results of this example show that compared with the LALA mutation, the Fc mutant obtained in the present application has a larger reduction effect on the ADCC effect.

The antibody mutants of the present application obtained by mutation modifications (e.g., deletion and substitution) of one or more amino acids at positions 329, 330, 234, or 235 of the Fc region of the antibody substantially eliminate ADCC effector function, thereby indicating that the amino acid positions described

above are critical for ADCC/ADCP effector function of the antibody. When the target antibody needs to avoid ADCC/ADCP effector function in real need, those skilled in the art will be able to select, based on the present disclosure, a corresponding modification on one or more of the amino acids at positions 329, 330, 234, or 235 of the Fc region to produce an actual technical effect. Specifically, deletion of the amino acid at position 329, deletion of the amino acid at positions 329-330, deletion of the amino acid at position 329 and substitution of the amino acid at position 320 of the Fc region of the antibody, and combined use of the modifications described above with the LALA modification (L234A + L235A) are contemplated to obtain an antibody molecule that eliminates the ADCC/ADCP effector function.

CLAIMS

1. An Fc mutant, comprising one or more amino acid modifications relative to a human wild-type Fc region, wherein the modification is selected from amino acid position 329, 234, 235, or 330, according to EU index numbering as in Kabat.

2. The Fc mutant according to claim 1, comprising the following modification:

- 1) a deletion at amino acid position 329 ($\Delta 329$) according to EU index numbering as in Kabat; or
- 2) a deletion at amino acid positions 329 and 330 ($\Delta 329$ and $\Delta 330$) according to EU index numbering as in Kabat; or
- 4) the following modification, according to EU index numbering as in Kabat: $\Delta 329 + A330G$ or $\Delta 329 + S330G$; or
- 5) the following modification, according to EU index numbering as in Kabat: $L234A + L235A + \Delta 329$, $V234A + \Delta 329$, or $F234A + L235A + \Delta 329$; or
- 6) the following modification, according to EU index numbering as in Kabat: $L234A + L235A + \Delta 329 + \Delta 330$, $V234A + \Delta 329 + \Delta 330$, or $F234A + L235A + \Delta 329 + \Delta 330$; or
- 7) the following modification, according to EU index numbering as in Kabat: $L234A + L235A + A330G + \Delta 329$, $L234A + L235A + S330G + \Delta 329$, $V234A + L235A + A330G + \Delta 329$, $V234A + L235A + S330G + \Delta 329$, $F234A + L235A + S330G + \Delta 329$, or $F234A + L235A + A330G + \Delta 329$.

3. The Fc mutant according to claim 1 or 2, wherein the Fc mutant is a human IgG Fc mutant; preferably, the Fc mutant is an IgG1, IgG2, or IgG4 Fc mutant.

4. The Fc mutant according to any one of claims 1-3, comprising the following sequence:

- 1) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 2, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 2) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 3, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 3) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 4, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 4) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 5, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or
- 5) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 6, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the

6) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 7, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

8) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 11, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

10) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 13, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

12) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 15, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

14) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 17, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

16) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 20, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

18) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 22, or an amino acid

sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

19) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 23, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

20) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 24, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

21) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 25, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

22) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 27, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

23) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 28, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

24) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 29, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

25) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 30, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

26) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 31, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

27) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 32, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence, or

28) a sequence of amino acid positions 221-447 according to EU index in SEQ ID NO: 33, or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even more identity to the sequence, or consisting of the sequence.

5. A polypeptide, comprising the Fc mutant according to any one of claims 1-4.

6. The polypeptide according to claim 5, wherein the polypeptide is an antibody molecule; preferably, the antibody molecule is an IgG antibody molecule.

7. The antibody molecule comprising the Fc mutant according to claim 6, comprising the following heavy chain and light chain:

- 1) comprising a heavy chain set forth in SEQ ID NO: 2 and a light chain set forth in SEQ ID NO: 9; or
- 2) comprising a heavy chain set forth in SEQ ID NO: 3 and a light chain set forth in SEQ ID NO: 9; or
- 3) comprising a heavy chain set forth in SEQ ID NO: 4 and a light chain set forth in SEQ ID NO: 9; or
- 4) comprising a heavy chain set forth in SEQ ID NO: 5 and a light chain set forth in SEQ ID NO: 9; or
- 5) comprising a heavy chain set forth in SEQ ID NO: 6 and a light chain set forth in SEQ ID NO: 9; or
- 6) comprising a heavy chain set forth in SEQ ID NO: 7 and a light chain set forth in SEQ ID NO: 9; or
- 7) comprising a heavy chain set forth in SEQ ID NO: 8 and a light chain set forth in SEQ ID NO: 9; or
- 8) comprising a heavy chain set forth in SEQ ID NO: 11 and a light chain set forth in SEQ ID NO: 9; or
- 9) comprising a heavy chain set forth in SEQ ID NO: 12 and a light chain set forth in SEQ ID NO: 9; or
- 10) comprising a heavy chain set forth in SEQ ID NO: 13 and a light chain set forth in SEQ ID NO: 9; or
- 11) comprising a heavy chain set forth in SEQ ID NO: 14 and a light chain set forth in SEQ ID NO: 9; or
- 12) comprising a heavy chain set forth in SEQ ID NO: 15 and a light chain set forth in SEQ ID NO: 9; or
- 13) comprising a heavy chain set forth in SEQ ID NO: 16 and a light chain set forth in SEQ ID NO: 9; or
- 14) comprising a heavy chain set forth in SEQ ID NO: 17 and a light chain set forth in SEQ ID NO: 9; or
- 15) comprising a heavy chain set forth in SEQ ID NO: 19 and a light chain set forth in SEQ ID NO: 9; or
- 16) comprising a heavy chain set forth in SEQ ID NO: 20 and a light chain set forth in SEQ ID NO: 9; or
- 17) comprising a heavy chain set forth in SEQ ID NO: 21 and a light chain set forth in SEQ ID NO: 9; or
- 18) comprising a heavy chain set forth in SEQ ID NO: 22 and a light chain set forth in SEQ ID NO: 9; or
- 19) comprising a heavy chain set forth in SEQ ID NO: 23 and a light chain set forth in SEQ ID NO: 9; or
- 20) comprising a heavy chain set forth in SEQ ID NO: 24 and a light chain set forth in SEQ ID NO: 9; or
- 21) comprising a heavy chain set forth in SEQ ID NO: 25 and a light chain set forth in SEQ ID NO: 9; or
- 22) comprising a heavy chain set forth in SEQ ID NO: 27 and a light chain set forth in SEQ ID NO: 34; or
- 23) comprising a heavy chain set forth in SEQ ID NO: 28 and a light chain set forth in SEQ ID NO: 34; or
- 24) comprising a heavy chain set forth in SEQ ID NO: 29 and a light chain set forth in SEQ ID NO: 34; or
- 25) comprising a heavy chain set forth in SEQ ID NO: 30 and a light chain set forth in SEQ ID NO: 34; or
- 26) comprising a heavy chain set forth in SEQ ID NO: 31 and a light chain set forth in SEQ ID NO: 34; or
- 27) comprising a heavy chain set forth in SEQ ID NO: 32 and a light chain set forth in SEQ ID NO: 34; or
- 28) comprising a heavy chain set forth in SEQ ID NO: 33 and a light chain set forth in SEQ ID NO: 34.

8. A pharmaceutical composition, comprising the Fc mutant according to any one of claims 1-4, or the polypeptide according to any one of claims 5-7, and a pharmaceutically acceptable carrier.

9. Use of the Fc mutant according to any one of claims 1-4 in reducing or eliminating ADCC, ADCP, or CDC effector functions.

10. A nucleic acid molecule encoding the Fc mutant according to any one of claims 1-4, or encoding the

polypeptide according to any one of claims 5-7.

11. A vector, comprising the nucleic acid molecule according to claim 10.

12. A host cell, comprising the nucleic acid molecule according to claim 10 or the vector according to claim 11.

13. A method for treating a tumor in a subject, comprising administering an effective amount of the pharmaceutical composition according to claim 8 or the Fc mutant according to any one of claims 1-4 or the polypeptide according to any one of claims 5-7 to a subject in need thereof.

14. A kit, comprising the Fc mutant according to any one of claims 1-4 or the polypeptide according to any one of claims 5-7.

15. A method for preparing the Fc mutant according to any one of claims 1-4, or preparing the polypeptide according to any one of claims 5-7, comprising expressing the nucleic acid molecule according to claim 10 or expressing the vector according to claim 11 in the host cell according to claim 12 under appropriate conditions, wherein the method optionally further comprises recovering the expressed Fc mutant or polypeptide.

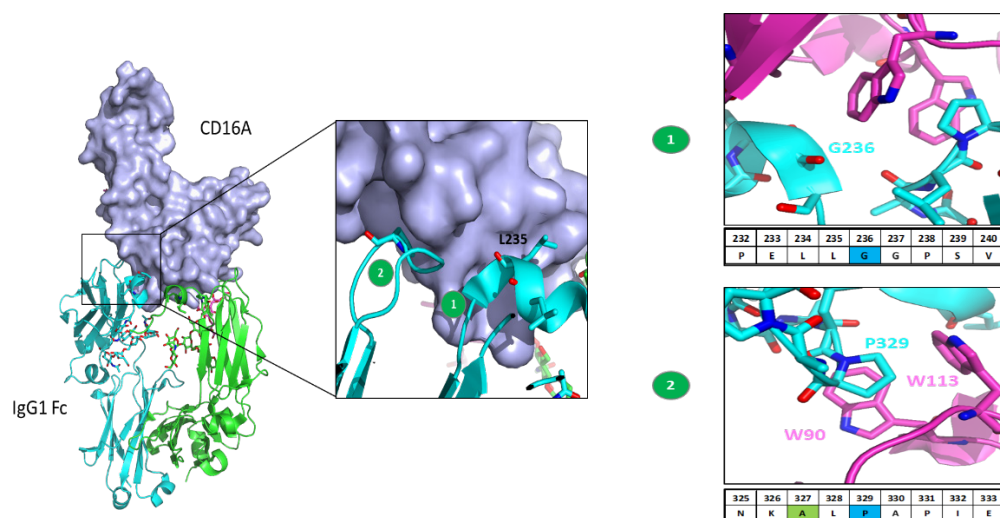


FIG. 1: crystal structure of human IgG1 Fc and human CD16A (PDB: 3SGJ)

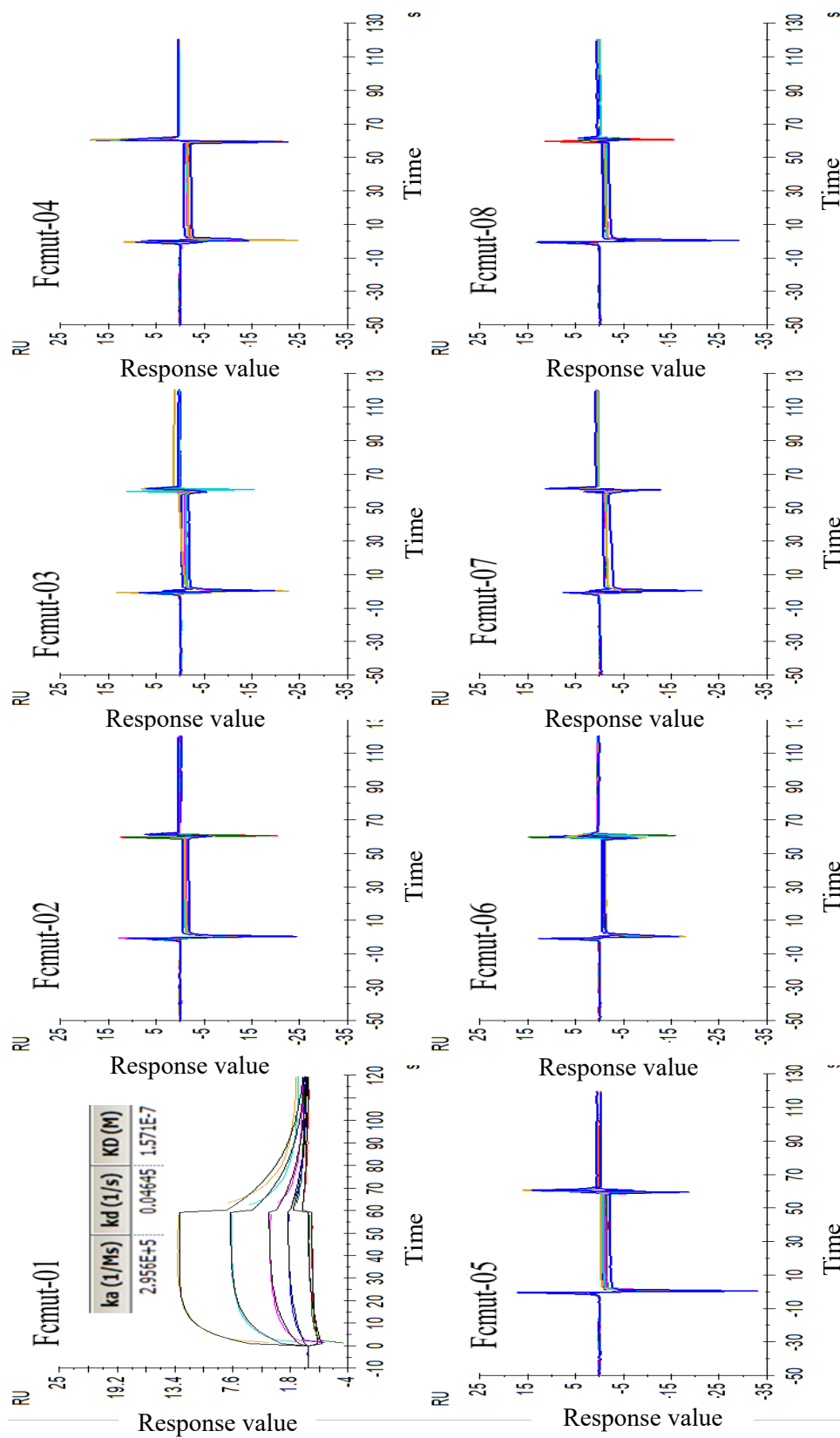


FIG. 2a

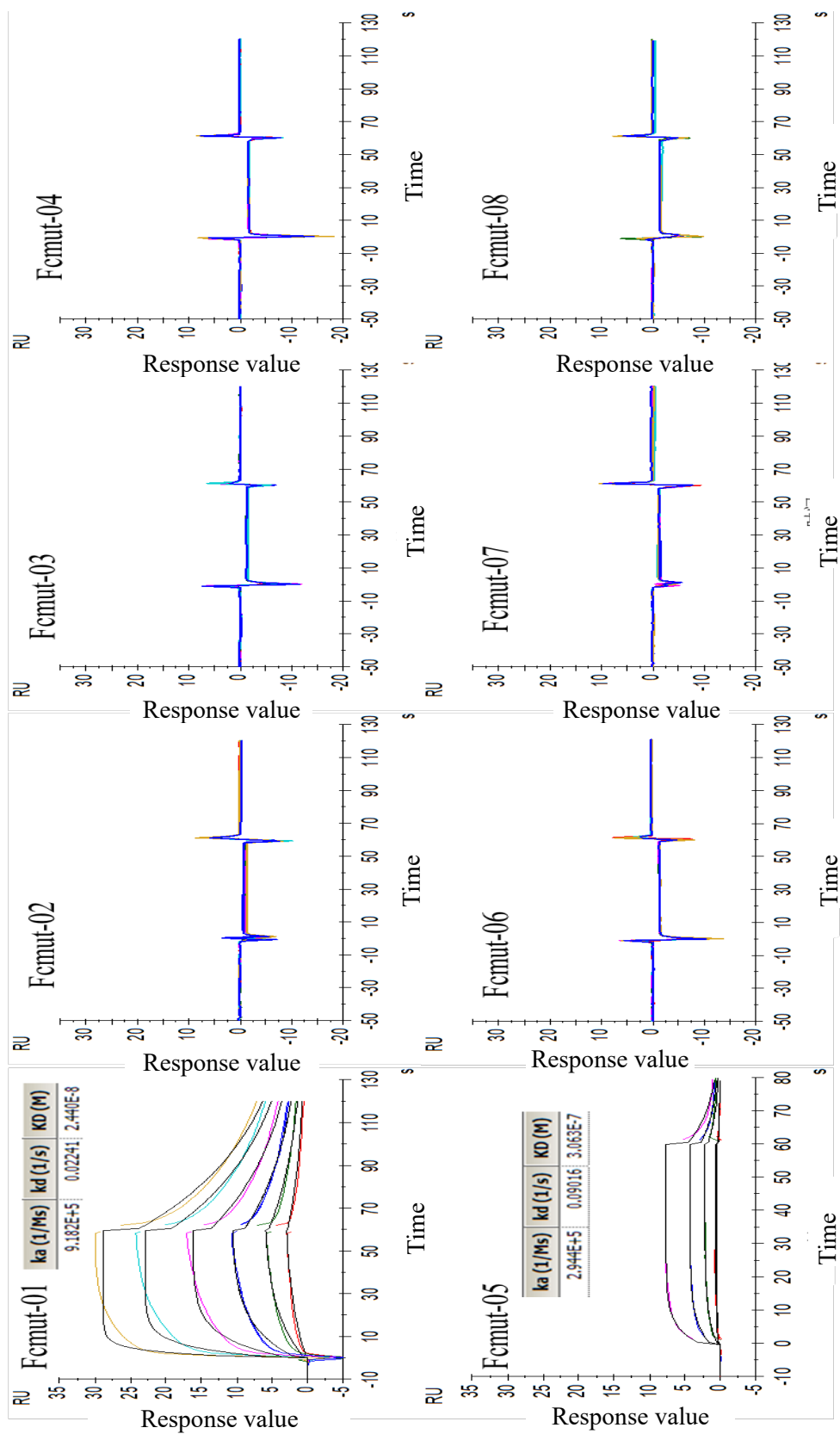


FIG. 2b

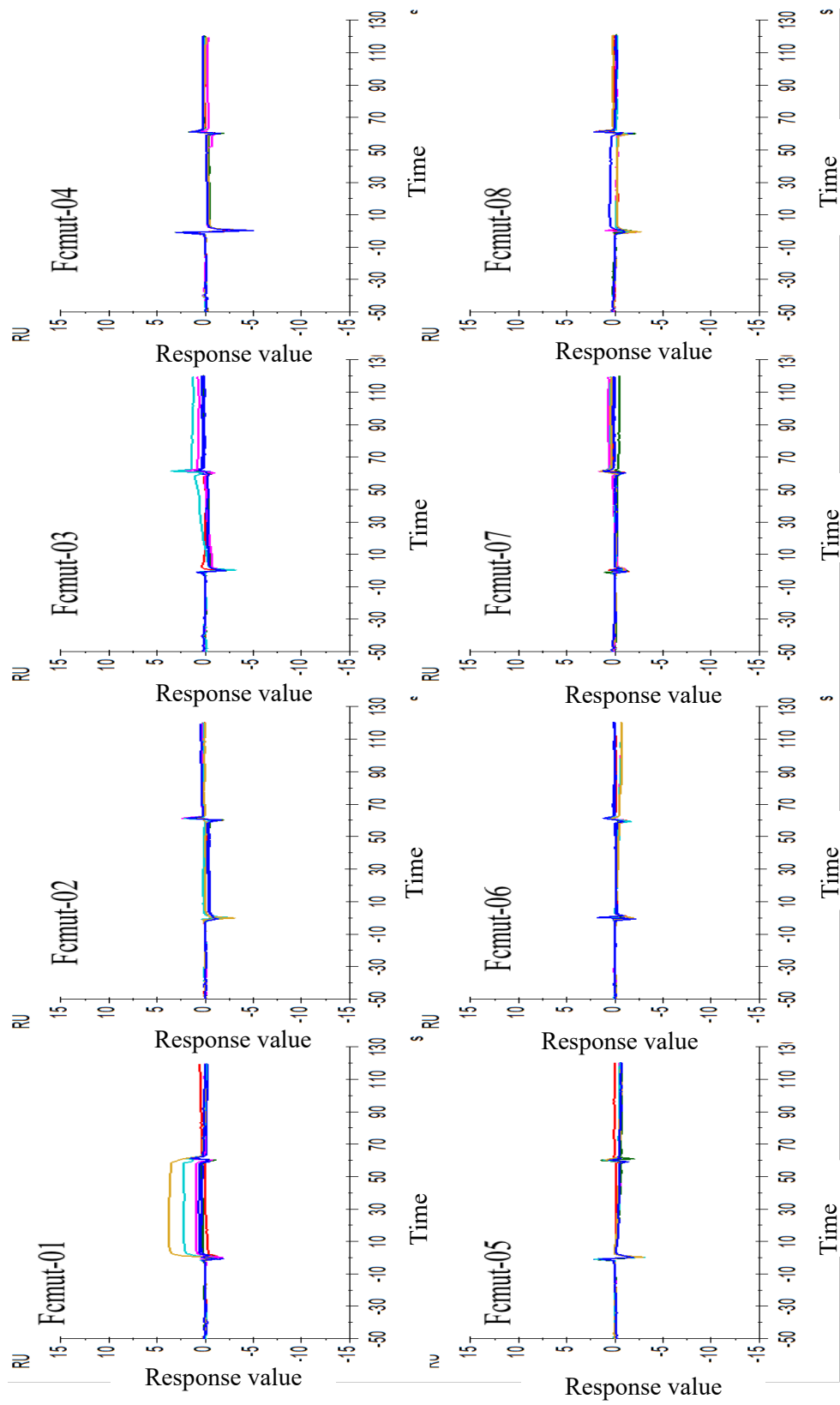


FIG. 2c

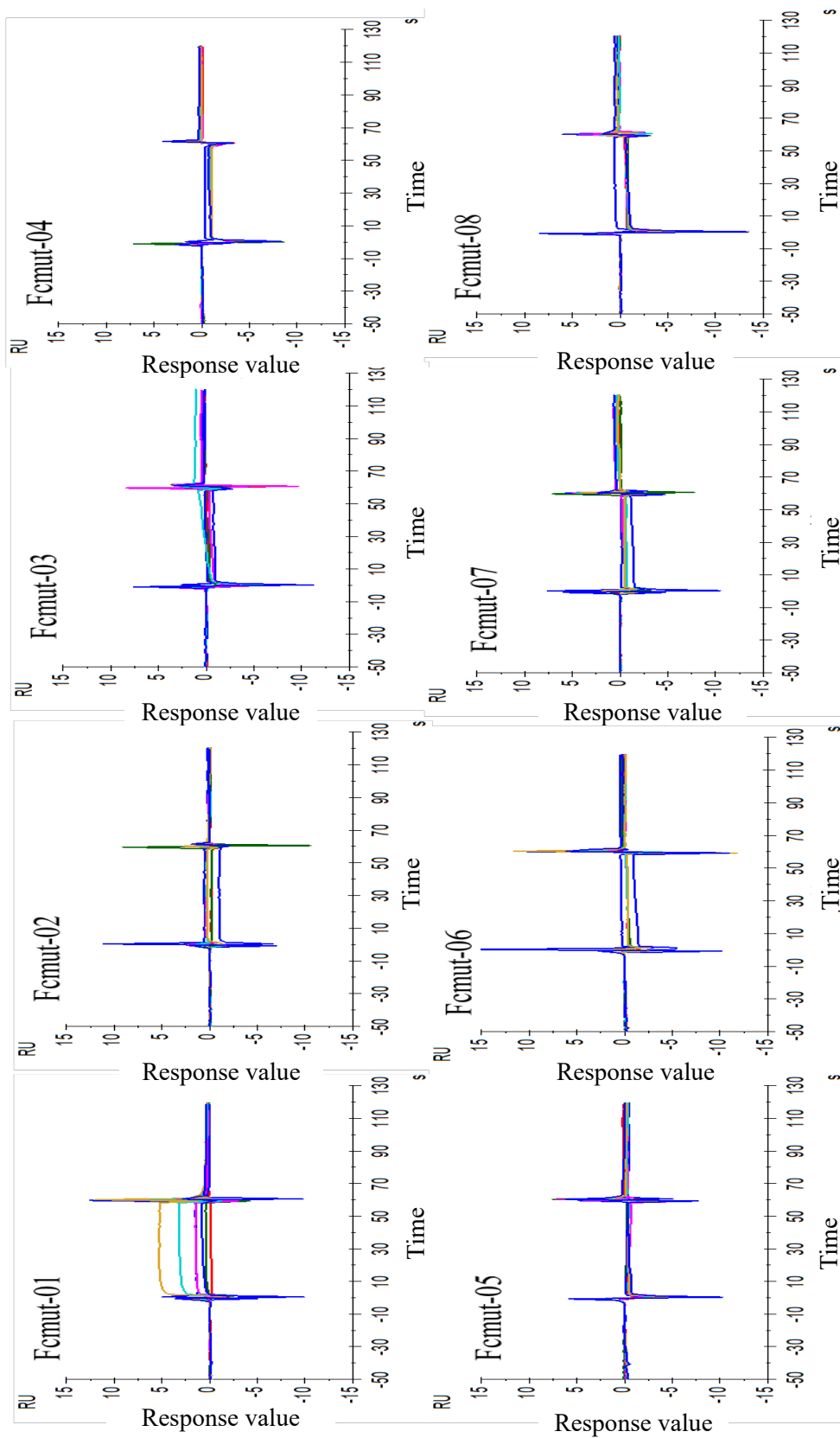


FIG. 2d

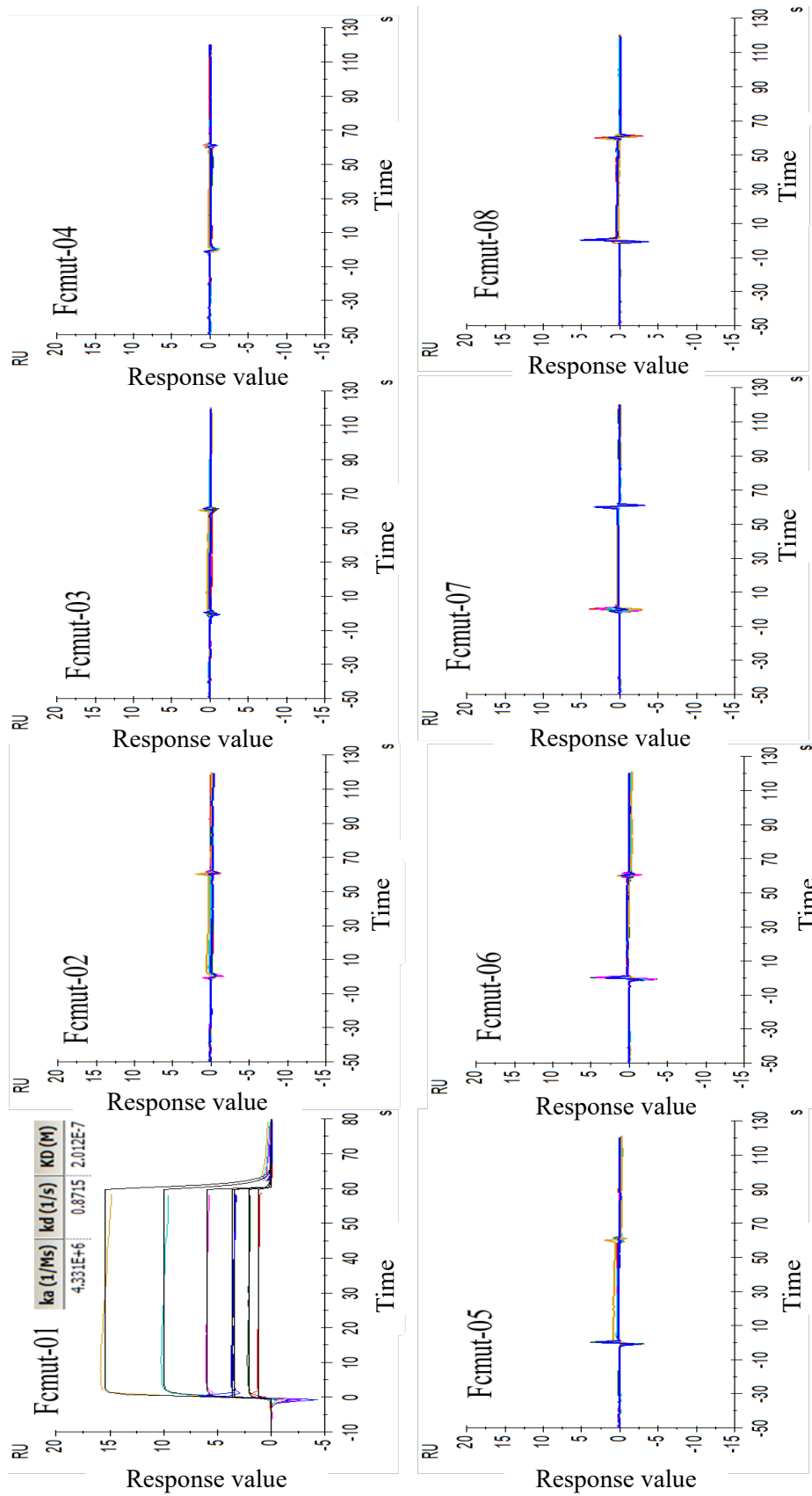


FIG. 2e

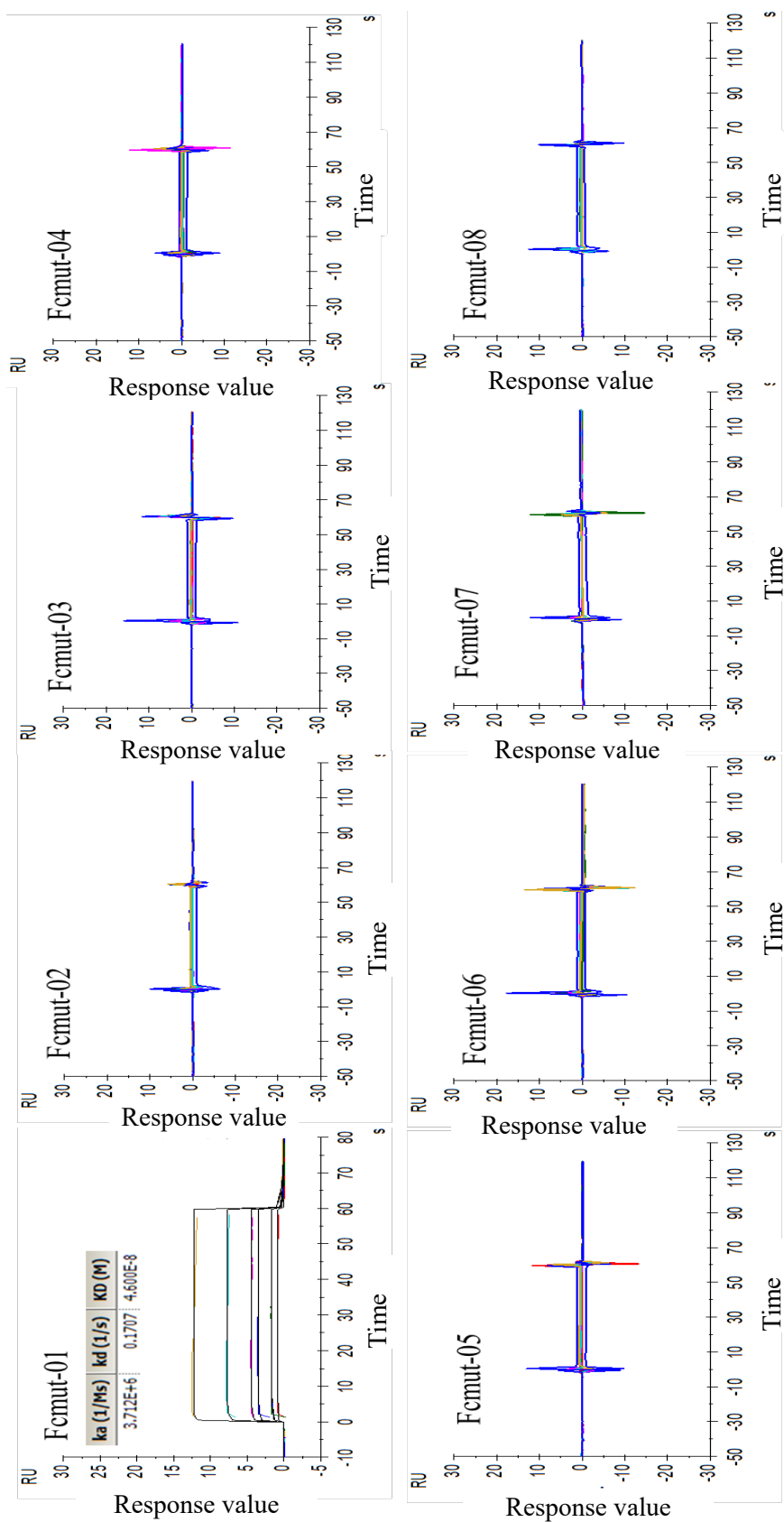


FIG. 2f

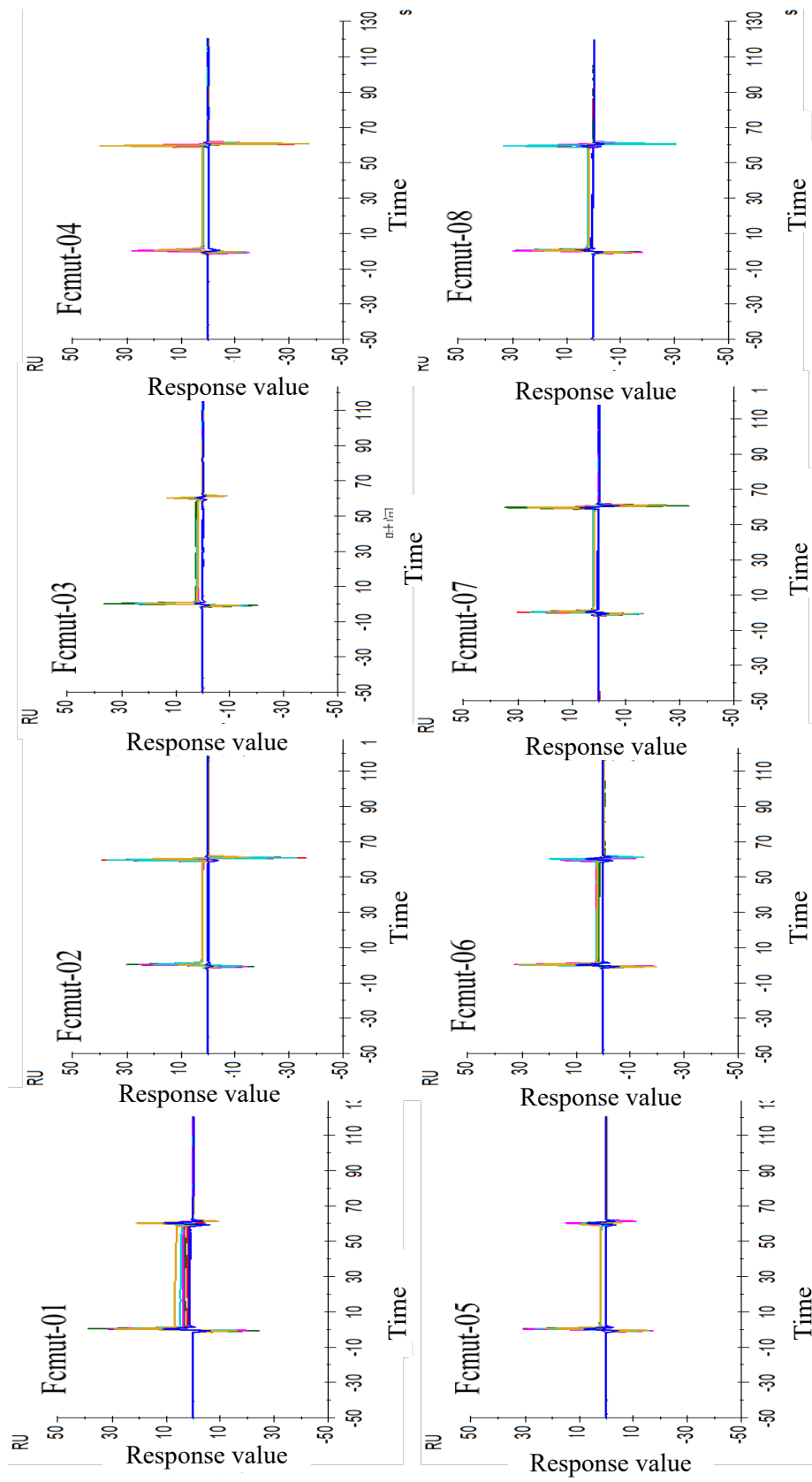


FIG. 2g

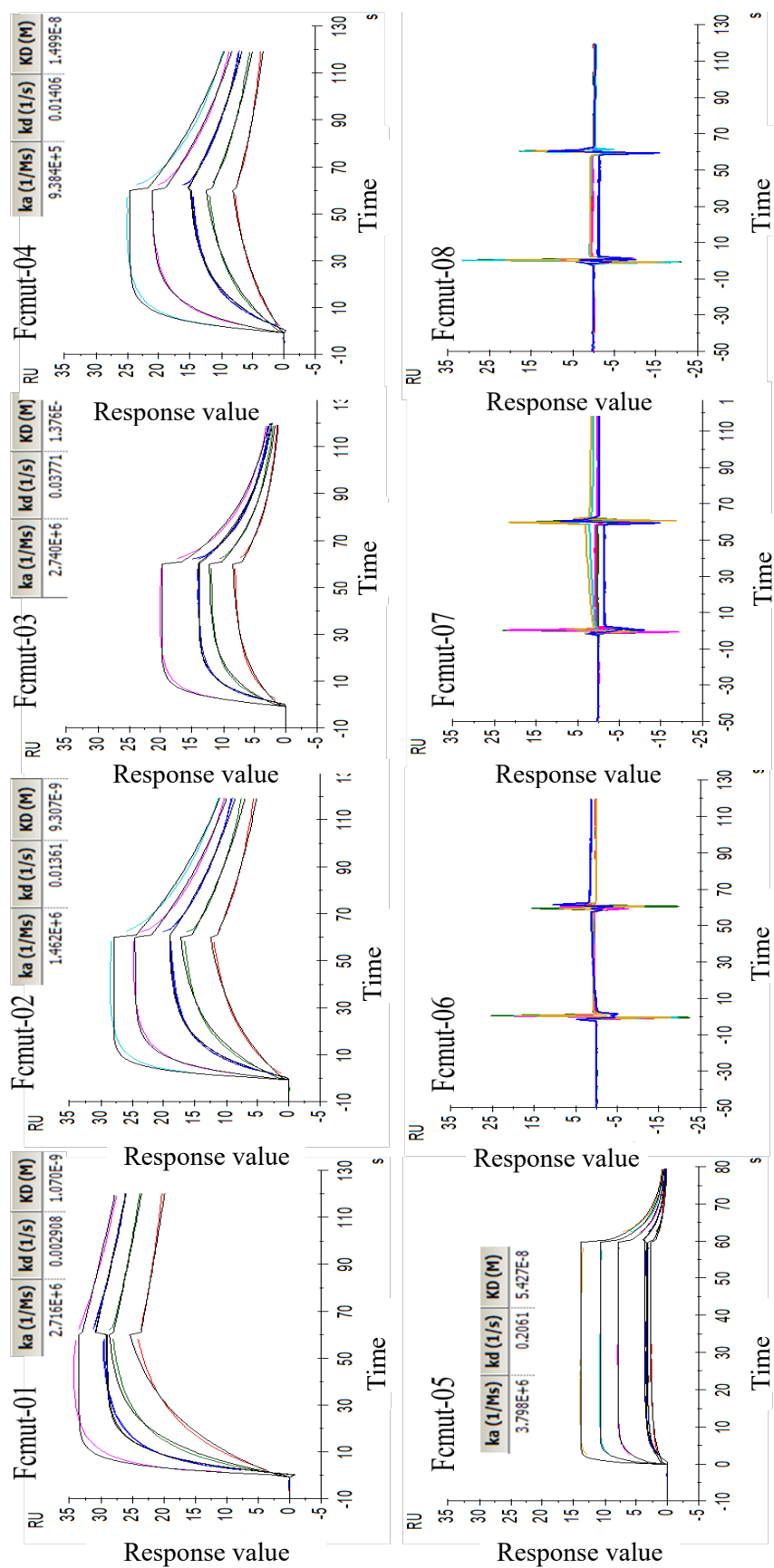


FIG. 2h

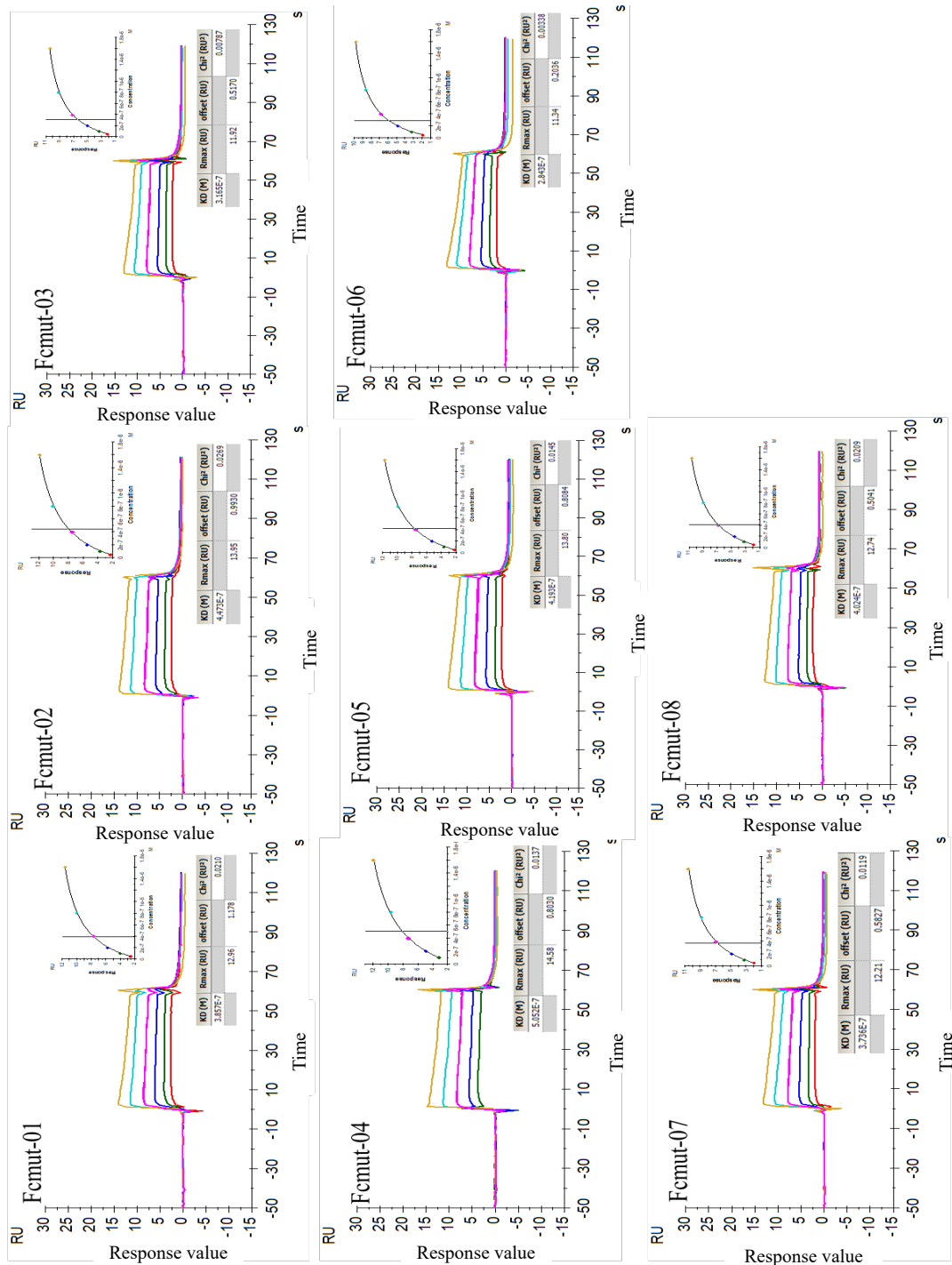


FIG. 2i

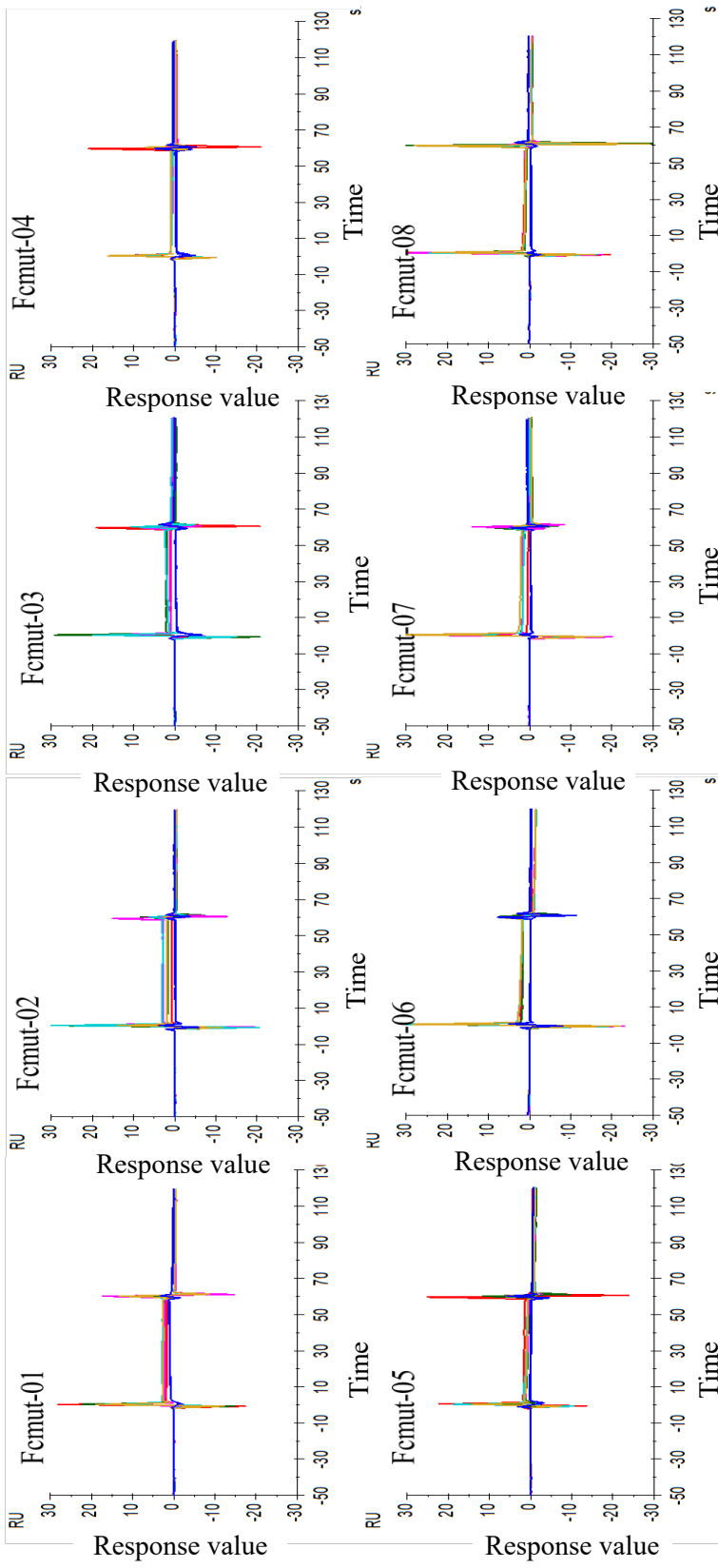


FIG. 2j

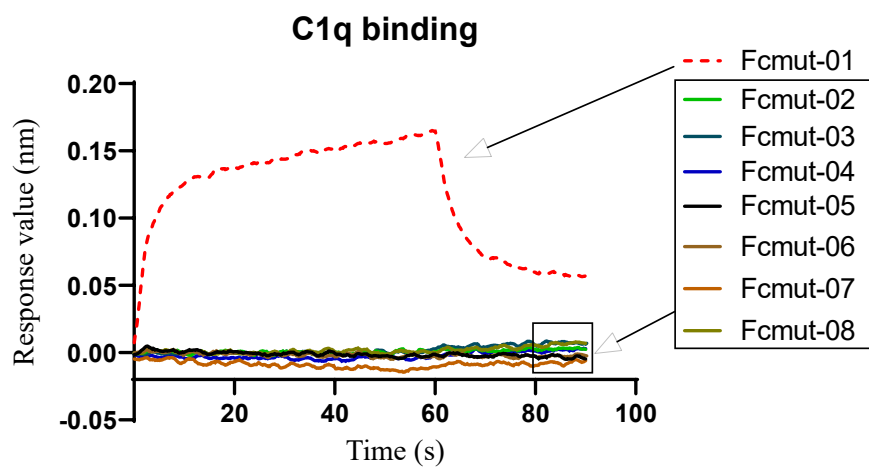
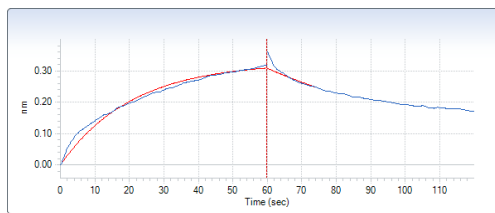
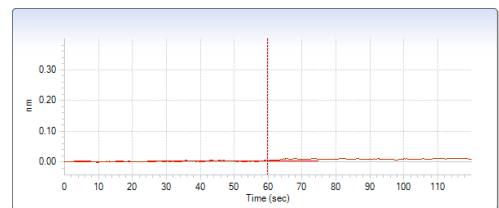


FIG. 2k

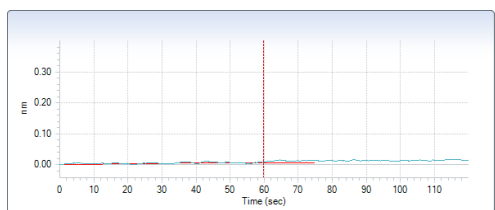
Fc-25



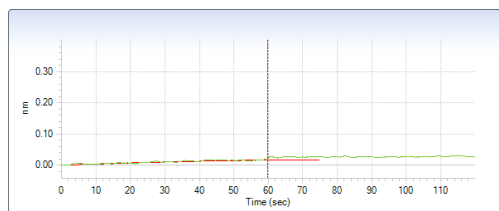
Fc-26



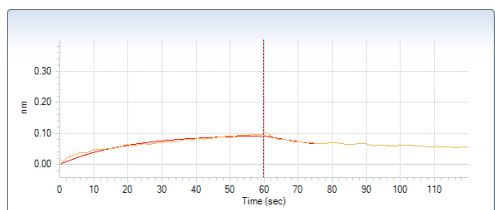
Fc-27



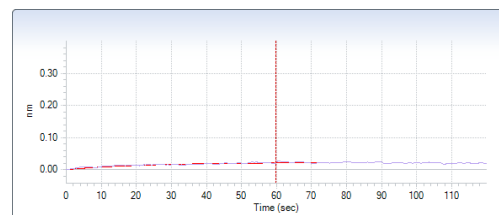
Fc-28

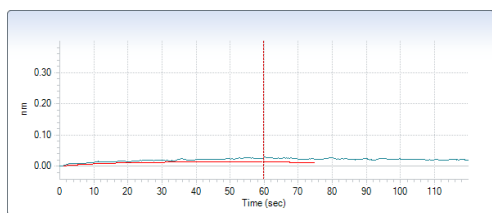
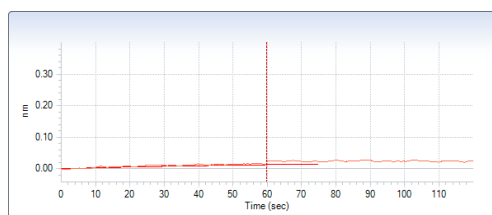
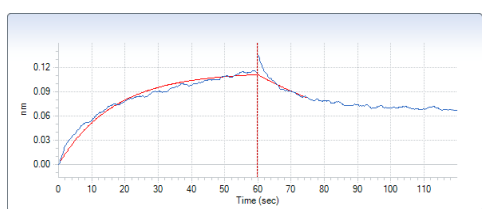
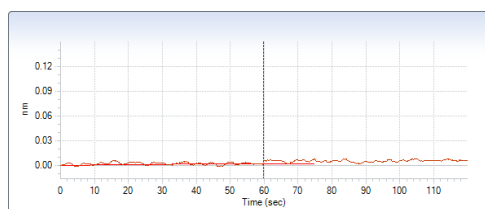
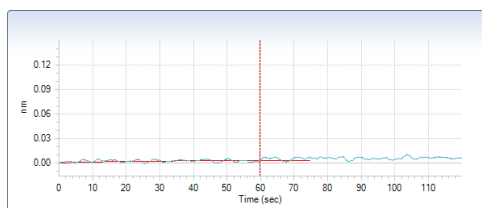
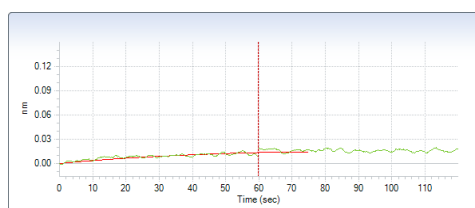
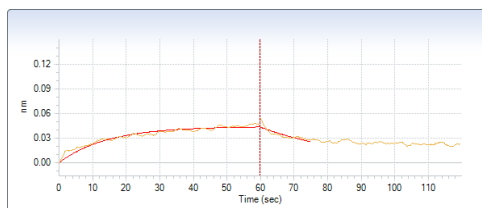
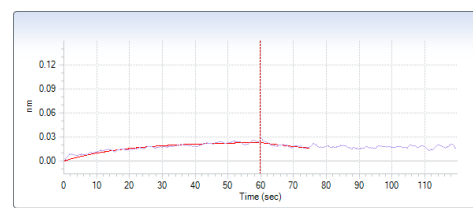
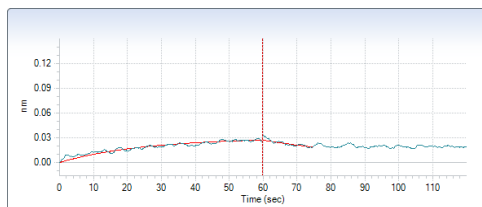
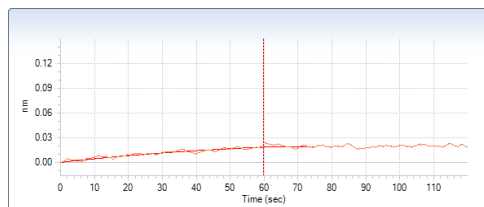


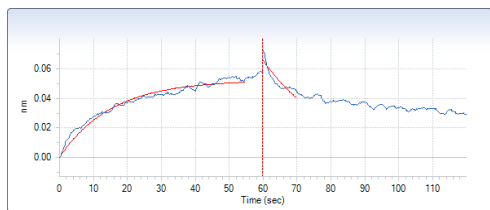
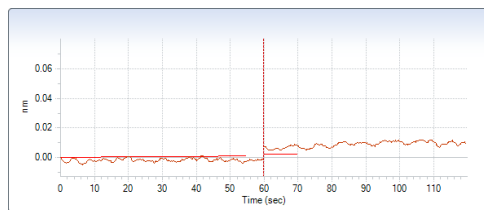
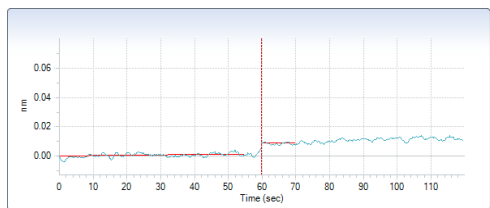
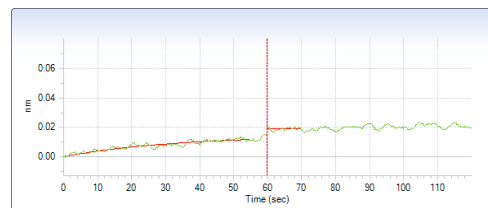
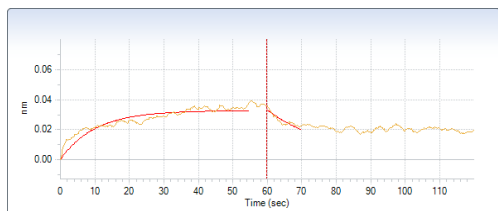
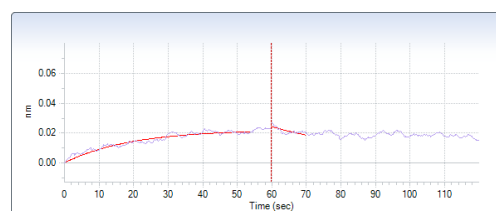
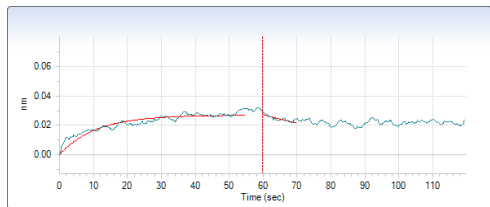
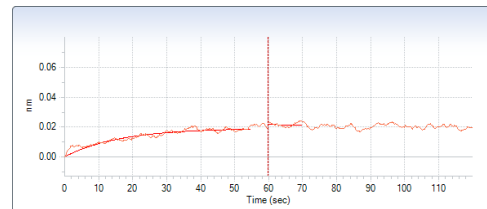
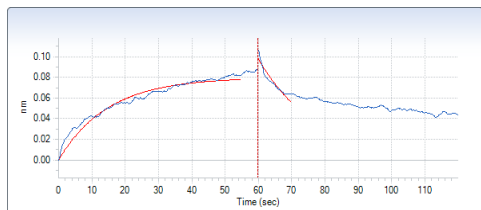
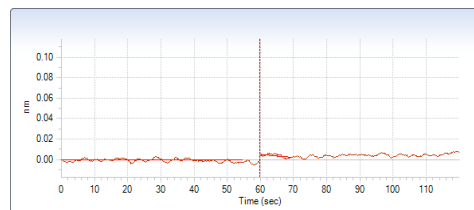
Fc-29



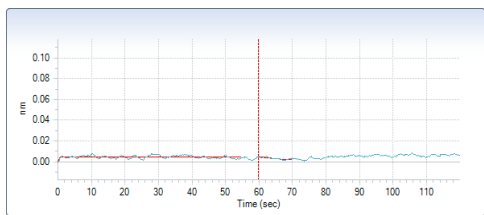
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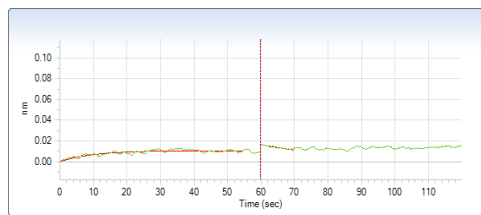
Fc-31**Fc-32****FIG. 3a****Fc-25****Fc-26****Fc-27****Fc-28****Fc-29****Fc-30****Fc-31****Fc-32****FIG. 3b**

Fc-25**Fc-26****Fc-27****Fc-28****Fc-29****Fc-30****Fc-31****Fc-32****FIG. 3c****Fc-25****Fc-26**

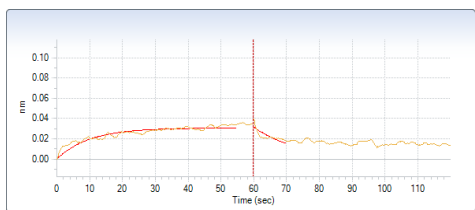
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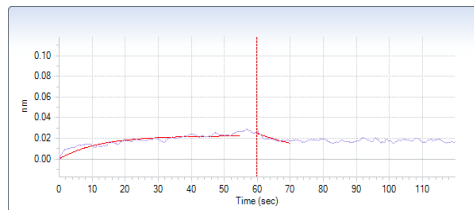
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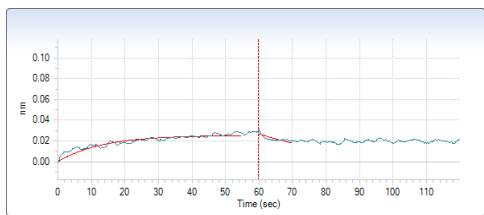
Fc-29



Fc-30



Fc-31



Fc-32

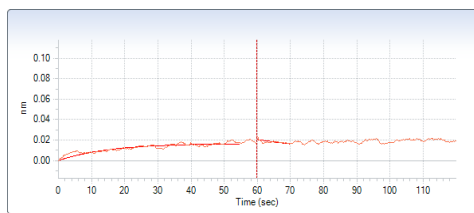
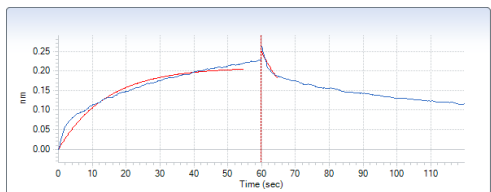
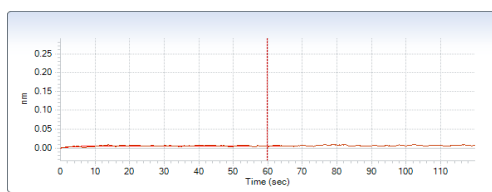


FIG. 3d

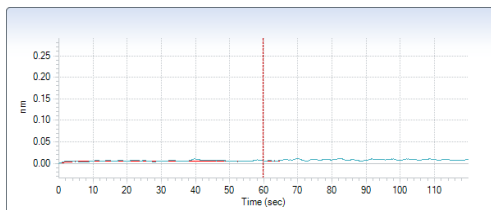
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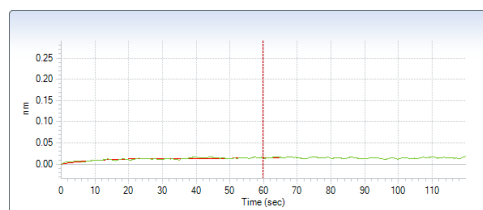
Fc-26

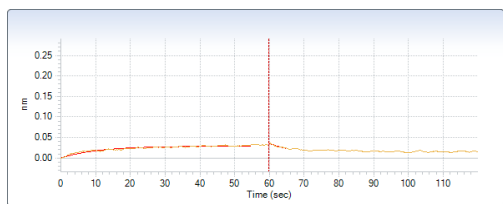
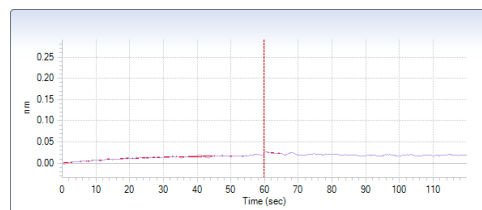
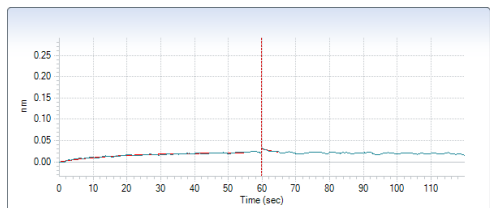
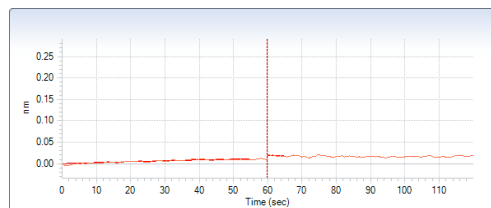
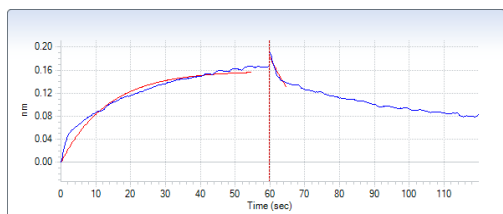
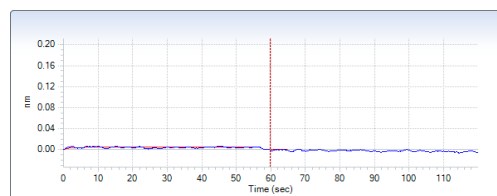
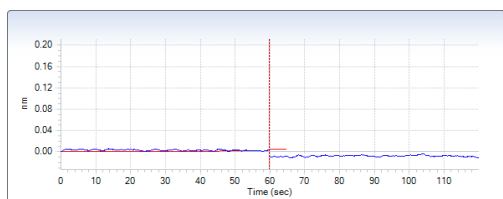
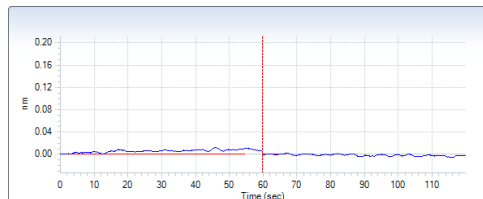
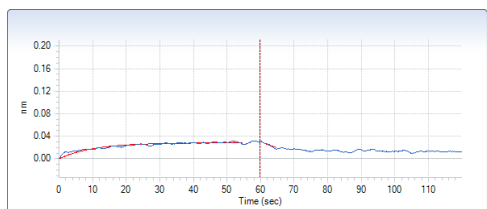
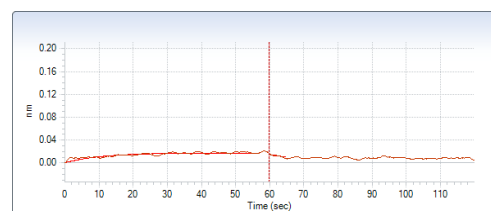


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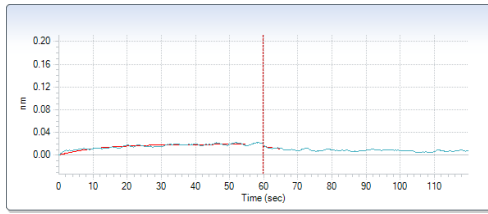


Fc-28



Fc-29**Fc-30****Fc-31****Fc-32****FIG. 3e****Fc-25****Fc-26****Fc-27****Fc-28****Fc-29****Fc-30**

Fc-31



Fc-32

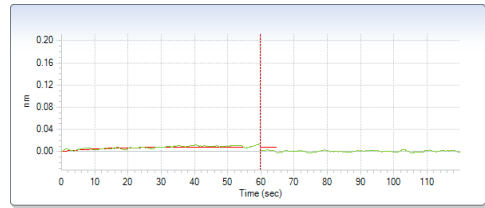
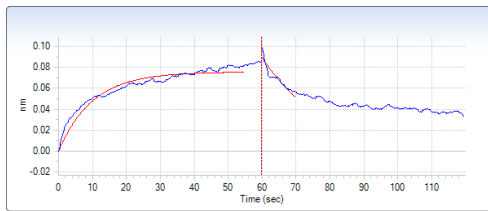
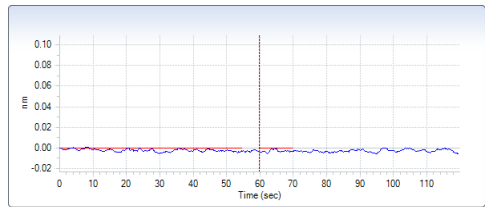


FIG. 3f

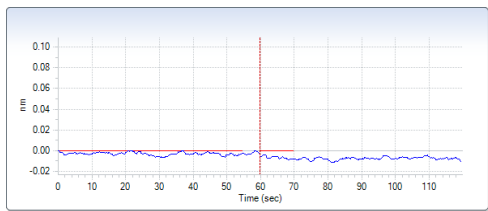
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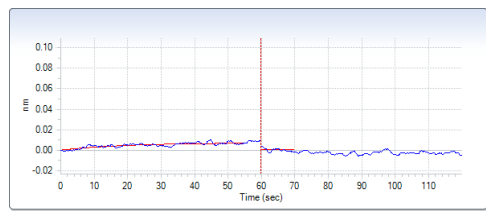
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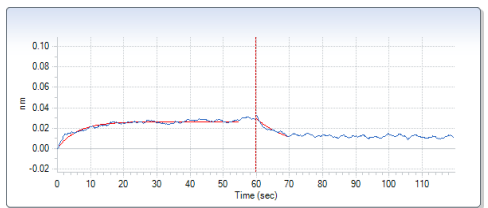
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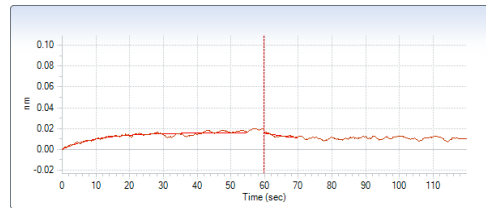
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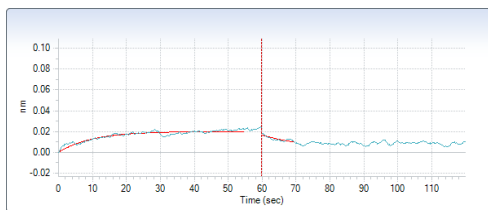
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Fc-30



Fc-31



Fc-32

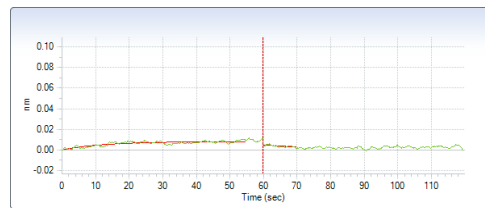
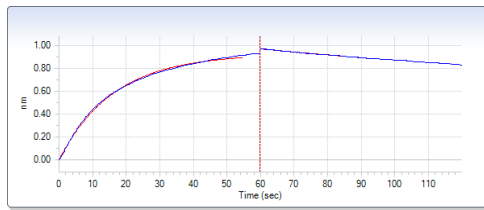
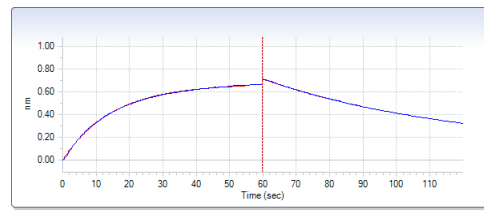
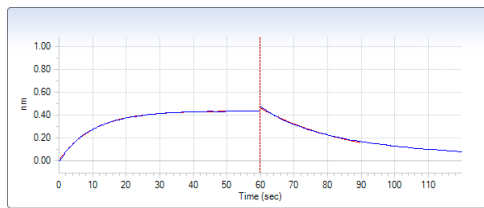
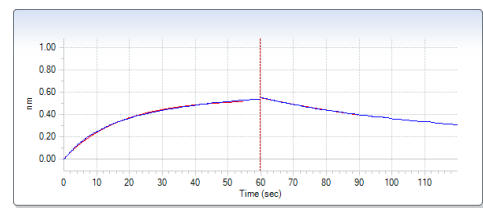
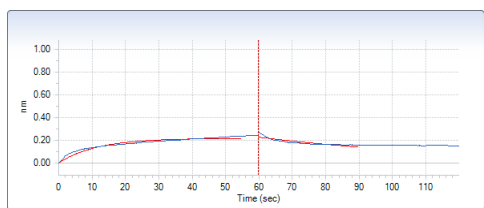
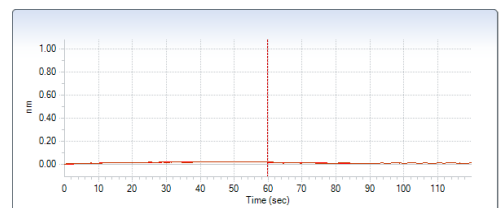
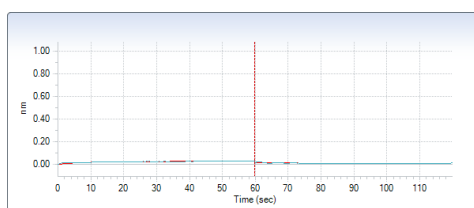
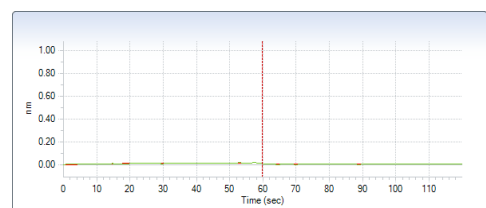
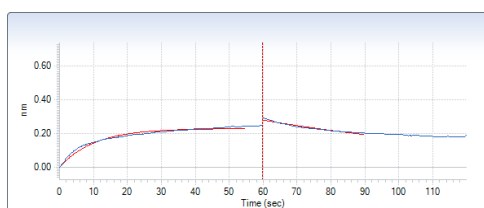
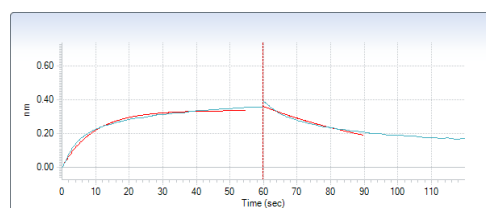
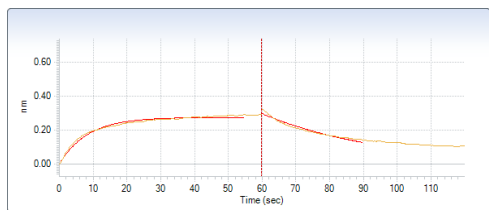


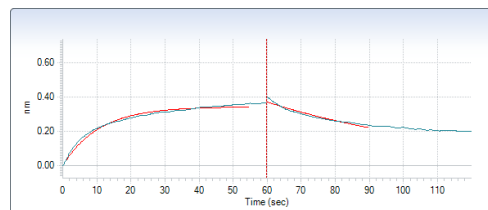
FIG. 3g

Fc-25**Fc-26****Fc-27****Fc-28****Fc-29****Fc-30****Fc-31****Fc-32****FIG. 3h****Fc-25****Fc-26**

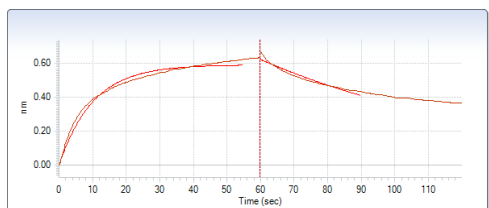
Fc-27



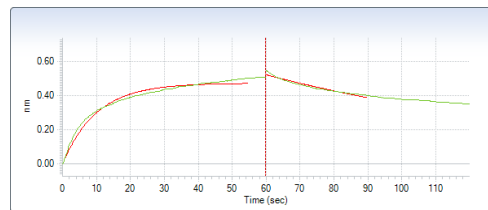
Fc-28



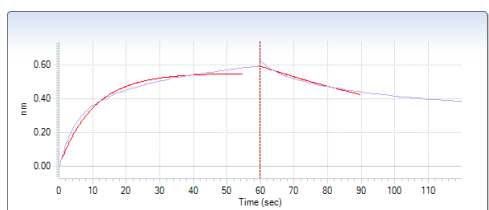
Fc-29



Fc-30



Fc-31



Fc-32

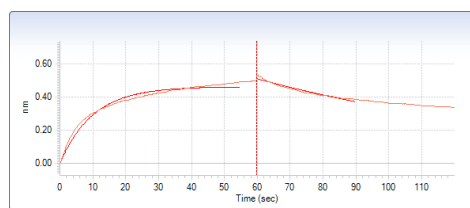


FIG. 3i

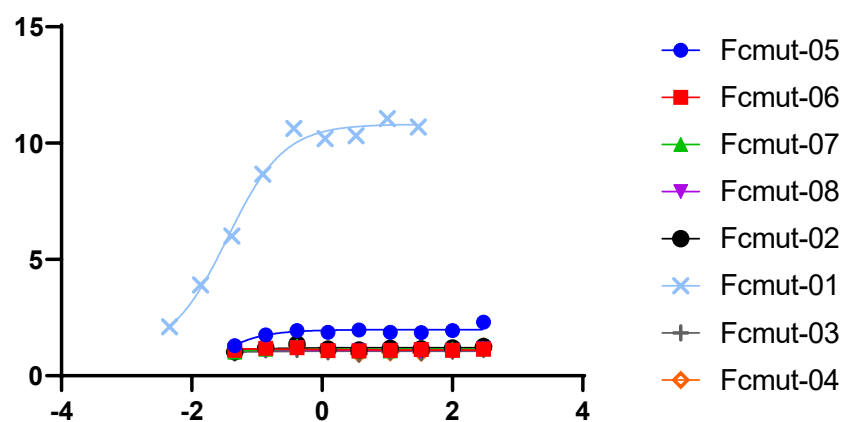


FIG. 4

SEQUENCE LISTING

<110> Innovent Biologics (Suzhou) Co., Ltd.

<120> FC MUTANT WITH ALTERED BINDING TO FC RECEPTOR

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<150> CN202110495363.7

<151> 2021-05-07

<150> CN202210436873.1

<151> 2022-04-25

<160> 34

<170> PatentIn version 3.3

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<213> Artificial sequence

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

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Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
		115					120					125			
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
	130					135					140				
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
145					150					155					160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
				165					170					175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
		195					200					205			
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
		210				215					220				
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
225					230					235					240
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245					250					255	
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
			260					265					270		
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
		275					280					285			
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
	290					295					300				
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
305					310					315					320
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr

				325						330						335			
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu				
			340					345					350						
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys				
		355					360					365							
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser				
	370					375					380								
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp				
385					390					395					400				
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser				
				405					410					415					
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala				
			420					425					430						
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys				
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			20				25					30							
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met				
		35				40						45							
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe				
	50					55					60								

Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr	65	70	75	80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	85	90	95	
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	100	105	110	
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	115	120	125	
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	130	135	140	
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	145	150	155	160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	165	170	175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	180	185	190	
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	195	200	205	
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	210	215	220	
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	225	230	235	240
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	245	250	255	
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	260	265	270	
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	275	280	285	
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	290	295	300	

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 305 310 315 320
 Lys Cys Lys Val Ser Asn Lys Ala Leu Ala Pro Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350
 Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
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 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Ser Tyr
 20 25 30
 Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly 50	Tyr	Ile	Ala	Pro	Phe	Gln 55	Gly	Asp	Ser	Arg	Tyr 60	Asn	Gln	Lys	Phe
Lys 65	Gly	Arg	Val	Thr	Ile 70	Thr	Ala	Asp	Lys	Ser 75	Thr	Ser	Thr	Ala	Tyr 80
Met	Glu	Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala	Arg	Leu	Asn 100	Arg	Gly	Asn	Ser	Leu	Asp 105	Tyr	Trp	Gly	Gln 110	Gly	Thr
Leu	Val 115	Thr	Val	Ser	Ser	Ala	Ser 120	Thr	Lys	Gly	Pro	Ser 125	Val	Phe	Pro
Leu	Ala 130	Pro	Ser	Ser	Lys	Ser 135	Thr	Ser	Gly	Gly	Thr 140	Ala	Ala	Leu	Gly
Cys 145	Leu	Val	Lys	Asp	Tyr 150	Phe	Pro	Glu	Pro	Val 155	Thr	Val	Ser	Trp	Asn 160
Ser	Gly	Ala	Leu	Thr 165	Ser	Gly	Val	His	Thr 170	Phe	Pro	Ala	Val	Leu 175	Gln
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Ser	Leu	Gly 195	Thr	Gln	Thr	Tyr	Ile 200	Cys	Asn	Val	Asn	His 205	Lys	Pro	Ser
Asn 210	Thr	Lys	Val	Asp	Lys	Lys 215	Val	Glu	Pro	Lys	Ser 220	Cys	Asp	Lys	Thr
His 225	Thr	Cys	Pro	Pro	Cys 230	Pro	Ala	Pro	Glu	Leu 235	Leu	Gly	Gly	Pro	Ser 240
Val	Phe	Leu	Phe	Pro 245	Pro	Lys	Pro	Lys	Asp 250	Thr	Leu	Met	Ile	Ser 255	Arg
Thr	Pro	Glu	Val 260	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His	Glu 270	Asp	Pro
Glu	Val	Lys 275	Phe	Asn	Trp	Tyr	Val 280	Asp	Gly	Val	Glu	Val 285	His	Asn	Ala

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

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

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

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
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Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

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

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
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Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe
	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
			115					120					125		
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
	130					135					140				
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
145					150					155					160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
				165					170					175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
		195					200					205			
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
	210					215					220				
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
225					230					235					240
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245					250					255	
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro

260						265						270					
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala		
275						280						285					
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val		
290						295						300					
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr		
305						310						315					
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ile	Glu	Lys	Thr	Ile	Ser		
325						330						335					
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro		
340						345						350					
Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val		
355						360						365					
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly		
370						375						380					
Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp		
385						390						395					
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp		
405						410						415					
Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His		
420						425						430					
Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys				
435						440						445					

<210> 5

<211> 448

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 5

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser	1	5	10	15
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr	20	25	30	
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	35	40	45	
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe	50	55	60	
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr	65	70	75	80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	85	90	95	
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	100	105	110	
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	115	120	125	
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	130	135	140	
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	145	150	155	160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	165	170	175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	180	185	190	
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	195	200	205	
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	210	215	220	
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	225	230	235	240

Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	
				245					250					255		
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	
			260					265					270			
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	
		275					280					285				
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	
	290					295					300					
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	
305					310					315					320	
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	
				325					330					335		
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	
			340					345					350			
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	
		355					360					365				
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	
	370					375					380					
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	
385					390					395					400	
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	
				405					410					415		
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	
			420					425					430			
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	
		435					440					445				

<210> 6

<211> 447

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 6

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

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

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

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

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

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

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

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

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

210					215					220					
His 225	Thr	Cys	Pro	Pro	Cys 230	Pro	Ala	Pro	Glu	Ala 235	Ala	Gly	Gly	Pro	Ser 240
Val	Phe	Leu	Phe	Pro 245	Pro	Lys	Pro	Lys	Asp 250	Thr	Leu	Met	Ile	Ser 255	Arg
Thr	Pro	Glu	Val 260	Thr	Cys	Val	Val	Val	Asp 265	Val	Ser	His	Glu 270	Asp	Pro
Glu	Val	Lys 275	Phe	Asn	Trp	Tyr	Val 280	Asp	Gly	Val	Glu	Val 285	His	Asn	Ala
Lys	Thr 290	Lys	Pro	Arg	Glu	Glu 295	Gln	Tyr	Asn	Ser	Thr 300	Tyr	Arg	Val	Val
Ser 305	Val	Leu	Thr	Val	Leu 310	His	Gln	Asp	Trp	Leu 315	Asn	Gly	Lys	Glu	Tyr 320
Lys	Cys	Lys	Val	Ser 325	Asn	Lys	Ala	Leu	Ala 330	Pro	Ile	Glu	Lys	Thr 335	Ile
Ser	Lys	Ala	Lys 340	Gly	Gln	Pro	Arg	Glu 345	Pro	Gln	Val	Tyr	Thr 350	Leu	Pro
Pro	Ser 355	Arg	Glu	Glu	Met	Thr	Lys 360	Asn	Gln	Val	Ser	Leu 365	Thr	Cys	Leu
Val 370	Lys	Gly	Phe	Tyr	Pro	Ser 375	Asp	Ile	Ala	Val	Glu 380	Trp	Glu	Ser	Asn
Gly 385	Gln	Pro	Glu	Asn	Asn 390	Tyr	Lys	Thr	Thr	Pro 395	Pro	Val	Leu	Asp	Ser 400
Asp	Gly	Ser	Phe	Phe 405	Leu	Tyr	Ser	Lys	Leu 410	Thr	Val	Asp	Lys	Ser 415	Arg
Trp	Gln	Gln	Gly 420	Asn	Val	Phe	Ser	Cys 425	Ser	Val	Met	His	Glu 430	Ala	Leu
His	Asn 435	His	Tyr	Thr	Gln	Lys	Ser 440	Leu	Ser	Leu	Ser	Pro 445	Gly	Lys	

<210> 7

<211> 447
<212> PRT
<213> Artificial sequence

<220>
<223> Synthesized

<400> 7

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

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

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

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

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

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

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

Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	195	200	205
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	210	215	220
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	225	230	235
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	245	250	255
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	260	265	270
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	275	280	285
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	290	295	300
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	305	310	315
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Gly	Pro	Ile	Glu	Lys	Thr	Ile	325	330	335
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	340	345	350
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	355	360	365
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	370	375	380
Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	385	390	395
Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	405	410	415
Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	420	425	430

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

<210> 8

<211> 446

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 8

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

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

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

Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe
50						55					60				

Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80

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

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

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

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

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

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

165								170				175			
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
		195					200					205			
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
	210					215					220				
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
225					230					235					240
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245					250					255	
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
			260					265					270		
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
		275					280					285			
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
	290					295					300				
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
305					310					315					320
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ile	Glu	Lys	Thr	Ile	Ser
				325					330					335	
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro
			340					345					350		
Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val
		355					360					365			
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly
	370					375					380				
Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp
385					390					395					400
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp

				405						410						415
Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	
			420					425					430			
Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys			
		435					440					445				
<210> 9																
<211> 220																
<212> PRT																
<213> Artificial sequence																
<220>																
<223> Synthesized																
<400> 9																
Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly	
1				5					10					15		
Glu	Arg	Ala	Thr	Ile	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Leu	Phe	Asn	Ser	
			20					25					30			
Gly	Asn	Gln	Arg	Asn	Tyr	Leu	Thr	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	
		35					40					45				
Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Val	
		50				55					60					
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	
65					70					75				80		
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	Asn	
			85						90					95		
Asn	Tyr	Ile	Tyr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	
			100					105					110			
Lys	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	
		115					120					125				
Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	
	130					135					140					

Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu
145					150					155					160
Gln	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp
			165						170					175	
Ser	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr
			180					185					190		
Glu	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser
		195					200					205			
Ser	Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys				
	210					215					220				

<210> 10
 <211> 444
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Synthesized

<400> 10

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr
			20					25					30		
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe
	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		

Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	115	120	125
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	130	135	140
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	145	150	155
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	165	170	175
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	180	185	190
Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	195	200	205
Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	210	215	220
Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	225	230	235
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	245	250	255
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	260	265	270
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	275	280	285
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	290	295	300
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	305	310	315
Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	325	330	335
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	340	345	350

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

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

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

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

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

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

<210> 11

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 11

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85								90				95			
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
		115					120					125			
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly
	130					135					140				
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
145					150					155					160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
				165					170					175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser
		195					200					205			
Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys
	210					215					220				
Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe
225					230					235					240
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
				245					250					255	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe
			260					265					270		
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
		275					280					285			
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr
	290					295					300				
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
305					310					315					320

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

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

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 355 360 365

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

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
 385 390 395 400

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

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

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440

<210> 12
 <211> 443
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Synthesized

<400> 12

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
 50 55 60

Lys 65	Gly	Arg	Val	Thr	Ile 70	Thr	Ala	Asp	Lys	Ser 75	Thr	Ser	Thr	Ala	Tyr 80
Met	Glu	Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala	Arg	Leu	Asn 100	Arg	Gly	Asn	Ser	Leu	Asp 105	Tyr	Trp	Gly	Gln 110	Gly	Thr
Leu	Val	Thr 115	Val	Ser	Ser	Ala	Ser 120	Thr	Lys	Gly	Pro	Ser 125	Val	Phe	Pro
Leu	Ala 130	Pro	Cys	Ser	Arg	Ser 135	Thr	Ser	Glu	Ser	Thr 140	Ala	Ala	Leu	Gly
Cys 145	Leu	Val	Lys	Asp	Tyr 150	Phe	Pro	Glu	Pro	Val 155	Thr	Val	Ser	Trp	Asn 160
Ser	Gly	Ala	Leu	Thr 165	Ser	Gly	Val	His	Thr 170	Phe	Pro	Ala	Val	Leu	Gln 175
Ser	Ser	Gly	Leu 180	Tyr	Ser	Leu	Ser	Ser 185	Val	Val	Thr	Val	Pro 190	Ser	Ser
Asn	Phe	Gly 195	Thr	Gln	Thr	Tyr	Thr 200	Cys	Asn	Val	Asp	His 205	Lys	Pro	Ser
Asn 210	Thr	Lys	Val	Asp	Lys	Thr 215	Val	Glu	Arg	Lys	Cys 220	Cys	Val	Glu	Cys
Pro 225	Pro	Cys	Pro	Ala	Pro 230	Pro	Val	Ala	Gly	Pro 235	Ser	Val	Phe	Leu	Phe 240
Pro	Pro	Lys	Pro	Lys 245	Asp	Thr	Leu	Met	Ile 250	Ser	Arg	Thr	Pro	Glu	Val 255
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His 265	Glu	Asp	Pro	Glu	Val	Gln	Phe 270
Asn	Trp	Tyr 275	Val	Asp	Gly	Val	Glu 280	Val	His	Asn	Ala	Lys 285	Thr	Lys	Pro
Arg 290	Glu	Glu	Gln	Phe	Asn	Ser 295	Thr	Phe	Arg	Val	Val 300	Ser	Val	Leu	Thr

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

Ser Asn Lys Gly Leu Gly Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
325 330 335

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

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
355 360 365

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

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
385 390 395 400

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

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

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 13

<211> 442

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 13

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

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

Asn Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35					40					45					
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe
50						55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
		115					120					125			
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly
	130					135					140				
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
145					150					155					160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
				165					170					175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser
		195					200					205			
Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys
	210					215					220				
Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe
225					230					235					240
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
				245					250					255	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe
			260					265					270		

Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	
		275						280					285			
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	
		290						295					300			
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	
		305						310					315		320	
Ser	Asn	Lys	Gly	Leu	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	
		325						330					335			
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	
		340						345					350			
Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	
		355						360					365			
Pro	Ser	Asp	Ile	Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	
		370						375					380			
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	
		385						390					395		400	
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	
		405						410					415			
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	
		420						425					430			
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys							
		435						440								
<210>		14														
<211>		444														
<212>		PRT														
<213>		Artificial sequence														
<220>																
<223>		Synthesized														
<400>		14														
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser	
1		5						10					15			

Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr			
			20					25					30					
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met			
		35					40					45						
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe			
	50					55					60							
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr			
65					70					75					80			
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys			
				85					90					95				
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr			
			100					105					110					
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro			
		115					120					125						
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly			
	130					135					140							
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn			
145					150					155					160			
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln			
				165					170					175				
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser			
			180					185					190					
Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser			
		195					200					205						
Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys			
	210					215					220							
Pro	Pro	Cys	Pro	Ala	Pro	Pro	Ala	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe			
225					230					235					240			
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val			
				245					250					255				

Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe			
			260					265					270					
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro			
		275					280					285						
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr			
	290					295					300							
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val			
305					310					315					320			
Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr			
				325					330					335				
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg			
			340					345					350					
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly			
		355					360					365						
Phe	Tyr	Pro	Ser	Asp	Ile	Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro			
	370					375					380							
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser			
385					390					395					400			
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln			
				405					410					415				
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His			
		420						425					430					
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys							
		435					440											

<210> 15

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 15

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser		
1				5					10					15			
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr		
			20					25					30				
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met		
		35					40					45					
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe		
	50					55					60						
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr		
65					70					75					80		
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
				85					90					95			
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr		
			100					105					110				
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro		
		115					120					125					
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly		
	130					135					140						
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn		
145					150					155					160		
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln		
				165					170					175			
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser		
			180					185					190				
Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser		
		195					200					205					
Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys		
	210					215					220						
Pro	Pro	Cys	Pro	Ala	Pro	Pro	Ala	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe		

225					230						235				240
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
				245					250					255	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe
			260					265					270		
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
		275					280					285			
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr
	290					295					300				
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
305					310					315					320
Ser	Asn	Lys	Gly	Leu	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys
				325					330					335	
Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu
			340					345					350		
Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe
		355					360					365			
Tyr	Pro	Ser	Asp	Ile	Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu
	370					375					380				
Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe
385					390					395					400
Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly
				405					410					415	
Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr
			420					425					430		
Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys					
		435					440								

<210> 16

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 16

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

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

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140

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

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

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

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
195 200 205

Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	210	215	220	
Pro	Pro	Cys	Pro	Ala	Pro	Pro	Ala	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	225	230	235	240
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	245	250	255	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	260	265	270	
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	275	280	285	
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	290	295	300	
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	305	310	315	320
Ser	Asn	Lys	Gly	Leu	Gly	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	325	330	335	
Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	340	345	350	
Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	355	360	365	
Tyr	Pro	Ser	Asp	Ile	Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	370	375	380	
Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	385	390	395	400
Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	405	410	415	
Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	420	425	430	
Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						435	440		

<210> 17
<211> 442
<212> PRT
<213> Artificial sequence

<220>
<223> Synthesized

<400> 17

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

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

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140

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

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

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

Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	195	200	205	
Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	210	215	220	
Pro	Pro	Cys	Pro	Ala	Pro	Pro	Ala	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	225	230	235	240
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	245	250	255	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	260	265	270	
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	275	280	285	
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	290	295	300	
Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	305	310	315	320
Ser	Asn	Lys	Gly	Leu	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	325	330	335	
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	340	345	350	
Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	355	360	365	
Pro	Ser	Asp	Ile	Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	370	375	380	
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	385	390	395	400
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	405	410	415	
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	420	425	430	

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 18

<211> 445

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 18

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

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

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140

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

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

165								170				175			
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser
		195					200					205			
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys
	210					215					220				
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	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	Gln	Glu	Asp	Pro	Glu	Val	Gln
			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	Phe	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	Gly	Leu	Pro	Ser	Ser	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		
Gln	Glu	Glu	Met	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
						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	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln

				405						410						415			
Glu	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	Leu	Gly	Lys							
		435					440					445							

<210> 19
 <211> 444
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Synthesized

<400> 19

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser				
1				5					10					15					
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr				
			20					25					30						
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met				
		35					40					45							
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe				
	50					55					60								
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr				
65					70					75					80				
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys				
				85					90					95					
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr				
			100					105					110						
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro				
		115					120					125							
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly				
	130					135					140								

Cys 145	Leu	Val	Lys	Asp	Tyr 150	Phe	Pro	Glu	Pro	Val 155	Thr	Val	Ser	Trp	Asn 160
Ser	Gly	Ala	Leu	Thr 165	Ser	Gly	Val	His	Thr 170	Phe	Pro	Ala	Val	Leu	Gln 175
Ser	Ser	Gly	Leu 180	Tyr	Ser	Leu	Ser	Ser 185	Val	Val	Thr	Val	Pro 190	Ser	Ser
Ser	Leu	Gly 195	Thr	Lys	Thr	Tyr	Thr 200	Cys	Asn	Val	Asp	His 205	Lys	Pro	Ser
Asn 210	Thr	Lys	Val	Asp	Lys	Arg 215	Val	Glu	Ser	Lys	Tyr 220	Gly	Pro	Pro	Cys
Pro 225	Pro	Cys	Pro	Ala	Pro	Glu 230	Phe	Leu	Gly	Gly 235	Pro	Ser	Val	Phe	Leu 240
Phe	Pro	Pro	Lys	Pro 245	Lys	Asp	Thr	Leu	Met 250	Ile	Ser	Arg	Thr	Pro 255	Glu
Val	Thr	Cys	Val 260	Val	Val	Asp	Val	Ser 265	Gln	Glu	Asp	Pro	Glu 270	Val	Gln
Phe	Asn 275	Trp	Tyr	Val	Asp	Gly 280	Val	Glu	Val	His	Asn	Ala 285	Lys	Thr	Lys
Pro 290	Arg	Glu	Glu	Gln	Phe	Asn 295	Ser	Thr	Tyr	Arg	Val 300	Val	Ser	Val	Leu
Thr 305	Val	Leu	His	Gln	Asp 310	Trp	Leu	Asn	Gly	Lys 315	Glu	Tyr	Lys	Cys	Lys 320
Val	Ser	Asn	Lys	Gly 325	Leu	Ser	Ser	Ile	Glu 330	Lys	Thr	Ile	Ser	Lys 335	Ala
Lys	Gly	Gln	Pro 340	Arg	Glu	Pro	Gln	Val 345	Tyr	Thr	Leu	Pro	Pro 350	Ser	Gln
Glu	Glu	Met 355	Thr	Lys	Asn	Gln	Val 360	Ser	Leu	Thr	Cys	Leu 365	Val	Lys	Gly
Phe 370	Tyr	Pro	Ser	Asp	Ile	Ala 375	Val	Glu	Trp	Glu	Ser 380	Asn	Gly	Gln	Pro

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

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
405 410 415

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

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 20

<211> 444

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 20

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

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

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

	115					120					125					
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	
	130					135					140					
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	
145					150					155					160	
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	
				165					170					175		
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	
			180					185					190			
Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	
		195					200					205				
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	
	210					215					220					
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	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	Gln	Glu	Asp	Pro	Glu	Val	Gln	
			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	Phe	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	Gly	Leu	Gly	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	
				325					330					335		
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	
			340					345					350			
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	

355		360		365											
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro
	370					375					380				
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser
385					390					395					400
Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu
				405					410					415	
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His
			420					425					430		
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys				
		435					440								

<210> 21
 <211> 443
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Synthesized

<400> 21

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1				5				10					15		
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr
			20				25					30			
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe
		50				55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65				70				75						80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85				90						95		

Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr		
			100					105					110				
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro		
		115					120					125					
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly		
	130					135					140						
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn		
145					150					155					160		
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln		
				165					170					175			
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser		
			180					185					190				
Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser		
		195					200					205					
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys		
	210					215					220						
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	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	Gln	Glu	Asp	Pro	Glu	Val	Gln		
			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	Phe	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	Gly	Leu	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys		
				325					330					335			

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

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
355 360 365

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

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

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
405 410 415

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

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 22

<211> 445

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 22

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

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

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

Gly Tyr Ile Ala Pro Phe Gln Gly Asp Ser Arg Tyr Asn Gln Lys Phe
50 55 60

Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr	
65					70					75					80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
			85						90					95		
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	
			100					105					110			
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	
		115					120					125				
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	
	130					135					140					
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	
145					150					155					160	
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	
				165					170					175		
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	
			180					185					190			
Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	
		195					200					205				
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	
						215						220				
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	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	Gln	Glu	Asp	Pro	Glu	Val	Gln	
			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	Phe	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	Gly	Leu	Pro	Ser	Ser	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	
Gln	Glu	Glu	Met	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	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	405	410	415	
Glu	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	Leu	Gly	Lys				435	440	445	

<210> 23
 <211> 444
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Synthesized

<400> 23

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser	1	5	10	15
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr	20	25	30	
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	35	40	45	

Gly 50	Tyr	Ile	Ala	Pro	Phe	Gln 55	Gly	Asp	Ser	Arg	Tyr 60	Asn	Gln	Lys	Phe
Lys 65	Gly	Arg	Val	Thr	Ile 70	Thr	Ala	Asp	Lys	Ser 75	Thr	Ser	Thr	Ala	Tyr 80
Met	Glu	Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala	Arg	Leu	Asn 100	Arg	Gly	Asn	Ser	Leu	Asp 105	Tyr	Trp	Gly	Gln 110	Gly	Thr
Leu	Val 115	Thr	Val	Ser	Ser	Ala	Ser 120	Thr	Lys	Gly	Pro	Ser 125	Val	Phe	Pro
Leu	Ala 130	Pro	Cys	Ser	Arg	Ser 135	Thr	Ser	Glu	Ser	Thr 140	Ala	Ala	Leu	Gly
Cys 145	Leu	Val	Lys	Asp	Tyr 150	Phe	Pro	Glu	Pro	Val 155	Thr	Val	Ser	Trp	Asn 160
Ser	Gly	Ala	Leu	Thr 165	Ser	Gly	Val	His	Thr 170	Phe	Pro	Ala	Val	Leu 175	Gln
Ser	Ser	Gly	Leu 180	Tyr	Ser	Leu	Ser	Ser 185	Val	Val	Thr	Val	Pro 190	Ser	Ser
Ser	Leu	Gly 195	Thr	Lys	Thr	Tyr	Thr 200	Cys	Asn	Val	Asp	His 205	Lys	Pro	Ser
Asn 210	Thr	Lys	Val	Asp	Lys	Arg 215	Val	Glu	Ser	Lys	Tyr 220	Gly	Pro	Pro	Cys
Pro 225	Pro	Cys	Pro	Ala	Pro 230	Glu	Ala	Ala	Gly	Gly 235	Pro	Ser	Val	Phe	Leu 240
Phe	Pro	Pro	Lys	Pro 245	Lys	Asp	Thr	Leu	Met 250	Ile	Ser	Arg	Thr	Pro 255	Glu
Val	Thr	Cys	Val 260	Val	Val	Asp	Val	Ser 265	Gln	Glu	Asp	Pro	Glu 270	Val	Gln
Phe	Asn	Trp 275	Tyr	Val	Asp	Gly	Val 280	Glu	Val	His	Asn	Ala 285	Lys	Thr	Lys

Pro Arg Glu Glu Gln Phe 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 Gly Leu Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
325 330 335

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

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

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

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
405 410 415

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

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 24

<211> 444

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 24

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Ser Tyr

20					25					30					
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe
	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
		115					120					125			
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly
	130					135					140				
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
145					150					155					160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
				165					170					175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
			180					185					190		
Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser
		195					200					205			
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys
	210					215					220				
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	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	Gln	Glu	Asp	Pro	Glu	Val	Gln

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	Phe	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					
Val	Ser	Asn	Lys	Gly	Leu	Gly	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala		
320						325						330					
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln		
335						340						345					
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly		
350						355						360					
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro		
365						370						375					
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser		
380						385						390					
Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu		
395						400						405					
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His		
410						415						420					
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys						
425						430						435					
440						445						450					

<210> 25

<211> 443

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 25

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser	1	5	10	15
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Ser	Ser	Tyr	20	25	30	
Asn	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	35	40	45	
Gly	Tyr	Ile	Ala	Pro	Phe	Gln	Gly	Asp	Ser	Arg	Tyr	Asn	Gln	Lys	Phe	50	55	60	
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr	65	70	75	80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	85	90	95	
Ala	Arg	Leu	Asn	Arg	Gly	Asn	Ser	Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	100	105	110	
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	115	120	125	
Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	130	135	140	
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	145	150	155	160
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	165	170	175	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	180	185	190	
Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	195	200	205	
Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	210	215	220	
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	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	Gln	Glu	Asp	Pro	Glu	Val	Gln	
			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	Phe	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	Gly	Leu	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	
				325					330					335		
Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	
			340					345					350			
Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	
		355					360					365				
Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	
	370					375					380					
Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	
385					390					395					400	
Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	
				405					410					415		
Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	
			420					425					430			
Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys						
		435					440									

<210> 26

<211> 450

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 26

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
1				5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Asn	Ile	Lys	Asp	Thr	
			20					25					30			
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
Ala	Arg	Ile	Tyr	Pro	Thr	Asn	Gly	Tyr	Thr	Arg	Tyr	Ala	Asp	Ser	Val	
	50					55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr	
65					70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Ser	Arg	Trp	Gly	Gly	Asp	Gly	Phe	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	
			100					105					110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
		115					120					125				
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	
	130					135					140					
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
145					150					155					160	
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
				165					170					175		
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	
			180					185					190			
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	
		195					200					205				
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	
	210					215					220					

Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	225	230	235	240
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	245	250	255	
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	260	265	270	
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	275	280	285	
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	290	295	300	
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	305	310	315	320
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	325	330	335	
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	340	345	350	
Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	355	360	365	
Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	370	375	380	
Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	385	390	395	400
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	405	410	415	
Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	420	425	430	
Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	435	440	445	
Gly	Lys															450			

<210> 27
<211> 449
<212> PRT
<213> Artificial sequence

<220>
<223> Synthesized

<400> 27

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
1				5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Asn	Ile	Lys	Asp	Thr	
			20					25					30			
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
Ala	Arg	Ile	Tyr	Pro	Thr	Asn	Gly	Tyr	Thr	Arg	Tyr	Ala	Asp	Ser	Val	
	50					55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr	
65					70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Ser	Arg	Trp	Gly	Gly	Asp	Gly	Phe	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	
			100					105					110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
		115					120					125				
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	
	130					135					140					
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
145					150					155					160	
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
				165					170					175		
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	

180							185					190				
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	
		195					200					205				
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	
	210					215					220					
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	
225					230					235					240	
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	
				245					250					255		
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	
			260					265					270			
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	
		275					280					285				
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	
	290					295					300					
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	
305					310					315					320	
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	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	Glu	Glu	Met	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 Gly
435 440 445

Lys

<210> 28

<211> 449

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 28

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

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

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

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

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

Leu 145	Gly	Cys	Leu	Val	Lys 150	Asp	Tyr	Phe	Pro	Glu 155	Pro	Val	Thr	Val	Ser 160
Trp	Asn	Ser	Gly	Ala 165	Leu	Thr	Ser	Gly	Val 170	His	Thr	Phe	Pro	Ala	Val 175
Leu	Gln	Ser	Ser 180	Gly	Leu	Tyr	Ser	Leu 185	Ser	Ser	Val	Val	Thr	Val	Pro 190
Ser	Ser	Ser 195	Leu	Gly	Thr	Gln	Thr 200	Tyr	Ile	Cys	Asn	Val 205	Asn	His	Lys
Pro	Ser 210	Asn	Thr	Lys	Val	Asp 215	Lys	Lys	Val	Glu	Pro 220	Lys	Ser	Cys	Asp
Lys 225	Thr	His	Thr	Cys	Pro 230	Pro	Cys	Pro	Ala	Pro 235	Glu	Leu	Leu	Gly	Gly 240
Pro	Ser	Val	Phe	Leu 245	Phe	Pro	Pro	Lys	Pro 250	Lys	Asp	Thr	Leu	Met	Ile 255
Ser	Arg	Thr	Pro 260	Glu	Val	Thr	Cys	Val 265	Val	Val	Asp	Val	Ser	His	Glu 270
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp 280	Tyr	Val	Asp	Gly	Val 285	Glu	Val	His
Asn 290	Ala	Lys	Thr	Lys	Pro	Arg 295	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
Val 305	Val	Ser	Val	Leu	Thr 310	Val	Leu	His	Gln	Asp 315	Trp	Leu	Asn	Gly	Lys 320
Glu	Tyr	Lys	Cys	Lys 325	Val	Ser	Asn	Lys	Ala 330	Leu	Gly	Pro	Ile	Glu	Lys 335
Thr	Ile	Ser	Lys 340	Ala	Lys	Gly	Gln	Pro 345	Arg	Glu	Pro	Gln	Val	Tyr	Thr 350
Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met 360	Thr	Lys	Asn	Gln	Val 365	Ser	Leu	Thr
Cys 370	Leu	Val	Lys	Gly	Phe	Tyr 375	Pro	Ser	Asp	Ile	Ala 380	Val	Glu	Trp	Glu

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 Gly
435 440 445

Lys

<210> 29

<211> 448

<212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 29

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

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

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln

100						105						110					
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val		
		115					120					125					
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala		
	130					135					140						
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser		
145					150					155					160		
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val		
				165					170					175			
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro		
			180					185					190				
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys		
		195					200					205					
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp		
	210					215					220						
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly		
225					230					235					240		
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile		
				245					250					255			
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu		
			260					265					270				
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His		
		275					280					285					
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg		
	290					295					300						
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys		
305					310					315					320		
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ile	Glu	Lys	Thr		
				325					330					335			
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu		

			340					345					350				
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys		
		355					360					365					
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser		
	370					375					380						
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp		
385					390					395					400		
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser		
				405					410					415			
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala		
			420					425					430				
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys		
	435						440					445					

<210> 30
 <211> 450
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Synthesized

<400> 30

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Asn	Ile	Lys	Asp	Thr		
			20					25					30				
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ala	Arg	Ile	Tyr	Pro	Thr	Asn	Gly	Tyr	Thr	Arg	Tyr	Ala	Asp	Ser	Val		
	50					55					60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr		
65					70					75					80		

Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Ser	Arg	Trp	Gly	Gly	Asp	Gly	Phe	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	
			100					105					110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
		115					120					125				
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	
	130					135					140					
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
145					150					155					160	
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
				165					170					175		
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	
			180					185					190			
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	
		195					200					205				
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	
	210					215					220					
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	
225					230					235					240	
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	
				245					250					255		
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	
			260					265					270			
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	
		275					280					285				
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	
	290					295					300					
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	
305					310					315					320	

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

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

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

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

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

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

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

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

Gly Lys
450

<210> 31
<211> 449
<212> PRT
<213> Artificial sequence

<220>
<223> Synthesized

<400> 31

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35					40					45					
Ala	Arg	Ile	Tyr	Pro	Thr	Asn	Gly	Tyr	Thr	Arg	Tyr	Ala	Asp	Ser	Val
50						55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ser	Arg	Trp	Gly	Gly	Asp	Gly	Phe	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
		115					120					125			
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
	130					135					140				
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
145					150					155					160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
				165					170					175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
			180					185					190		
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
		195					200					205			
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp
	210					215					220				
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly
225					230					235					240
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
				245					250					255	
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
			260					265					270		
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His

275					280					285					
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
290					295					300					
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
305					310					315					320
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	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	Glu	Glu	Met	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	Gly
435					440					445					

Lys

<210> 32
 <211> 449
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Synthesized

<400> 32

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
1				5				10						15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Asn	Ile	Lys	Asp	Thr	
			20					25					30			
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
Ala	Arg	Ile	Tyr	Pro	Thr	Asn	Gly	Tyr	Thr	Arg	Tyr	Ala	Asp	Ser	Val	
	50					55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr	
65					70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Ser	Arg	Trp	Gly	Gly	Asp	Gly	Phe	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	
			100					105					110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
		115					120					125				
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	
	130					135					140					
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
145					150					155					160	
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
				165					170					175		
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	
			180					185					190			
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	
		195					200					205				
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	
	210					215					220					
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	
225					230					235					240	

Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	
				245					250					255		
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	
			260					265					270			
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	
		275					280					285				
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	
	290					295					300					
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	
305					310					315					320	
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Gly	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	Glu	Glu	Met	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	Gly	
		435					440					445				

Lys

<210> 33
 <211> 448
 <212> PRT

<213> Artificial sequence

<220>

<223> Synthesized

<400> 33

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Asn	Ile	Lys	Asp	Thr		
			20					25					30				
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ala	Arg	Ile	Tyr	Pro	Thr	Asn	Gly	Tyr	Thr	Arg	Tyr	Ala	Asp	Ser	Val		
	50					55					60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr		
65					70					75					80		
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
				85					90					95			
Ser	Arg	Trp	Gly	Gly	Asp	Gly	Phe	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln		
			100					105					110				
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val		
		115					120					125					
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala		
	130					135					140						
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser		
145					150					155					160		
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val		
				165					170					175			
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro		
			180					185					190				
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys		
		195					200					205					

Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp
210						215					220				
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly
225					230					235					240
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
				245					250					255	
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
			260					265					270		
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
		275					280					285			
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
	290					295					300				
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
305					310					315					320
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ile	Glu	Lys	Thr
				325					330					335	
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			340					345					350		
Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
		355					360					365			
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
	370					375					380				
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
385					390					395					400
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser
				405					410					415	
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420					425					430		
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
		435					440					445			

<210> 34
<211> 214
<212> PRT
<213> Artificial sequence

<220>
<223> Synthesized

<400> 34

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 Val Asn Thr Ala
20 25 30

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

180

185

190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210