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(54) **Title**: METHODS AND COMPOSITIONS RELATING TO ANTI-IL-21 RECEPTOR ANTIBODIES

(57) **Abstract**: The present invention provides compositions and methods relating to antigen binding proteins against IL-21 receptor.

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METHODS AND COMPOSITIONS RELATING TO ANTI-IL-21 RECEPTOR ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Patent Application Serial Number 13/830,844, filed March 14, 2013, and U.S. Provisional Patent Application No. 61/715,156, filed October 17, 2012. The above-identified applications are incorporated herein by reference.

BACKGROUND

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

The cytokine IL-21 signals through a heterodimeric receptor consisting of the common gamma chain and IL-21-specific receptor called "IL-21 receptor" or "IL-21R." IL-21 receptor is expressed on a number of types of cells of the immune system, including dendritic cells, macrophages, NK cells, B cells, and CD4+ CD8+ T cells. With respect to T cells, IL-21 signaling stimulates CD8+ T cell proliferation and expansion. It causes naïve T cells to differentiate into Th17 cells, which it stabilizes and maintains. IL-21 signaling also down-regulates induced regulatory T cells and inhibits the suppressive effects of Tregs. Pathologic autoantibodies can be produced in germinal centers, the formation of which depends on IL-21 signaling. IL-21 also affects B cell activation plasma cell differentiation.

IL-21 signaling is associated with several pathologic conditions. Elevated levels of IL-21 are found in the sera of systemic lupus erythematosus (SLE) patients. Polymorphisms in IL-21 and IL-21 receptor have been implicated in increased susceptibility to developing SLE. Mouse models of SLE further implicate a role for IL-21 signaling.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides an isolated anti-IL-21 receptor antigen binding protein, wherein said antigen binding protein comprises either the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; the heavy chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; the heavy chain variable domain and the light chain variable domain of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a light chain variable domain sequence that is at least 90%, 95%, 97%, or 99% identical to the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a heavy chain variable domain sequence that is at least 90%, 95%, 97%, or 99% identical to the heavy chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a light chain variable domain sequence and a heavy chain variable domain sequence that each is at least 90%, 95%, 97%, or 99% identical to the light chain variable domain sequence and the heavy chain variable domain sequence, respectively, of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a light chain variable domain sequence that differs at no more than 15, 12, 10, 8, 5, or 3 amino acid positions from the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a heavy chain variable domain sequence that differs at no more than 15, 12, 10, 8, 5, or 3 amino acid positions from the heavy chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a light chain variable domain sequence and a heavy chain variable domain sequence that each differs at no more than 15, 12, 10, 8, 5, or 3 amino acid positions from the light chain variable domain sequence and the heavy chain variable domain sequence, respectively, of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a light chain variable domain sequence that is encoded by a nucleic acid sequence that is at least 90%, 95%, 97%, or 99% identical to the nucleic acid sequence encoding the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3 as provided in Figure 5; a heavy chain variable domain sequence that is encoded by a nucleic acid sequence that is at least 90%, 95%, 97%, or 99% identical to the nucleic acid sequence encoding the heavy chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3, as provided in Figure 3; a light chain variable domain sequence that is encoded by a nucleic acid sequence that is at least 90%, 95%, 97%, or 99% identical to the nucleic acid sequence encoding the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3, as provided in Figure 5, and a heavy chain variable domain sequence that is encoded by a nucleic acid sequence that is at least 90%, 95%, 97%, or 99% identical to the nucleic acid sequence encoding the heavy chain variable domain sequence of the same antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3, as provided in Figure 3; a light chain variable domain sequence that is encoded by a nucleic acid sequence that hybridizes under moderately stringent, stringent, or highly stringent conditions to the nucleic acid sequence encoding the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3 as provided in Figure 5; a heavy chain variable domain sequence that is encoded by a nucleic acid sequence that hybridizes under moderately stringent, stringent, or highly stringent conditions to the nucleic acid sequence encoding the heavy chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3 as provided in Figure 3; a light chain variable domain sequence that is encoded by a nucleic acid sequence that hybridizes under moderately stringent, stringent, or highly stringent conditions to the nucleic acid sequence encoding the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3, as provided in Figure 5, and a heavy chain variable domain sequence that is encoded by a nucleic acid sequence that hybridizes under moderately stringent, stringent, or highly stringent conditions to the nucleic acid sequence encoding the heavy chain variable domain sequence of the same antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3, as provided in Figure 3; CDR1, CDR2, and CDR3 of the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; CDR1, CDR2, and CDR3 of the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; CDR1, CDR2, and CDR3 of the light chain variable domain sequence, and CDR1, CDR2, and CDR3 of the heavy chain variable domain sequence, of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; light chain variable domain CDR1, CDR2, and CDR3 sequences that each differs at no more than 3, 2, or 1 amino acid positions from the light chain variable domain CDR1, CDR2, and CDR3 sequences, respectively, of the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; heavy chain variable domain CDR1, CDR2, and CDR3 sequences that each differs at no more than 3, 2, or 1 amino acid positions from the heavy chain variable domain CDR1, CDR2, and CDR3 sequences, respectively, of the heavy chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; or light chain variable domain CDR1, CDR2, and CDR3 sequences that each differs at no more than 3, 2, or 1 amino acid positions from the light chain variable domain CDR1, CDR2, and CDR3 sequences, respectively, of the light chain variable domain sequence of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3, and heavy chain variable domain CDR1, CDR2, and CDR3 sequences that each differs at no more than 3, 2, or 1 amino acid positions from the heavy chain variable domain CDR1, CDR2, and CDR3 sequences, respectively, of the heavy chain variable domain sequence of the same antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3.

In one embodiment, the anti-IL-21 receptor antigen binding protein comprises: a heavy chain variable domain sequence disclosed in Figure 2; a light chain variable domain sequence disclosed in Figure 4; a heavy chain variable domain sequence disclosed in Figure 2 and a light chain variable domain sequence disclosed in Figure 4; the CDR1, CDR2, and CDR3 sequences of a heavy chain sequence disclosed in Figure 2; the CDR1, CDR2, and CDR3 sequences of a light chain sequence disclosed in Figure 4; the CDR1, CDR2, and CDR3 sequences of a heavy chain sequence disclosed in Figure 2 and the CDR1, CDR2, and CDR3 sequences of a light chain sequence disclosed in Figure 4; the heavy chain constant region disclosed in Figure 7; the lambda light chain constant region disclosed in Figure 7; the kappa light chain constant region disclosed in Figure 7; the heavy chain constant region disclosed in Figure 7 and either the lambda light constant region disclosed in Figure 7 or the kappa light chain constant region disclosed in Figure 7; a heavy chain sequence disclosed in Figure 8; a light chain sequence disclosed in Figure 9; a heavy chain sequence disclosed in Figure 8 and a light chain sequence disclosed in Figure 9, wherein said heavy chain and said light chain sequence are from the same antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3; a heavy chain sequence disclosed in Figure 10; a light chain sequence disclosed in Figure 11; a heavy chain sequence disclosed in Figure 10 and a light chain sequence disclosed in Figure 11, wherein said heavy chain and said light chain sequence are from the same antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3.

In another embodiment, the isolated anti-IL-21 receptor antigen binding protein competes for binding to a human IL-21 receptor with antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3.

In another embodiment, the isolated anti-IL-21 receptor antigen binding protein of claim 1, wherein said antigen binding protein comprises either: a light chain variable domain that differs from the light chain variable domain of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3 only in that one or more non-germline amino acid residues are replaced with the corresponding germline residues; a heavy chain variable domain that differs from the heavy chain variable domain of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3 only in that one or more non-germline amino acid residues are replaced with the corresponding germline residues; or a light chain variable domain that differs from the light chain variable domain of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3 only in that one or more non-germline amino acid residues are replaced with the corresponding germline residues, and a heavy chain variable domain that differs from the heavy chain variable domain of the same antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3 only in that one or more non-germline amino acid residues are replaced with the corresponding germline residues.

In another embodiment, the antigen binding protein comprises: a human antibody; a humanized antibody; a chimeric antibody; a monoclonal antibody; a polyclonal antibody; a recombinant antibody; an antigen-binding antibody fragment; a single chain antibody; a diabody; a triabody; a tetrabody; a Fab fragment; a F(ab')2 fragment; a domain antibody; an IgD antibody; an IgE antibody; an IgM antibody; an IgG1 antibody; an IgG2 antibody; an IgG3 antibody; an IgG4 antibody; or an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

In another embodiment, the antigen binding protein inhibits binding of IL-21 to IL-21 receptor.

In another embodiment, the antigen binding protein shows activity in the B/T co-culture assay, the B cell IgA production assay, the CD8 IFN-γ production assay, or the whole blood pSTAT3 stimulation assay, of Example 3.

In another embodiment, the antigen binding protein has a potency about equal to or greater than the potency shown in Table 2 for antibodies 34H7 or 29G8 in the B/T co-culture assay, the B cell IgA production assay, the CD8 IFN-γ production assay, or the whole blood pSTAT3 stimulation assay of Example 3.

In another aspect, the present invention provides an isolated polynucleotide comprising a sequence that encodes the light chain, the heavy chain, or both of one of the aforementioned anti-IL-21 receptor antigen binding proteins.

In one embodiment, the isolated polynucleotide comprises a light chain variable domain nucleic acid sequence of Figure 5 and/or a heavy chain variable domain nucleic acid sequence of Figure 3.

In another aspect, the present invention provides a plasmid comprising an aforementioned isolated polynucleotide.

In one embodiment, the plasmid is an expression vector.

In another aspect, the present invention provides an isolated cell comprising an aforementioned isolated polynucleotide.

In one embodiment, a chromosome of the cell comprises the polynucleotide.

In another embodiment, the cell is a hybridoma.

In another embodiment, an expression vector comprises the polynucleotide.

In another embodiment, the cell is a CHO cell.

In another embodiment, the cell is a bacterial cell.

In another embodiment, the cell is an E. coli cell.

In another embodiment, the cell is a yeast cell.

In another embodiment, the cell is an animal cell.

In another embodiment, the cell is a human cell.

In another aspect, the present invention provides a method of making an anti-IL-21 receptor antigen binding protein, comprising incubating an aforementioned isolated cell under conditions that allow it to express said antigen binding protein.

In another aspect, the present invention provides a pharmaceutical composition comprising an aforementioned anti-IL-21 receptor antigen binding protein.

In another aspect, the present invention provides a method of treating a condition in a subject, comprising administering to said subject an aforementioned anti-IL-21 receptor antigen binding protein or the aforementioned pharmaceutical composition, wherein said condition is treated or prevented by a reduction in IL-21 receptor activity.

In one embodiment, about 15 milligrams to about 300 milligrams, about 30 milligrams to about 200 milligrams, about 50 milligrams to about 150 milligrams, or about 75 milligrams to about 125 milligrams of an aforementioned antigen binding protein is administered to the patient.

In another embodiment, administration of said antigen binding protein is repeated three times per day, twice per day, once per day, once every two days, once every three days, once per week, twice per week, three times per week, four times per month, three times per month, twice per month, once per month, once every two months, once every three months, once every four months, once every six months, or once per year.

In another embodiment, a dose and a frequency of administration of the antigen binding protein are used such as to maintain serum levels of the antigen binding protein in the patient at or above a desired level.

In another embodiment, the condition is an infectious, inflammatory, or autoimmune condition.

In another embodiment, the condition is Acquired Immune Deficiency Syndrome (AIDS), rheumatoid arthritis including juvenile rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, Addison's disease, diabetes (type I), epididymitis, glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hemolytic anemia, systemic lupus erythematosus (SLE), lupus nephritis, myasthenia gravis, pemphigus, psoriasis, psoriatic arthritis, atherosclerosis, erythropoietin resistance, graft versus host disease, transplant rejection, autoimmune hepatitis-induced hepatic injury, biliary cirrhosis, alcohol-induced liver injury, alcoholic cirrhosis, rheumatic fever, sarcoidosis, scleroderma, Sjogren's syndrome, a spondyloarthropathy, ankylosing spondylitis, thyroiditis, vasculitis, atherosclerosis, coronary artery disease, or heart disease.

In another embodiment, the method further comprises administering to the subject a second treatment.

In another embodiment, the second treatment is an anti-inflammatory, anti-infectious disease, or anti-autoimmune disorder treatment.

In another embodiment, the antigen binding protein or pharmaceutical composition is administered subcutaneously or intravenously.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A provides the amino acid sequence of human IL-21 receptor (SEQ ID NO: 5). Figure 1B provides the amino acid sequence of murine IL-21 receptor (SEQ ID NO: 6).

Figure 2 provides amino acid sequences of the heavy chain variable domains of anti-IL-21 receptor antibodies (SEQ ID NOS 7-16, respectively, in order of appearance). CDR 1, 2, and 3 sequences (from left to right) are indicated in bold and underlined.

Figures 3A and B provide nucleic acid sequence encoding the heavy chain variable domains of anti-IL-21 receptor (SEQ ID NOS 17-26, respectively, in order of appearance).

Figure 4 provides amino acid sequences of the light chain variable domains of anti-IL-21 receptor (SEQ ID NOS 27-36, respectively, in order of appearance). CDR 1, 2, and 3 sequences (from left to right) are indicated in bold and underlined.

Figures 5A and B provide nucleic acid sequences encoding light chain variable domains of anti-IL-21 receptor (SEQ ID NOS 37-46, respectively, in order of appearance).

Figure 6 provides amino acid sequences for heavy and light chain CDRs of anti-IL-21 receptor antibodies. Hyphens are numerical placeholders for numbering purposes (Heavy chain CDR1 sequences disclosed as SEQ ID NOS 47-48, 48-49, 49, 49, 49, 49-50, and 49, heavy chain CDR2 sequences disclosed as SEQ ID NOS 51-57, 56, 58 and 54, and heavy chain CDR3 sequences disclosed as SEQ ID NOS 59-65, 64, 66 and 62, all respectively, in order of appearance; Light chain CDR1 sequences disclosed as SEQ ID NOS 67-73, 72, 74 and 70, light chain CDR2 sequences disclosed as SEQ ID NOS 75-79, 79-80, 79, 81 and 78, and light chain CDR3 sequences disclosed as SEQ ID NOS 82-87, 87, 87-88 and 85, all respectively, in order of appearance).

Figure 7 provides amino acid and nucleic acid sequences for heavy and light chain constant sequences (SEQ ID NOS 89-94, respectively, in order of appearance).

Figures 8A and 8B provide amino acid sequences for heavy chain variable domain and constant domain sequences for anti-IL-21 receptor antibodies (SEQ ID NOS 95-104, respectively, in order of appearance).

Figures 9A and 9B provide amino acid sequences for light chain variable domain and constant domain sequences for anti-IL-21 receptor antibodies (SEQ ID NOS 105-114, respectively, in order of appearance).

Figures 10A and 10B provide amino acid sequences for signal sequences, heavy variable domain and constant domain sequences for anti-IL-21 receptor antibodies (SEQ ID NOS 115-123, respectively, in order of appearance).

Figures 11A and 11B provide amino acid sequences for signal sequences, light variable domain and constant domain sequences for anti-IL-21 receptor antibodies (SEQ ID NOS 124-133, respectively, in order of appearance).

Figures 12A-E provide heavy chain variable domain sequence groups ('10C2 Group' sequences disclosed as SEQ ID NOS 7 and 134-140, '8B9 Group' sequences disclosed as SEQ ID NOS 8-9 and 141-160, '29G8 Group' sequences disclosed as SEQ ID NOS 10 and 161-162, '31C5 Group' sequences disclosed as SEQ ID NOS 11 and 163, '29G2 Group' sequence disclosed as SEQ ID NO: 12, '31E7 Group' sequences disclosed as SEQ ID NOS 13 and 164-165, '34H7 Group' sequences disclosed as SEQ ID NOS 14 and 166-171, '30G3 Group' sequence disclosed as SEQ ID NO: 15, and '37G3 Group' sequences disclosed as SEQ ID NOS 16 and 172-173, all respectively, in order of appearance).

Figures 13A-C provide light chain variable domain sequence groups ('10C2 Group' sequence disclosed as SEQ ID NO: 27, '8B9 Group' sequences disclosed as SEQ ID NOS 28-29 and 174-177, '29G8 Group' sequences disclosed as SEQ ID NOS 30 and 178, '31C5 Group' sequence disclosed as SEQ ID NO: 31, '29G2 Group' sequence disclosed as SEQ ID NO: 32, '31E7 Group' sequences disclosed as SEQ ID NOS 33 and 179-180, '34H7 Group' sequences disclosed as SEQ ID NOS 34 and 181-182, '30G3 Group' sequences disclosed as SEQ ID NOS 35 and 183, and '37G3 Group' sequences disclosed as SEQ ID NOS 36 and 184, all respectively, in order of appearance).

DETAILED DESCRIPTION

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Unless otherwise defined herein, scientific and technical terms used in connection with the present application shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

Generally, the terminology and techniques of cell and tissue culture, molecular biology, immunology, microbiology, genetics, protein and nucleic acid chemistry, manufacturing, formulation, pharmacology, and medicine described herein are those well known and commonly used in the art. The methods and techniques of the present application are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001), Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art, or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

This invention is not limited to the particular methodology, protocols, reagents, etc., described herein. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention as defined by the claims.

Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about" as that term would be interpreted by the person skilled in the relevant art.

Definitions

The term "polynucleotide" or "nucleic acid" includes nucleotide polymers of any length. They can be, for example, single-stranded, double-stranded, or triple-stranded, or a combination of single- and/or double- and/or triple-stranded. Where a nucleotide polymer comprises more than one strand, each strand is itself understood to be a polynucleotide or nucleic acid. Where a nucleotide polymer is double-stranded, typically each of the strands is complementary to the other, although their complementarity need not be perfect and in some instances is sufficient to allow the stable association or hybridization of the two strands only under certain hybridization conditions. The nucleotides comprising the polynucleotide can be naturally-occurring or artificial nucleotide analogs, such as, for example, ribonucleotides, deoxyribonucleotides, or modified forms of either type of nucleotide, or a combination of different types of nucleotides and/or nucleotide analogs. Said modifications include, for example, base modifications, such as bromouridine and inosine derivatives, ribose modifications, such as 2',3'-dideoxyribose, and internucleotide linkage modifications, such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate and phosphoroamidate. The terms “polynucleotide” and “nucleic acid” include nucleotide polymers that have been covalently or non-covalently modified by the addition of one or more non-polynucleotide chemical entities, such as, for example, labels, (e.g., radiolabels), fluorescent labels, haptens or antigenic labels as well as nucleotide polymers that have been covalently or non-covalently bound to a solid object or surface, such as a hybridization membrane (e.g., a nitrocellulose hybridization membrane), a bead, a vessel wall, or the like.

The term "oligonucleotide" refers generally to shorter polynucleotide or nucleic acid sequences. The length of a particular oligonucleotide will depend on how it is made and/or its intended use. Typically, it refers to a polynucleotide comprising 200 or fewer nucleotides. In some embodiments, oligonucleotides are 10 to 60 bases in length. In other embodiments, oligonucleotides are 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 nucleotides in length. Oligonucleotides may be, for example, single-, double-, or triple-stranded. Single stranded oligonucleotides may be sense or antisense oligonucleotides. Oligonucleotides have many uses, including, for example, as PCR primers, cloning primers, adapters for joining two or more polynucleotides, and hybridization probes.

An "isolated nucleic acid molecule" means a DNA or RNA of genomic, mRNA, cDNA, or synthetic origin, or some combination thereof, which is at least partially removed from its natural environment. Examples of isolated nucleic acid molecules include nucleic acids that have sequences found in nature but that are produced synthetically, naturally-occurring nucleic acids that are not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, naturally-occurring nucleic acids that are linked to a polynucleotide to which they are not linked in nature, and naturally-occurring nucleic acids that have been at least partially removed from their natural cellular environment. For purposes of this disclosure, it should be understood that "a nucleic acid molecule comprising" a particular nucleotide sequence does not encompass intact naturally-occurring chromosomes. Isolated nucleic acid molecules "comprising" specified nucleic acid sequences may include other sequences as well, such as, for example, one or more other coding sequences, operably linked regulatory sequences that control or affect expression of the coding region of the recited nucleic acid sequences, vector or plasmid sequences, sequences controlling or affecting replication of the nucleic acid, restriction sites, primer binding sites, and the like.

Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence provided herein is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences;" sequence regions on the DNA strand having the same sequence as the RNA transcript that are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences."

The term "control sequence" refers to a polynucleotide sequence that can affect the expression and/or processing of a coding sequence to which it is ligated. The nature of such control sequences may depend upon the host organism. In particular embodiments, control sequences for prokaryotes may include a promoter, a ribosomal binding site, and a transcription termination sequence. Examples of control sequences for eukaryotes include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, and transcription termination sequences. The term "control sequences" can refer to leader sequences and/or fusion partner sequences as well.

The term "vector" means any molecule or entity (e.g., nucleic acid, plasmid, bacteriophage or virus) used to transfer protein coding information into a host cell.

The terms "expression vector," “expression plasmid,” and "expression construct" each refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that allows (in conjunction with the host cell) expression of one or more heterologous coding regions operatively linked thereto. An expression construct may include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto.

As used herein, "operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent or desired functions under suitable conditions. An example of a control sequence that is "operably linked" to a protein coding sequence in a vector is an enhancer region that is ligated (either directly or via intermediary sequences) to the protein coding sequence such that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the enhancer region.

The term "host cell" means a cell capable of expressing, under the correct conditions, a coding sequence of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent cell, so long as the coding sequence of interest is present. A “host cell” can be a cell that has been transformed, or is capable of being transformed, with a nucleic acid sequence and thereby express a coding sequence of interest.

The term "transduction" means the transfer of genes from one bacterium to another, usually by bacteriophage. "Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by replication defective retroviruses.

The term "transfection" means the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced into the cell. A number of transfection techniques are well known in the art and are disclosed herein. See, e.g., Graham et al., 1973, Virology 52:456; Sambrook et al., 2001, Molecular Cloning: A Laboratory Manual, supra; Davis et al., 1986, Basic Methods in Molecular Biology, Elsevier; Chu et al., 1981, Gene 13:197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells. Depending on the technique used to make the transfected cell and the desired use of the transfected cell, a cell can be transfected either stably or transiently.

The term "transformation" refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain new DNA or RNA. For example, a cell is transformed where it is genetically modified from its native state by introducing new genetic material via, for example, transfection or transduction, or via another technique, such as a chemical, ballistic, or electroporation technique. Following transformation, the transforming DNA may recombine with that of the cell by physically integrating into a chromosome of the cell, or may be maintained transiently as an episomal element without being replicated and/or stably propagated during cellular division, or it may replicate independently as a plasmid. A cell is considered to have been "stably transformed" when the transforming DNA is replicated as part of the host cell’s cycle of cell division.

The terms "polypeptide" or "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms also apply to amino acid polymers in which one or more amino acid residues is an analog, derivative, or mimetic of a naturally occurring amino acid, as well as to naturally occurring amino acid polymers. The terms also encompass amino acid polymers that have been modified. Such modifications include any naturally-occurring or artificial modification of a polypeptide. Some such modifications will alter the sequence of the polypeptide, but others will not. Examples of such modifications include the addition of carbohydrate residues and phosphorylation. Polypeptides and proteins can be produced and/or modified by a naturally-occurring and non-recombinant cell or they can be produced by a genetically-engineered or recombinant cell. “Polypeptides” and “proteins” comprise molecules having the amino acid sequence of a native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of, the native sequence. The terms "polypeptide" and "protein" specifically encompass IL-21 receptor antigen-binding proteins, antibodies, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acids of an antigen-binding protein. The term "polypeptide fragment" refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length protein. Such fragments may also contain modified amino acids as compared with the full-length protein. In certain embodiments, fragments are about five to 500 amino acids long. For example, fragments may be at least 5, 6, 8, 10, 14, 20, 50, 70, 100, 110, 150, 200, 250, 300, 350, 400, or 450 amino acids long. Useful polypeptide fragments include immunologically functional fragments of antibodies, including binding domains. In the case of an IL-21 receptor-binding antibody, useful fragments include but are not limited to a CDR region, a variable domain of a heavy or light chain, a portion of an antibody chain or just its variable region including two CDRs, and the like.

An "isolated protein" (1) is free of at least some other proteins or cellular components with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent bonds) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature. An "isolated protein" can constitute at least about 5%, at least about 10%, at least about 25%, or at least about 50% of a given sample. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof may encode such an isolated protein. In some embodiments, the isolated protein is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

A "variant" of a polypeptide (e.g., of an antigen binding protein or of an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. A fusion protein comprising all or part of a polypeptide is one example of a variant of the polypeptide.

A "derivative" of a polypeptide is a polypeptide (e.g., an antigen binding protein, or an antibody) that has been chemically modified in some manner distinct from the insertion, deletion, and/or substitution of amino acids, e.g., via conjugation to another chemical moiety. An antigen binding protein that contains all or most of either the light- or heavy-chain variable domain of an antibody, but lacks most or all of the other variable domain of the antibody, is an example of a derivative of the antibody.

The term "naturally occurring" as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature.

An "antigen binding protein" as used herein means a protein that specifically binds a specified target antigen, such as IL-21 receptor or human IL-21-receptor.

An antigen binding protein, such as an antibody or antibody fragment, variant, or derivative, is said to "specifically bind" its target antigen when it binds immunospecifically to its target antigen. In some embodiments, a specifically binding antigen binding protein has a dissociation constant (K_D) of l to 10 x 10^{-8} M. The antibody specifically binds antigen with "high affinity" when the K_D is l to 10 x 10^{-9} M, and with "very high affinity" when the K_D is l to 10 x 10^{-10} M. In one embodiment, the antibody has a K_D of l to 10 x 10^{-9} M and an off-rate of about 1 x 10^{-4} /sec. In one embodiment, the off-rate is about 1 x 10^{-5}

/sec. In other embodiments, the antibodies will bind to IL-21 receptor, or human IL-21 receptor, with a K_D of between about 10^{-8} M and 10^{-10} M, and in yet another embodiment it will bind with a K_D of l to 2 x 10^{-10}.

"Antigen binding region" means the portion of an antibody or other antigen binding protein, or a fragment, derivative, or variant thereof, that specifically binds a specified antigen. An antigen binding region can include one or more "complementarity determining regions" ("CDRs"). Certain antigen binding regions also include one or more "framework" regions. Residues within the framework regions of some antibodies and other antigen binding proteins can contribute directly to the specific binding of the antibody or antigen binding protein to its antigen, but typically framework regions aid in maintaining a conformation of the CDRs that allows binding between the antigen binding region and the antigen.

In certain aspects, recombinant antigen binding proteins that bind Il-21 receptor, or human IL-21 receptor, are provided. In this context, a "recombinant protein" is a protein made using recombinant techniques, e.g., through the expression of a recombinant nucleic acid. Methods and techniques for the production of recombinant proteins are well known in the art.

The term "antibody" refers to an intact antigen-binding immunoglobulin of any kind, or a fragment thereof that itself specifically binds to the antibody's target antigen, and includes, for example, chimeric, humanized, fully human, and bispecific antibodies. An "antibody" is a type of an antigen binding protein. In some embodiments, an intact antibody comprises two full-length heavy chains and two full-length light chains. In other embodiments, an intact antibody includes fewer chains such as antibodies naturally occurring in camelids, which may comprise only heavy chains. In other embodiments, a fragment or derivative of an antibody is made that lacks part or all of the antibody's light chains or light chain variable regions. In other embodiments, a fragment or derivative of an antibody is made that lacks some or all of the antibody's heavy chains. Such derivatives or fragments typically will comprise one or more linker or other amino acid sequences to join the light chains or light chain fragments and/or allow them to adopt a conformation that allows for binding of the fragment or derivative to its antigen.

The amino acid sequences of an antibody may be derived solely from a single source, or may be "chimeric"; that is, different portions of the antibody may be derived from two different antibodies as described further below. The antigen binding proteins, antibodies, or binding fragments may be produced in hybridomas, by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and mutations thereof.

The term "light chain" includes full-length light chain as well as fragments, derivatives, and variants thereof having a variable region sequence that is sufficient, in combination, as needed, with a suitable heavy chain or heavy chain fragment, derivative, or variant, to confer specific binding to an antigen. A full-length light chain includes a variable region domain, V_L, and a constant region domain, C_L. Examples of light chains include kappa light chains and lambda light chains.

The term "heavy chain" includes a full-length heavy chain as well as fragments, derivatives, and variants thereof having a variable region sequence that is sufficient, in combination, as needed, with a suitable light chain or light chain fragment, derivative, or variant, to confer specific binding to an antigen. A full-length heavy chain includes a variable region domain, V_H, and three constant region domains, C_{H1}, C_{H2}, and C_{H3}. Heavy chains may be of any isotype, including IgG (including IgG1, IgG2, IgG3 and IgG4 subtypes), IgA (including IgA1 and IgA2 subtypes), IgM and IgE, as well as derivatives and variants thereof.

The term "immunologically functional fragment" of an antibody or immunoglobulin chain (heavy or light chain), as used herein, is an antigen binding protein comprising a portion (regardless of how that portion is obtained or synthesized) of an antibody that lacks at least some of the amino acids present in a full-length chain but which is capable of specifically binding to an antigen. Such fragments are biologically active in that they bind specifically to the target antigen. In some embodiment, such a fragment will retain at least one CDR present in the full-length light or heavy chain, and in some embodiments will comprise a single heavy chain and/or light chain or portion thereof. These biologically active fragments may be produced by, for example, recombinant DNA techniques or by enzymatic or chemical cleavage of antigen binding proteins, including of intact antibodies. Immunologically functional immunoglobulin fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv, domain antibodies and single-chain antibodies, and may be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit. It is contemplated further that a functional portion of the antigen binding proteins disclosed herein, for example, one or more CDRs, could be covalently bound to a second protein or to a small molecule to create a therapeutic agent directed to a particular target in the body, possessing bifunctional therapeutic properties, or having a prolonged serum half-life.

"Single-chain antibodies" are Fv molecules in which the heavy and light chain variable regions have been connected by a flexible linker to form a single polypeptide chain, which forms an antigen-binding region. Single chain antibodies are discussed in detail in International Patent Application

Publication No. WO 88/01649 and U.S. Pat. No. 4,946,778 and No. 5,260,203, the disclosures of which are incorporated by reference.

A "domain antibody" is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody may target the same or different antigens.

A "bivalent antigen binding protein" or "bivalent antibody" comprises two antigen binding sites. In some embodiments, the two binding sites have the same antigen specificities. In other embodiments, the bivalent antigen binding proteins and bivalent antibodies are bispecific.

A multispecific antigen binding protein" or "multispecific antibody" is one that specifically binds more than one antigen or epitope.

A "bispecific," "dual-specific" or "bifunctional" antigen binding protein or antibody is a hybrid antigen binding protein or antibody, respectively, having two antigen binding sites that each specifically binds to a different epitope. The two epitopes can be present on the same molecule (e.g., on the IL-21 receptor protein) or on different molecules (e.g., on the IL-21 receptor protein and on IL-21, or on IL-21 receptor and on the common gamma chain). Bispecific antigen binding proteins and antibodies are a species of multispecific antigen binding protein or multispecific antibody and may be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai and Lachmann, 1990, Clin. Exp. Immunol. 79:315-321; Kostelny et al., 1992, J. Immunol. 148:1547-1553.

The terms “inhibitory antigen binding protein,” “inhibitory antibody,” “antagonistic antigen binding protein,” “antagonistic antibody,” "neutralizing antigen binding protein" and "neutralizing antibody" refers to an antigen binding protein or antibody, respectively, that specifically binds to its target and thereby reduces or prevents a biological activity of the target, such as, for example, its ability to bind with a ligand, receptor, binding partner, regulatory molecule, or substrate, catalyze a reaction, send or propagate a signal, or phosphorylate or de-phosphorylate itself or another protein.

The term "compete" when used in the context of antigen binding proteins (e.g., neutralizing antigen binding proteins or neutralizing antibodies) that bind to the same target means competition between antigen binding proteins is determined by an assay in which the antigen binding protein (e.g., antibody or immunologically functional fragment thereof) under test prevents, reduces or inhibits specific binding of a reference antigen binding protein (e.g., a ligand, or a reference antibody) to a common antigen (e.g., IL-21 receptor or a fragment thereof). Numerous types of competitive binding assays can be used, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, e.g., Stahli et al., 1983, Methods in Enzymology 9:242-253); solid phase direct biotin-avidin EIA (see, e.g., Kirkland et al., 1986, J. Immunol. 137:3614-3619) solid phase direct labeled assay, solid phase direct labeled sandwich assay (see, e.g., Harlow and Lane, 1988, Antibodies, A Laboratory Manual, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (see, e.g., Morel et al., 1988, Molec. Immunol. 25:7-15); solid phase direct biotin-avidin EIA (see, e.g., Cheung, et al., 1990, Virology 176:546-552); and direct labeled RIA (Moldenhauer et al., 1990, Scand. J. Immunol. 32:77-82). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabelled test antigen binding protein and a labeled reference antigen binding protein. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen binding protein. Usually the test antigen binding protein is present in excess. Antigen binding proteins identified by competition assay (competing antigen binding proteins) include antigen binding proteins binding to the same epitope as the reference antigen binding proteins, an epitope that overlaps the epitope as the reference antigen binding proteins, and epitopes that do not overlap but that allow for steric hindrance to occur between the test and reference antigen binding proteins. A specific method for determining competitive binding is provided in the examples herein. Usually, when a competing antigen binding protein is present in excess, it will inhibit specific binding of a reference antigen binding protein to a common antigen by at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antigen binding protein (including, e.g., an antibody or immunological functional fragment thereof), and additionally capable of being used in an animal to produce antibodies capable of binding to that antigen. An antigen may possess one or more epitopes that are capable of interacting with different antigen binding proteins, e.g., antibodies.

The term "epitope" is the portion of a molecule that is bound by an antigen binding protein (for example, an antibody). The term includes any determinant capable of specifically binding to an antigen binding protein, such as an antibody or to a T-cell receptor. An epitope can be contiguous or non-contiguous (e.g., in a polypeptide, amino acid residues that are not contiguous to one another in the polypeptide sequence but that within in context of the molecule are bound by the antigen binding protein). In certain embodiments, epitopes may be mimetic in that they comprise a three dimensional structure that is similar to an epitope used to generate the antigen binding protein, yet comprise none or only some of the amino acid residues found in that epitope used to generate the antigen binding protein. Most often, epitopes reside on proteins, but in some instances may reside on other kinds of molecules, such as nucleic acids. Epitope determinants may include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and may have specific three dimensional structural characteristics, and/or specific charge characteristics. Generally, antibodies specific for a particular target antigen will preferentially recognize an epitope on the target antigen in a complex mixture of proteins and/or macromolecules.

The term "identity" refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. "Percent identity" means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) must be addressed by a particular mathematical model or computer program (i.e., an "algorithm"). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in Computational Molecular Biology, (Lesk, A. M., ed.), 1988, New York: Oxford University Press; Biocomputing Informatics and Genome Projects, (Smith, D. W., ed.), 1993, New York: Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., 1987, Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo et al., 1988, SIAM J. Applied Math. 48:1073.

In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. The computer program used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., 1984, Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see, Dayhoff et al., 1978, Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., 1992, Proc. Natl. Acad. Sci. USA. 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

Parameters for determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following:

Algorithm: Needleman et al., 1970, J. Mol. Biol. 48:443-453;

Comparison matrix: BLOSUM 62 from Henikoff et al., 1992, supra;

Gap Penalty: 12 (but with no penalty for end gaps)

Gap Length Penalty: 4

Threshold of Similarity: 0

Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

As used herein, "substantially pure" means that the described species of molecule is the predominant species present, that is, on a molar basis it is more abundant than any other individual species in the same mixture. In certain embodiments, a substantially pure molecule is a composition wherein the object species comprises at least 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise at least 80%, 85%, 90%, 95%, or 99% of all macromolecular species present in the composition. In other embodiments, the object species is purified to essential homogeneity wherein contaminating species cannot be detected in the composition by conventional detection methods and thus the composition consists of a single detectable macromolecular species.

The term "treating" refers to any indicia of success in the prevention, prophylaxis, treatment or amelioration of an injury, pathology, disease or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, certain methods presented herein successfully treat inflammatory conditions by decreasing the incidence of inflammation, causing remission of inflammation and/or ameliorating a symptom associated with inflammation.

An "effective amount" of a therapeutic treatment is generally an amount sufficient to reduce the severity and/or frequency of symptoms, eliminate the symptoms and/or underlying cause, prevent the occurrence of symptoms and/or their underlying cause, and/or improve or remediate the damage that results from or is associated with symptoms or their underlying cause. In some embodiments, the effective amount is a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" is an amount sufficient to remedy a disease state (e.g. inflammation) or symptoms, particularly a state or symptoms associated with the disease state, or otherwise prevent, hinder, retard or reverse the progression of the disease state or any other undesirable symptom associated with the disease in any way whatsoever. A "prophylactically effective amount" is an amount of a pharmaceutical composition that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of inflammation, or reducing the likelihood of the onset (or reoccurrence) of inflammation or inflammation symptoms. The full therapeutic or prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically or prophylactically effective amount may be administered in one or more administrations.

"Amino acid" includes its normal meaning in the art. The twenty naturally-occurring amino acids and their abbreviations follow conventional usage. See, Immunology--A Synthesis, 2nd Edition, (E. S. Golub and D. R. Green, eds.), Sinauer Associates: Sunderland, Mass. (1991), incorporated herein by reference for any purpose. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as [alpha]-, [alpha]-disubstituted amino acids, N-alkyl amino acids, and other unconventional amino acids may also be suitable components for polypeptides and are included in the phrase "amino acid." Examples of unconventional amino acids include: 4-hydroxyproline, [gamma]-carboxyglutamate, [epsilon]-N,N,N-trimethyllysine, [epsilon]-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, [sigma]-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxyl-terminal direction, in accordance with standard usage and convention.

The term "IL-21 receptor mediated disease" includes, but is not limited to, inflammatory, infectious, and autoimmune diseases. An "autoimmune disease" as used herein refers to disease states and conditions wherein a patient's immune response is directed toward the patient's own constituents. For example, IL-21 receptor mediated diseases include, but are not limited to, Acquired Immune Deficiency Syndrome (AIDS), rheumatoid arthritis including juvenile rheumatoid arthritis, inflammatory bowel diseases including ulcerative colitis and Crohn's disease, multiple sclerosis, Addison's disease, diabetes (type I), diabetes (type 2), insulin resistance, metabolic syndrome, heart disease, coronary artery disease, epididymitis, glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hemolytic anemia, systemic lupus erythematosus (SLE), lupus nephritis, myasthenia gravis, pemphigus, psoriasis, psoriatic arthritis, atherosclerosis, erythropoietin resistance, graft versus host disease, transplant rejection, autoimmune hepatitis-induced hepatic injury, biliary cirrhosis, alcohol-induced liver injury including alcoholic cirrhosis, rheumatic fever, sarcoidosis, scleroderma, Sjogren's syndrome, spondyloarthropathies including ankylosing spondylitis, thyroiditis, vasculitis, atherosclerosis, coronary artery disease, and heart disease. The term "IL-21 receptor mediated disease" also encompasses any medical condition associated with increased levels of IL-21 or IL-21 receptor or increased sensitivity to IL-21.

Antigen binding proteins

In one aspect, the present invention provides antigen binding proteins (e.g., antibodies, antibody fragments, antibody derivatives, antibody muteins, and antibody variants), that bind to IL-21 receptor, e.g., human IL-21 receptor.

Antigen binding proteins in accordance with the present invention include antigen binding proteins that inhibit a biological activity of IL-21 receptor. Examples of such biological activities include binding a signaling molecule (e.g., IL-21), and transducing a signal in response to binding a signaling molecule.

Different antigen binding proteins may bind to different domains or epitopes of IL-21 receptor or act by different mechanisms of action. Examples include but are not limited to antigen binding proteins that interfere with binding of IL-21 to IL-21 receptor or that inhibit signal transduction. The site of action may be, for example, intracellular (e.g., by interfering with an intracellular signaling cascade) or extracellular. An antigen binding protein need not completely inhibit an IL-21 induced activity to find use in the present invention; rather, antigen binding proteins that reduce a particular activity of IL-21 are contemplated for use as well. (Discussions herein of particular mechanisms of action for IL-21 receptor-binding antigen binding proteins in treating particular diseases are illustrative only, and the methods presented herein are not bound thereby.)

In another aspect, the present invention provides IL-21 receptor antigen binding proteins that comprise a light chain variable region and/or a heavy chain variable region selected from the sequences provided herein, or that comprise one or more CDR sequences selected from the sequences provided herein. Examples of antigen binding proteins of the present invention include antigen binding proteins, antibodies, and antibody derivatives and fragments comprising all or part of the sequences of antibodies 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, and 37G3 as disclosed in Figures 2 through 13 or in the Examples. Specific fragments of these antibodies that are found in various embodiments of the invention include their signal sequences, variable domains, CDRs, framework regions, and constant regions. In one such embodiment, the antigen binding protein comprises the heavy chain variable domain of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3. In another such embodiment, the antigen binding protein comprises the light chain variable domain of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3. In another such embodiment, the antigen binding protein comprises the light chain variable domain and the heavy chain variable domain of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3. In another such embodiment, the antigen binding protein comprises the heavy chain CDR sequences of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3. In another such embodiment, the antigen binding protein comprises the light chain CDR sequences of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3. In another such embodiment, the antigen binding protein comprises the heavy chain CDR sequences and the light chain CDR sequences of antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3. In some such embodiments, the antigen binding protein is an antibody or an antigen-binding fragment of an antibody.

In one embodiment, the present invention provides an IL-21 receptor antigen binding protein comprising a heavy chain variable domain selected from the 31C5 group, the 29G2 group, the 31E7 group, the 34H7 group, the 30G3 group, or the 37G3 group, of Figure 12. In another embodiment, the present invention provides an IL-21 receptor antigen binding protein comprising a light chain variable domain selected from the 10C2 group, the 8B9 group, the 29G8 group, the 31C5 group, the 29G2 group, the 31E7 group, 34H7 group, the 30G3 group, or the 37G3 group, of Figure 13. In another embodiment, the present invention provides an IL-21 receptor antigen binding protein comprising a heavy chain variable domain selected from the 31C5 group, the 29G2 group, the 31E7 group, the 34H7 group, the 30G3 group, or the 37G3 group, of Figure 12, and a light chain variable domain selected from the corresponding group of Figure 13. In another embodiment, the present invention provides an IL-21 receptor antigen binding protein comprising a light chain variable domain selected from the 10C2 group, the 8B9 group, the 29G8 group, the 31C5 group, the 29G2 group, the 31E7 group, 34H7 group, the 30G3 group, or the 37G3 group, of Figure 13, and a heavy chain variable domain selected from the corresponding group of Figure 12. In another embodiment, the present invention provides an IL-21 receptor antigen binding protein comprising heavy chain CDR 1, 2, and 3 sequences selected from one or more antibodies within the 31C5 group, the 29G2 group, the 31E7 group, the 34H7 group, the 30G3 group, or the 37G3 group, of Figure 12, and light chain CDR 1, 2, and 3 sequences selected from one or more antibodies within the corresponding group of Figure 13.

In another embodiment, the present invention provides an IL-21 receptor antigen binding protein comprising a light chain variable domain comprising a sequence of amino acids that differs from the sequence of a light chain variable domain disclosed in Figure 4, 9, 11, or 13, or in the Examples, only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residues, wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the light-chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of a light chain variable domain selected from the light chain variable domain sequences disclosed in Figure 4, 9, 11, or 13, or in the Examples. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to a nucleotide sequence disclosed in Figure 5A or 5B. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide disclosed in Figure 5A or 5B. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide disclosed in Figure 5A or 5B. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to a complement of a light chain polynucleotide disclosed in Figure 5A or 5B.

In another embodiment, the present invention provides an IL-21 receptor antigen binding protein comprising a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of a heavy chain variable domain selected disclosed in Figure 2, 8, 10, or 12, or in the Examples, only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residue(s), wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is at least

70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of a heavy chain variable domain sequence disclosed in Figure 2, 8, 10, or 12, or in the Examples. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to a nucleotide sequence disclosed in Figure 3A or 3B. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide disclosed in Figure 3A or 3B. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide disclosed in Figure 3A or 3B. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to a complement of a heavy chain polynucleotide disclosed in Figure 3A or 3B.

Particular embodiments of antigen binding proteins of the present invention comprise one or more amino acid sequences that are identical to the amino acid sequences of one or more of the CDRs and/or FRs disclosed in Figures 2, 4, 6, 8, 9, 10, 11, 12 or 13, or in the Examples. In one embodiment, the antigen binding protein comprises a light chain CDR1 sequence disclosed in Figure 4, 6, or 13, or in the Examples. In another embodiment, the antigen binding protein comprises a light chain CDR2 sequence disclosed in Figure 4, 6, or 13, or in the Examples. In another embodiment, the antigen binding protein comprises a light chain CDR3 sequence disclosed in Figure 4, 6, or 13, or in the Examples. In another embodiment, the antigen binding protein comprises a heavy chain CDR1 sequence disclosed in Figure 2, 6, or 12, or in the Examples. In another embodiment, the antigen binding protein comprises a heavy chain CDR2 sequence disclosed in Figure 2, 6, or 12, or in the Examples. In another embodiment, the antigen binding protein comprises a heavy chain CDR3 sequence disclosed in Figure 2, 6, or 12, or in the Examples. In another embodiment, the antigen binding protein comprises a light chain FR1 sequence disclosed herein. In another embodiment, the antigen binding protein comprises a light chain FR2 sequence disclosed herein. In another embodiment, the antigen binding protein comprises a light chain FR3 sequence disclosed herein. In another embodiment, the antigen binding protein comprises a light chain FR4 sequence disclosed herein. In another embodiment, the antigen binding protein comprises a heavy chain FR1 sequence disclosed herein. In another embodiment, the antigen binding protein comprises a heavy chain FR2 sequence disclosed herein. In another embodiment, the antigen binding protein comprises a heavy chain FR3 sequence disclosed herein. In another embodiment, the antigen binding protein comprises a heavy chain FR4 sequence disclosed herein.

In one embodiment, the present invention provides an antigen binding protein that comprises one or more CDR sequences that each differs from a CDR sequence disclosed in Figure 2, 6, 12, or 13, or in the Examples, by no more than 5, 4, 3, 2, or 1 amino acid residues.

In another embodiment, the present invention provides antibodies that cross-compete with antibody 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, and/or 37G3 for binding to the extracellular domain human IL-21 receptor, wherein two antibodies “cross-compete” if each antibody reduces the binding of the other by at least 80% in the assay described in Example 4.

The nucleotide sequences or amino acid sequences disclosed herein can be altered, for example, by random mutagenesis or by site-directed mutagenesis (e.g., oligonucleotide-directed site-specific mutagenesis) to create an altered polynucleotide comprising one or more particular nucleotide substitutions, deletions, or insertions as compared to the non-mutated polynucleotide. Examples of techniques for making such alterations are described in Walder et al., 1986,Gene 42:133; Bauer et al.1985, Gene 37:73; Craik, BioTechniques, January 1985, 12-19; Smith et al., 1981, Genetic Engineering: Principles and Methods, Plenum Press; and U.S. Patent Nos. 4,518,584 and 4,737,462. These and other methods can be used to make, for example, derivatives of anti-IL-21 receptor antibodies that have a desired property, for example, increased affinity, avidity, or specificity for IL-21 receptor, increased activity or stability in vivo or in vitro, or reduced in vivo side-effects as compared to the underivatized antibody.

Other derivatives of anti- IL-21 receptor antibodies within the scope of this invention include covalent or aggregative conjugates of anti-IL-21 receptor antibodies, or fragments thereof, with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an anti-IL-21 receptor antibody polypeptide. For example, the conjugated peptide may be a heterologous signal (or leader) polypeptide, e.g., the yeast alpha-factor leader, or a peptide such as an epitope tag. Antigen binding protein-containing fusion proteins can comprise peptides added to facilitate purification or identification of antigen binding protein (e.g., poly-His). An antigen binding protein also can be linked to the FLAG peptide Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (DYKDDDDK) (SEQ ID NO: 1) as described in Hopp et al., Bio/Technology 6:1204, 1988, and U.S. Patent 5,011,912. The FLAG peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody (mAb), enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, MO).

Oligomers that contain one or more antigen binding proteins may be employed as IL-21 receptor antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more antigen binding protein are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc.

One embodiment is directed to oligomers comprising multiple antigen binding proteins joined via covalent or non-covalent interactions between peptide moieties fused to theantigen binding proteins. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of antigen binding proteins attached thereto, as described in more detail below.

In particular embodiments, the oligomers comprise from two to four antigen binding proteins. The antigen binding proteins of the oligomer may be in any form, such as any of the forms described above, e.g., variants or fragments. Preferably, the oligomers comprise antigen binding proteins that have IL-21 receptor binding activity.

In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., 1991, PNAS USA 88:10535; Byrn et al., 1990, Nature 344:677; and Hollenbaugh et al., 1992 "Construction of Immunoglobulin Fusion Proteins", in Current Protocols in Immunology, Suppl. 4, pages 10.19.1 - 10.19.11.

One embodiment of the present invention is directed to a dimer comprising two fusion proteins created by fusing an IL-21 receptor binding fragment of an anti- IL-21 receptor antibody to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 (hereby incorporated by reference), is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Patent 5,457,035 and in Baum et al., 1994, EMBO J. 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

In other embodiments, the variable portion of the heavy and/or light chains of an anti- IL-21 receptor antibody may be substituted for the variable portion of an antibody heavy and/or light chain.

Alternatively, the oligomer is a fusion protein comprising multiple antigen binding proteins, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233.

Another method for preparing oligomeric antigen binding proteins involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., 1988, Science 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., 1994, FEBS Letters 344:191, hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., 1994, Semin. Immunol. 6:267-78. In one approach, recombinant fusion proteins comprising an anti- IL-21 receptor antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric anti- IL-21 receptor antibody fragments or derivatives that form are recovered from the culture supernatant.

In another aspect, the present invention provides an antigen binding protein that binds to the ligand binding domain of human IL-21 receptor. Antigen binding proteins that bind to the ligand binding domain can be made using any technique known in the art. For example, such antigen binding proteins can be isolated using the full-length IL-21 receptor polypeptide (e.g., in a membrane-bound preparation), a soluble extracellular domain fragment of IL-21 receptor, or a smaller fragment of the IL-21 receptor extracellular domain comprising or consisting of the ligand binding domain. Antigen binding proteins so isolated can be screened to determine their binding specificity using any method known in the art. Examples of suitable assays are assays that test the antigen binding proteins for the ability to inhibit binding of IL-21 to cells expressing IL-21 receptor, or that test antigen binding proteins for the ability to reduce a biological or cellular response that results from the binding of IL-21 to cell surface IL-21 receptor receptors.

In another aspect, the present invention provides an antigen binding protein that binds to the same epitope as a reference antibody disclosed herein, for example, 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, or 37G3, as disclosed in Figures 2 through 13 or in the Examples. In one embodiment, the antigen binding protein competes for binding to human IL-21 receptor with the reference antibody. In another embodiment, the antigen binding protein and the reference antibody cross-compete for binding to human IL-21 receptor. In another embodiment, the epitope of the reference antibody and of the antigen binding protein is determined by solving the X-ray crystal structure of the antibody or antigen binding protein bound to human IL-21 receptor, for example, to a soluble fragment of human IL-21 receptor. In one such embodiment, the epitope is defined as those residues on the surface of human IL-21 receptor that show at least a 10% reduction in solvent accessibility when the reference antibody or the antigen binding protein is bound to it as compared to when it is bound to neither. In one embodiment, the epitope substantially overlaps the IL-21 binding domain of human IL-21 receptor.

In another aspect, the present invention provides an antigen binding protein that demonstrates species selectivity. In one embodiment, the antigen binding protein binds to one or more mammalian IL-21 receptors, for example, to human IL-21 receptor and to one or more of mouse, rat, guinea pig, hamster, gerbil, cat, rabbit, dog, goat, sheep, cow, horse, camel, and non-human primate IL-21 receptor. In another embodiment, the antigen binding protein binds to one or more primate IL-21 receptors, for example, to human IL-21 receptor and to one or more of cynomologous, marmoset, rhesus, and chimpanzee IL-21 receptors. In another embodiment, the antigen binding protein binds specifically to human, cynomologous, marmoset, rhesus, or chimpanzee IL-21 receptor. In another embodiment, the antigen binding protein does not bind to one or more of mouse, rat, guinea pig, hamster, gerbil, cat, rabbit, dog, goat, sheep, cow, horse, camel, and non-human primate IL-21 receptor. In another embodiment, the antigen binding protein does not bind to a New World monkey species such as a marmoset. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than IL-21 receptor. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than mammalian IL-21 receptor. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than primate IL-21 receptor. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than human IL-21 receptor. In another embodiment, the antigen binding protein specifically binds to mouse, rat, cynomolgus monkey, and human IL-21 receptor. In another embodiment, the antigen binding protein specifically binds to mouse, rat, cynomolgus monkey, and human IL-21 receptor with a similar binding affinity. In another embodiment, the antigen binding protein blocks binding of human IL-21 with mouse, rat, cynomolgus monkey, and human IL-21 receptor. In another embodiment, the antigen binding protein blocks binding of human IL-21 with mouse, rat, cynomolgus monkey, and human IL-21 receptor with similar K_i.

One may determine the selectivity of an antigen binding protein for an IL-21 receptor using methods well known in the art and following the teachings of the specification. For example, one may determine the selectivity using Western blot, FACS, ELISA or RIA.

Antigen-binding fragments of antigen binding proteins of the invention may be produced by conventional techniques. Examples of such fragments include, but are not limited to, Fab and F(ab')2 fragments. Antibody fragments and derivatives produced by genetic engineering techniques also are contemplated.

Additional embodiments include chimeric antibodies, e.g., humanized versions of non-human (e.g., murine) monoclonal antibodies. Such humanized antibodies may be prepared by known techniques, and offer the advantage of reduced immunogenicity when the antibodies are administered to humans. In one embodiment, a humanized monoclonal antibody comprises the variable domain of a murine antibody (or all or part of the antigen binding site thereof) and a constant domain derived from a human antibody. Alternatively, a humanized antibody fragment may comprise the antigen binding site of a murine monoclonal antibody and a variable domain fragment (lacking the antigen-binding site) derived from a human antibody. Procedures for the production of chimeric and further engineered monoclonal antibodies include those described in Riechmann et al., 1988, Nature 332:323, Liu et al., 1987, Proc. Nat. Acad. Sci. USA 84:3439, Larrick et al., 1989, Bio/Technology 7:934, and Winter et al., 1993, TIPS 14:139. In one embodiment, the chimeric antibody is a CDR grafted antibody. Techniques for humanizing antibodies are discussed in, e.g., U.S. Pat. App. No. 10/194,975 (published February 27, 2003), U.S. Pat. No.s 5,869,619, 5,225,539, 5,821,337, 5,859,205, Padlan et al., 1995, FASEB J. 9:133-39, and Tamura et al., 2000, J. Immunol. 164:1432-41.

Procedures have been developed for generating human or partially human antibodies in non-human animals. For example, mice in which one or more endogenous immunoglobulin genes have been inactivated by various means have been prepared. Human immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes. Antibodies produced in the animal incorporate human immunoglobulin polypeptide chains encoded by the human genetic material introduced into the animal. In one embodiment, a non-human animal, such as a transgenic mouse, is immunized with an IL-21 receptor polypeptide, such that antibodies directed against the IL-21 receptor polypeptide are generated in the animal. One example of a suitable immunogen is a soluble human IL-21 receptor, such as a polypeptide comprising its extracellular domain or other immunogenic fragment. Examples of techniques for production and use of transgenic animals for the production of human or partially human antibodies are described in U.S. Patents 5,814,318, 5,569,825, and 5,545,806, Davis et al., 2003, Production of human antibodies from transgenic mice in Lo, ed. Antibody Engineering: Methods and Protocols, Humana Press, NJ:191-200, Kellermann et al., 2002, Curr Opin Biotechnol. 13:593-97, Russel et al., 2000, Infect Immun. 68:1820-26, Gallo et al., 2000, Eur J Immun. 30:534-40, Davis et al., 1999, Cancer Metastasis Rev. 18:421-25, Green, 1999, J Immunol Methods. 231:11-23, Jakobovits, 1998, Advanced Drug Delivery Reviews 31:33-42, Green et al., 1998, J Exp Med. 188:483-95, Jakobovits A, 1998, Exp. Opin. Invest. Drugs. 7:607-14, Tsuda et al., 1997, Genomics. 42:413-21, Mendez et al., 1997, Nat Genet. 15:146-56, Jakobovits, 1994, Curr Biol. 4:761-63, Arbones et al., 1994, Immunity. 1:247-60, Green et al., 1994, Nat Genet. 7:13-21, Jakobovits et al., 1993, Nature. 362:255-58, Jakobovits et al., 1993, Proc Natl Acad Sci U S A. 90:2551-55. Chen, J., M. Trounstine, F. W. Alt, F. Young, C. Kurahara, J. Loring, D. Huszar. "Immunoglobulin gene rearrangement in B cell deficient mice generated by targeted deletion of the JH locus." International Immunology 5 (1993): 647-656, Choi et al., 1993, Nature Genetics 4: 117-23, Fishwild et al., 1996, Nature Biotechnology 14: 845-51, Harding et al., 1995, Annals of the New York Academy of Sciences, Lonberg et al., 1994, Nature 368: 856-59, Lonberg, 1994, Transgenic Approaches to Human Monoclonal Antibodies in Handbook of Experimental Pharmacology 113: 49-101, Lonberg et al., 1995, Internal Review of Immunology 13: 65-93, Neuberger, 1996, Nature Biotechnology 14: 826, Taylor et al., 1992, Nucleic Acids Research 20: 6287-95, Taylor et al., 1994, International Immunology 6: 579-91, Tomizuka et al., 1997, Nature Genetics 16: 133-43, Tomizuka et al., 2000, Proceedings of the National Academy of Sciences USA 97: 722-27, Tuaillon et al., 1993, Proceedings of the National Academy of Sciences USA 90: 3720-24, and Tuaillon et al., 1994, Journal of Immunology 152: 2912-20.

In another aspect, the present invention provides monoclonal antibodies that bind to IL-21 receptor. Monoclonal antibodies may be produced using any technique known in the art, e.g., by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, e.g., by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

In one embodiment, a hybridoma cell line is produced by immunizing an animal (e.g., a transgenic animal having human immunoglobulin sequences) with an IL-21 receptor immunogen; harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that binds an IL-21 receptor polypeptide. Such hybridoma cell lines, and anti-IL-21 receptor monoclonal antibodies produced by them, are encompassed by the present invention.

Monoclonal antibodies secreted by a hybridoma cell line can be purified using any technique known in the art. Hybridomas or mAbs may be further screened to identify mAbs with particular properties, such as the ability to block an IL-21 induced activity. Examples of such screens are provided in the examples below.

Molecular evolution of the complementarity determining regions (CDRs) in the center of the antibody binding site also has been used to isolate antibodies with increased affinity, for example, antibodies having increased affinity for c-erbB-2, as described by Schier et al., 1996, J. Mol. Biol. 263:551. Accordingly, such techniques are useful in preparing antibodies to IL-21 receptor.

Antigen binding proteins directed against an IL-21 receptor can be used, for example, in assays to detect the presence of IL-21 receptor polypeptides, either in vitro or in vivo. The antigen binding proteins also may be employed in purifying IL-21 receptor proteins by immunoaffinity chromatography. Those antigen binding proteins that additionally can block binding of IL-21 to IL-21 receptor may be used to inhibit a biological activity that results from such binding. Blocking antigen binding proteins can be used in the methods of the present invention. Such antigen binding proteins that function as IL-21 antagonists may be employed in treating any IL-21-induced condition, including but not limited to lupus, SLE, and arthritis. In one embodiment, a human anti- IL-21 receptor monoclonal antibody generated by procedures involving immunization of transgenic mice is employed in treating such conditions.

Antigen binding proteins may be employed in an in vitro procedure, or administered in vivo to inhibit an IL-21-induced biological activity. Disorders caused or exacerbated (directly or indirectly) by the interaction of IL-21 with cell surface IL-21 receptor, examples of which are provided above, thus may be treated. In one embodiment, the present invention provides a therapeutic method comprising in vivo administration of an IL-21 blocking antigen binding protein to a mammal in need thereof in an amount effective for reducing an IL-21-induced biological activity.

Antigen binding proteins of the invention include partially human and fully human monoclonal antibodies that inhibit a biological activity of IL-21. One embodiment is directed to a human monoclonal antibody that at least partially blocks binding of IL-21 to a cell that expresses human IL-21 receptor. In one embodiment, the antibodies are generated by immunizing a transgenic mouse with an IL-21 receptor immunogen. In another embodiment, the immunogen is a human IL-21 receptor polypeptide (e.g., a soluble fragment comprising all or part of the IL-21 receptor extracellular domain). Hybridoma cell lines derived from such immunized mice, wherein the hybridoma secretes a monoclonal antibody that binds IL-21 receptor, also are provided herein.

Although human, partially human, or humanized antibodies will be suitable for many applications, particularly those involving administration of the antibody to a human subject, other types of antigen binding proteins will be suitable for certain applications. The non-human antibodies of the invention can be, for example, derived from any antibody-producing animal, such as mouse, rat, rabbit, goat, donkey, or non-human primate (such as monkey (e.g., cynomologous or rhesus monkey) or ape (e.g., chimpanzee)). Non-human antibodies of the invention can be used, for example, in in vitro and cell-culture based applications, or any other application where an immune response to the antibody of the invention does not occur, is insignificant, can be prevented, is not a concern, or is desired. In one embodiment, a non-human antibody of the invention is administered to a non-human subject. In another embodiment, the non-human antibody does not elicit an immune response in the non-human subject. In another embodiment, the non-human antibody is from the same species as the non-human subject, e.g., a mouse antibody of the invention is administered to a mouse. An antibody from a particular species can be made by, for example, immunizing an animal of that species with the desired immunogen (e.g., a soluble IL-21 receptor polypeptide) or using an artificial system for generating antibodies of that species (e.g., a bacterial or phage display-based system for generating antibodies of a particular species), or by converting an antibody from one species into an antibody from another species by replacing, e.g., the constant region of the antibody with a constant region from the other species, or by replacing one or more amino acid residues of the antibody so that it more closely resembles the sequence of an antibody from the other species. In one embodiment, the antibody is a chimeric antibody comprising amino acid sequences derived from antibodies from two or more different species.

Antigen binding proteins may be prepared by any of a number of conventional techniques. For example, they may be purified from cells that naturally express them (e.g., an antibody can be purified from a hybridoma that produces it), or produced in recombinant expression systems, using any technique known in the art. See, for example, Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.), Plenum Press, New York (1980); and Antibodies: A Laboratory Manual, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1988).

Any expression system known in the art can be used to make the recombinant polypeptides of the invention. In general, host cells are transformed with a recombinant expression vector that comprises DNA encoding a desired polypeptide. Among the host cells that may be employed are prokaryotes, yeast or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example E. coli or bacilli. Higher eukaryotic cells include insect cells and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman et al., 1981, Cell 23:175), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, BHK (ATCC CRL 10) cell lines, and the CVI/EBNA cell line derived from the African green monkey kidney cell line CVI (ATCC CCL 70) as described by McMahan et al., 1991, EMBO J. 10: 2821. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (Cloning Vectors: A Laboratory Manual, Elsevier, New York, 1985).

The transformed cells can be cultured under conditions that promote expression of the polypeptide, and the polypeptide recovered by conventional protein purification procedures. One such purification procedure includes the use of affinity chromatography, e.g., over a matrix having all or a portion (e.g., the extracellular domain) of IL-21 receptor bound thereto. Polypeptides contemplated for use herein include substantially homogeneous recombinant mammalian anti- IL-21 receptor antibody polypeptides substantially free of contaminating endogenous materials.

Antigen binding proteins may be prepared, and screened for desired properties, by any of a number of known techniques. Certain of the techniques involve isolating a nucleic acid encoding a polypeptide chain (or portion thereof) of an antigen binding protein of interest (e.g., an anti-IL-21 receptor antibody), and manipulating the nucleic acid through recombinant DNA technology. The nucleic acid may be fused to another nucleic acid of interest, or altered (e.g., by mutagenesis or other conventional techniques) to add, delete, or substitute one or more amino acid residues, for example.

In one aspect, the present invention provides antigen-binding fragments of an anti-IL-21 receptor antibody of the invention. Such fragments can consist entirely of antibody-derived sequences or can comprise additional sequences. Examples of antigen-binding fragments include Fab, F(ab')2, single chain antibodies, diabodies, triabodies, tetrabodies, and domain antibodies. Other examples are provided in Lunde et al., 2002, Biochem. Soc. Trans. 30:500-06.

Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (VL and VH). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (e.g., dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt et al., 1997, Prot. Eng. 10:423; Kortt et al., 2001, Biomol. Eng. 18:95-108). By combining different VL and VH-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum et al., 2001, Biomol. Eng. 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Patent No. 4,946,778; Bird, 1988, Science 242:423; Huston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879; Ward et al., 1989, Nature 334:544, de Graaf et al., 2002, Methods Mol Biol. 178:379-87. Single chain antibodies derived from antibodies provided herein include, but are not limited to, scFvs comprising one or more variable domain sequences, or one or more CDR sequences from one or more variable domain sequences, disclosed herein.

In some embodiments, antigen binding proteins (e.g., antibodies, antibody fragments, and antibody derivatives) of the invention comprise a light chain and/or a heavy chain antibody constant region. Any antibody constant regions known in the art can be used. The light chain constant region can be, for example, a kappa- or lambda-type light chain constant region, e.g., a human kappa- or lambda-type light chain constant region. The heavy chain constant region can be, for example, an alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant regions, e.g., a human alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant region. In one embodiment, the light or heavy chain constant region is a fragment, derivative, variant, or mutein of a naturally occurring constant region.

Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, i.e., subclass switching. Thus, IgG antibodies may be derived from an IgM antibody, for example, and vice versa. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, e.g., DNA encoding the constant domain of an antibody of the desired isotype. See also Lantto et al., 2002, Methods Mol. Biol.178:303-16.

Accordingly, the antigen binding proteins of the present invention include those comprising, for example, one or more of the variable domain sequences disclosed herein and having a desired isotype (for example, IgA, IgG1, IgG2, IgG3, IgG4, IgM, IgE, and IgD), as well as Fab or F(ab')2 fragments thereof. Moreover, if an IgG4 is desired, it may also be desired to introduce a point mutation (CPSCP (SEQ ID NO: 2) -> CPPCP (SEQ ID NO: 3)) in the hinge region as described in Bloom et al., 1997, Protein Science 6:407, incorporated by reference herein) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

Techniques for deriving antigen binding proteins having different properties (i.e., varying affinities for the antigen to which they bind) are also known. One such technique, referred to as chain shuffling, involves displaying immunoglobulin variable domain gene repertoires on the surface of filamentous bacteriophage, often referred to as phage display. Chain shuffling has been used to prepare high affinity antibodies to the hapten 2-phenyloxazol-5-one, as described by Marks et al., 1992, BioTechnology, 10:779.

In another embodiment, the present invention provides an antigen binding protein that has a low dissociation rate from IL-21 receptor. In one embodiment, the antigen binding protein has a K_{off} of $1x10^{-4}$ s^{-1} or lower. In another embodiment, the K_{off} is $5x10^{-5}$ s^{-1} or lower. In another embodiment, the K_{off} is substantially the same as an antibody disclosed herein. In another embodiment, the antigen binding protein binds to IL-21 receptor with substantially the same K_{off} as an antibody disclosed herein. In another embodiment, the antigen binding protein binds to IL-21 receptor with substantially the same K_{off} as an antibody that comprises one or more CDRs from an antibody disclosed herein.

In another aspect, the present invention provides an antigen binding protein having a half-life of at least one day in vitro or in vivo (e.g., when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antigen binding protein has a half-life of four days or longer. In another embodiment, the antigen binding protein has a half-life of eight days or longer. In another embodiment, the antigen binding protein is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antigen binding protein. In another embodiment, the antigen binding protein contains one or more point mutations to increase serum half life, such as described in WO 00/09560, published Feb.24, 2000, incorporated by reference.

The present invention further provides multi-specific antigen binding proteins, for example, bispecific antigen binding protein, e.g., antigen binding protein that bind to two different epitopes of IL-21 receptor, or to an epitope of IL-21 receptor and an epitope of another molecule, via two different antigen binding sites or regions. Moreover, bispecific antigen binding protein as disclosed herein can comprise an IL-21 receptor binding site from one of the herein-described antibodies and a second IL-21 receptor binding region from another of the herein-described antibodies, including those described herein by reference to other publications. Alternatively, a bispecific antigen binding protein may comprise an antigen binding site from one of the herein described antibodies and a second antigen binding site from another IL-21 receptor antibody that is known in the art, or from an antibody that is prepared by known methods or the methods described herein.

Numerous methods of preparing bispecific antibodies are known in the art, and discussed in US Patent Application 09/839,632, filed April 20, 2001 (incorporated by reference herein). Such methods include the use of hybrid-hybridomas as described by Milstein et al., 1983, Nature 305:537, and others (U.S. Patent 4,474,893, U.S. Patent 6,106,833), and chemical coupling of antibody fragments (Brennan et al.,1985, Science 229:81; Glennie et al.,1987, J. Immunol. 139:2367; U.S. Patent 6,010,902). Moreover, bispecific antibodies can be produced via recombinant means, for example by using leucine zipper moieties (i.e., from the Fos and Jun proteins, which preferentially form heterodimers; Kostelny et al., 1992, J. Immnol. 148:1547) or other lock and key interactive domain structures as described in U.S. Patent 5,582,996. Additional useful techniques include those described in Kortt et al., 1997, supra; U.S. Patent 5,959,083; and U.S. Patent 5,807,706.

In another aspect, the antigen binding protein of the present invention comprises a derivative of an antibody. The derivatized antibody can comprise any molecule or substance that imparts a desired property to the antibody, such as increased half-life in a particular use. The derivatized antibody can comprise, for example, a detectable (or labeling) moiety (e.g., a radioactive, colorimetric, antigenic or enzymatic molecule, a detecable bead (such as a magnetic or electrodense (e.g., gold) bead), or a molecule that binds to another molecule (e.g., biotin or streptavidin)), a therapeutic or diagnostic moiety (e.g., a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antibody for a particular use (e.g., administration to a subject, such as a human subject, or other in vivo or in vitro uses). Examples of molecules that can be used to derivatize an antibody include albumin (e.g., human serum albumin) and polyethylene glycol (PEG). Albumin-linked and

PEGylated derivatives of antibodies can be prepared using techniques well known in the art. In one embodiment, the antibody is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyurrolidone), polyethylene glycols, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols. US Pat. App. No. 20030195154.

In another aspect, the present invention provides methods of screening for a molecule that binds to IL-21 receptor using the antigen binding proteins of the present invention. Any suitable screening technique can be used. In one embodiment, an IL-21 receptor molecule, or a fragment thereof to which an antigen binding protein of the present invention binds, is contacted with the antigen binding protein of the invention and with another molecule, wherein the other molecule binds to IL-21 receptor if it reduces the binding of the antigen binding protein to IL-21 receptor. Binding of the antigen binding protein can be detected using any suitable method, e.g., an ELISA. Detection of binding of the antigen binding protein to IL-21 receptor can be simplified by detectably labeling the antigen binding protein, as discussed above. In another embodiment, the IL-21 receptor-binding molecule is further analyzed to determine whether it inhibits IL-21 receptor-mediated signaling.

Nucleic acids

In one aspect, the present invention provides isolated nucleic acid molecules. The nucleic acids comprise, for example, polynucleotides that encode all or part of an antigen binding protein , for example, one or both chains of an antibody of the invention, or a fragment, derivative, mutein, or variant thereof, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide, anti-sense nucleic acids for inhibiting expression of a polynucleotide, and complementary sequences of the foregoing. The nucleic acids can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleotides in length, and/or can comprise one or more additional sequences, for example, regulatory sequences, and/or be part of a larger nucleic acid, for example, a vector. The nucleic acids can be single-stranded or double-stranded and can comprise RNA and/or DNA nucleotides, and artificial variants thereof (e.g., peptide nucleic acids).

Nucleic acids encoding antibody polypeptides (e.g., heavy or light chain, variable domain only, or full length) may be isolated from B-cells of mice that have been immunized with IL-21 receptor. The nucleic acid may be isolated by conventional procedures such as polymerase chain reaction (PCR).

Representative nucleic acid sequences encoding some of the antibodies of the invention are disclosed herein. Particular nucleic acid sequences encoding the variable domains of antibodies 10C2, 8B9, 8B9.13, 29G8, 31C5, 29G2, 31E7, 34H7, 30G3, and 37G3 are provided in Figures 3 and 5. The skilled artisan will appreciate that, due to the degeneracy of the genetic code, each of the polypeptide sequences disclosed herein is encoded by a large number of nucleic acid sequences. The present invention provides each degenerate nucleotide sequence encoding each antigen binding protein or other polypeptide of the invention.

The invention further provides nucleic acids that hybridize to other nucleic acids (e.g., nucleic acids comprising a nucleotide sequence disclosed herein) under particular hybridization conditions. Methods for hybridizing nucleic acids are well-known in the art. See, e.g., Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. As defined herein, a moderately stringent hybridization condition uses a prewashing solution containing 5X sodium chloride/sodium citrate (SSC), 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridization buffer of about 50% formamide, 6X SSC, and a hybridization temperature of 55° C (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42° C), and washing conditions of 60° C, in 0.5X SSC, 0.1% SDS. A stringent hybridization condition hybridizes in 6X SSC at 45° C, followed by one or more washes in 0.1X SSC, 0.2% SDS at 68° C. Furthermore, one of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that nucleic acids comprising nucleotide sequences that are at least 65, 70, 75, 80, 85, 90, 95, 98 or 99% identical to each other typically remain hybridized to each other. The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are set forth by, for example, Sambrook, Fritsch, and Maniatis (1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11; and Current Protocols in Molecular Biology, 1995, Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4), and can be readily determined by those having ordinary skill in the art based on, for example, the length and/or base composition of the DNA.

Changes can be introduced by mutation into a nucleic acid, thereby leading to changes in the amino acid sequence of a polypeptide (e.g., an antigen binding protein) that it encodes. Mutations can be introduced using any technique known in the art. In one embodiment, one or more particular amino acid residues are changed using, for example, a site-directed mutagenesis protocol. In another embodiment, one or more randomly selected residues is changed using, for example, a random mutagenesis protocol. However it is made, a mutant polypeptide can be expressed and screened for a desired property (e.g., binding to IL-21 receptor or blocking the binding of IL-21 to IL-21 receptor).

Mutations can be introduced into a nucleic acid without significantly altering the biological activity of a polypeptide that it encodes. For example, one can make nucleotide substitutions leading to amino acid substitutions at non-essential amino acid residues. In one embodiment, a nucleotide sequence provided herein, or a desired fragment, variant, or derivative thereof, is mutated such that it encodes an amino acid sequence comprising one or more deletions, substitutions, or additions of amino acid residues. In another embodiment, one or more mutations are introduced into a nucleic acid that selectively change the biological activity (e.g., binding of IL-21 receptor, inhibiting IL-21 binding, etc.) of a polypeptide that it encodes. For example, the mutation can quantitatively or qualitatively change the biological activity. Examples of quantitative changes include increasing, reducing or eliminating the activity. Examples of qualitative changes include changing the antigen specificity of an antigen binding protein.

In another aspect, the present invention provides nucleic acid molecules that are suitable for use as primers or hybridization probes for the detection of nucleic acid sequences of the invention. A nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding a full-length polypeptide of the invention, for example, a fragment that can be used as a probe or primer or a fragment encoding an active portion (e.g., an IL-21 receptor binding portion) of a polypeptide of the invention.

Probes based on the sequence of a nucleic acid of the invention can be used to detect the nucleic acid or similar nucleic acids, for example, transcripts encoding a polypeptide of the invention. The probe can comprise a label group, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used to identify a cell that expresses the polypeptide.

In another aspect, the present invention provides vectors comprising a nucleic acid encoding a polypeptide of the invention or a portion thereof. Examples of vectors include, but are not limited to, plasmids, viral vectors, non-episomal mammalian vectors and expression vectors, for example, recombinant expression vectors.

The recombinant expression vectors of the invention can comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. The recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cells (e.g., SV40 early gene enhancer, Rous sarcoma virus promoter and cytomegalovirus promoter), those that direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences, see Voss et al., 1986, Trends Biochem. Sci. 11:287, Maniatis et al., 1987, Science 236:1237, incorporated by reference herein in their entireties), and those that direct inducible expression of a nucleotide sequence in response to particular treatment or condition (e.g., the metallothionin promoter in mammalian cells and the tet-responsive and/or streptomycin responsive promoter in both prokaryotic and eukaryotic systems (see id.). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

In another aspect, the present invention provides host cells into which a recombinant expression vector of the invention has been introduced. A host cell can be any prokaryotic cell (for example, E. coli) or eukaryotic cell (for example, yeast, insect, or mammalian cells (e.g., CHO cells)). Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die), among other methods.

<u>Methods of Making Anti-IL-21 Receptor Antigen Binding Proteins</u>

A host cell comprising sequences that encode an anti-IL-21 receptor antigen binding protein of the invention can be used to make the anti-IL-21 receptor antigen binding protein. Typically, expression vectors used in a host cell will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as “flanking sequences” in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed below.

Optionally, the vector may contain a “tag”-encoding sequence, i.e., an oligonucleotide molecule located at the 5′ or 3′ end of the anti-IL-21 receptor antigen binding protein coding sequence(s); the oligonucleotide sequence encodes polyHis (such as hexaHis (SEQ ID NO: 4)), or another “tag” such as FLAG, HA (hemaglutinin influenza virus), or myc, for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification or detection of the anti-IL-21 receptor antigen binding protein from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified anti-IL-21 receptor antigen binding protein polypeptide by various means such as using certain peptidases for cleavage.

Flanking sequences may be homologous (i.e., from the same species and/or strain as the host cell), heterologous (ie., from a species other than the host cell species or strain), hybrid (i.e., a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

Flanking sequences useful in the vectors of this invention may be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using the methods described herein for nucleic acid synthesis or cloning.

Whether all or only a portion of the flanking sequence is known, it may be obtained using polymerase chain reaction (PCR) and/or by screening a genomic library with a suitable probe such as an oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagene® column chromatography (Chatsworth, Calif.), or other methods known to the skilled artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, Mass.) is suitable for most gram-negative bacteria, and various viral origins (e.g., SV40, polyoma, adenovirus, vesicular stomatitus virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it also contains the virus early promoter).

A transcription termination sequence is typically located 3′ to the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those described herein.

A selectable marker gene encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, tetracycline, or kanamycin for prokaryotic host cells; (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex or defined media. Preferred selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. Advantageously, a neomycin resistance gene may also be used for selection in both prokaryotic and eukaryotic host cells.

Other selectable genes may be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are required for production of a protein critical for growth or cell survival are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thymidine kinase genes. Mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selectable gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively increased, thereby leading to the amplification of both the selectable gene and the DNA that encodes another gene, such as an antibody that binds to IL-21 receptor polypeptide. As a result, increased quantities of a polypeptide such as an anti-IL-21 receptor antibody are synthesized from the amplified DNA.

A ribosome-binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgamo sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3′ to the promoter and 5′ to the coding sequence of the polypeptide to be expressed.

In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one may manipulate the various pre- or prosequences to improve glycosylation or yield. For example, one may alter the peptidase cleavage site of a particular signal peptide, or add pro-sequences, which also may affect glycosylation. The final protein product may have, in the -1 position (relative to the first amino acid of the mature protein) one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of some enzyme cleavage sites may result in a slightly truncated form of the desired polypeptide, if the enzyme cuts at such area within the mature polypeptide.

Expression and cloning vectors of the invention will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding the anti-IL-21 receptor antigen binding protein. Promoters are untranscribed sequences located upstream (i.e., 5′) to the start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, uniformly transcribe gene to which they are operably linked, that is, with little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding heavy chain or light chain comprising an anti-IL-21 receptor antigen binding protein of the invention by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses, hepatitis-B virus and most preferably Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

Additional promoters which may be of interest include, but are not limited to: SV40 early promoter (Benoist and Chambon, 1981, Nature 290:304-10); CMV promoter (Thomsen et al., 1984, Proc. Natl. Acad. USA 81:659-663); the promoter contained in the 3′ long terminal repeat of Rous sarcoma virus (Yamamoto, et al., 1980, Cell 22:787-97); herpes thymidine kinase promoter (Wagner et al., 1981, Proc. Natl. Acad. Sci. U.S.A. 78:144445); promoter and regulatory sequences from the metallothionine gene (Brinster et al., 1982, Nature 296:39-42); and prokaryotic promoters such as the beta-lactamase promoter (Villa-Kamaroff et al., 1978, Proc. Natl. Acad. Sci. U.S.A., 75:3727-31); or the tac promoter (DeBoer et al., 1983, Proc. Natl. Acad. Sci. U.S.A., 80:21-25). Also of interest are the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift et al., 1984, Cell 38:63946; Ornitz et al., 1986, Cold Spring Harbor Symp. Quant. Biol. 50:399409 (1986); MacDonald, 1987, Hepatology 7:425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, 1985, Nature 315:115-22); the immunoglobulin gene control region that is active in lymphoid cells (Grosschedl et al., 1984, Cell 38:647-58; Adames et al., 1985, Nature 318:533-38; Alexander et al., 1987, Mol. Cell. Biol, 7:1436-44); the mouse mammary tumor virus control region that is active in testicular, breast, lymphoid and mast cells (Leder et al., 1986, Cell 45:485-95); the albumin gene control region that is active in liver (Pinkert et al., 1987, Genes and Devel. 1:268-76); the alpha-feto-protein gene control region that is active in liver (Krumlauf et al., 1985, Mol. Cell. Biol., 5:1639-48; Hammer et al., 1987, Science 235:53-58); the alpha 1-antitrypsin gene control region that is active in liver (Kelsey et al., 1987, Genes and Devel. 1:161-71); the beta-globin gene control region that is active in myeloid cells (Mogram et al., 1985, Nature 315:33840; Kollias et al., 1986, Cell 46:89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead et al., 1987, Cell 48:703-12); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, 1985, Nature 314:283-86); and the gonadotropic releasing hormone gene control region that is active in the hypothalamus (Mason et al., 1986, Science 234:1372-78).

An enhancer sequence may be inserted into the vector to increase transcription of DNA encoding light chain or heavy chain comprising an anti-IL-21 receptor antigen binding protein of the invention by higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent, having been found at positions both 5′ and 3′ to the transcription unit. Several enhancer sequences available from mammalian genes are known (e.g., globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus is used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyorna enhancer, and adenovirus enhancers known in the art are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be positioned in the vector either 5′ or 3′ to a coding sequence, it is typically located at a site 5′ from the promoter.

A sequence encoding an appropriate native or heterologous signal sequence (leader sequence or signal peptide) can be incorporated into an expression vector, to promote extracellular secretion of the antibody. The choice of signal peptide or leader depends on the type of host cells in which the antibody is to be produced, and a heterologous signal sequence can replace the native signal sequence. Examples of signal peptides that are functional in mammalian host cells include the following: the signal sequence for interleukin-7 (IL-7) described in U.S. Pat. No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman et al. (1984, Nature 312: 768); the interleukin-4 receptor signal peptide described in EP Patent No. 0 367 566; the type I interleukin-1 receptor signal peptide described in U.S. Pat. No. 4,968,607; the type II interleukin-1 receptor signal peptide described in EP Patent No. 0 460 846; the signal sequence of human IgK; and the signal sequence of human growth hormone.

Expression vectors of the invention may be constructed from a starting vector such as a commercially available vector. Such vectors may or may not contain all of the desired flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well known to one skilled in the art.

After the vector has been constructed and a nucleic acid molecule encoding light chain, a heavy chain, or a light chain and a heavy chain comprising an anti-IL-21 receptor antibody has been inserted into the proper site of the vector, the completed vector may be inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector for an anti-IL-21 receptor antigen binding protein into a selected host cell may be accomplished by well known methods including transfection, infection, calcium phosphate co-precipitation, electroporation, microinjection, lipofection, DEAE-dextran mediated transfection, or other known techniques. The method selected will in part be a function of the type of host cell to be used.

A host cell, when cultured under appropriate conditions, synthesizes an anti-IL-21 receptor antigen binding protein that can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule.

Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. In certain embodiments, cell lines may be selected through determining which cell lines have high expression levels and constitutively produce antibodies with IL-21 receptor binding properties. In another embodiment, a cell line from the B cell lineage that does not make its own antibody but has a capacity to make and secrete a heterologous antibody can be selected.

Formulations

In some embodiments, the invention provides pharmaceutical compositions comprising a therapeutically effective amount of one or a plurality of the antibodies of the invention together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant. Preferably, acceptable formulation materials are nontoxic to recipients at the dosages and concentrations employed. In preferred embodiments, pharmaceutical compositions comprising a therapeutically effective amount of anti-IL-21 receptor antibodies are provided.

In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed.

In certain embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. See REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Edition, (A.R. Gennaro, ed.), 1990, Mack Publishing Company.

In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, supra. In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the antibodies of the invention.

In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In preferred embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and may further include sorbitol or a suitable substitute therefor. In certain embodiments of the invention, anti-IL-21 receptor antigen binding protein compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (REMINGTON'S PHARMACEUTICAL SCIENCES, supra) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, the , anti-IL-21 receptor antigen binding protein product may be formulated as a lyophilizate using appropriate excipients such as sucrose.

The pharmaceutical compositions of the invention can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art.

The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired anti-IL-21 receptor antigen binding protein in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the , anti-IL-21 receptor antigen binding protein is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that may provide controlled or sustained release of the product which can be delivered via depot injection. In certain embodiments, hyaluronic acid may also be used, having the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the desired antibody molecule.

Pharmaceutical compositions of the invention can be formulated for inhalation. In these embodiments, , anti-IL-21 receptor antigen binding proteins are advantageously formulated as a dry, inhalable powder. In preferred embodiments, , anti-IL-21 receptor antigen binding protein inhalation solutions may also be formulated with a propellant for aerosol delivery. In certain embodiments, solutions may be nebulized. Pulmonary administration and formulation methods therefore are further described in International Patent Application No. PCT/US94/001875, which is incorporated by reference and describes pulmonary delivery of chemically modified proteins.

It is also contemplated that formulations can be administered orally. Anti-IL-21 receptor antigen binding proteins that are administered in this fashion can be formulated with or without carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain embodiments, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the anti-IL-21 receptor antigen binding protein. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed.

A pharmaceutical composition of the invention is preferably provided to comprise an effective quantity of one or a plurality of anti-IL-21 receptor antigen binding proteins in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions may be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving anti-IL-21 receptor antigen binding proteins in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, International Patent Application No. PCT/US93/00829, which is incorporated by reference and describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (as disclosed in U.S. Pat. No. 3,773,919 and European Patent Application Publication No. EP 058481, each of which is incorporated by reference), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 22:547-556), poly (2-hydroxyethyl-methacrylate) (Langer et al., 1981, J. Biomed. Mater. Res. 15:167-277 and Langer, 1982, Chem. Tech. 12:98-105), ethylene vinyl acetate (Langer et al., supra) or poly-D(-)-3-hydroxybutyric acid (European Patent Application Publication No. EP 133,988). Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art. See e.g., Eppstein et al., 1985, Proc. Natl. Acad. Sci. USA 82:3688-3692; European Patent Application Publication Nos. EP 036,676; EP 088,046 and EP 143,949, incorporated by reference.

Pharmaceutical compositions used for in vivo administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, crystal, or as a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration.

The invention also provides kits for producing a single-dose administration unit. The kits of the invention may each contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments of this invention, kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are provided.

Indications

The methods and compositions of the present invention (including, for example, anti-IL-21 receptor antigen binding proteins, antibodies, antibody fragments, antibody derivatives, and other molecules of the present invention) can be used to treat a wide range of diseases, conditions, and indications. IL-21 has been shown to be essential for T-dependent antibody production in vitro (Kuchen at al. (2007) J Immunol. 179:5886) and may contribute to the overproduction of interferon-gamma ("IFN-γ") in SLE patients (Harigai et al. (2008) J Immunol. 181: 2211) and stimulates other pro-inflammatory effector mechanisms and molecules that are associated with a variety of autoimmune and/or inflammatory conditions, including, for example, SLE (Bauer et al. (2006), PLoS Med. 2(12): 2274-2284; Armañanzas et al. (2009), IEEE Transactions on Inform. Tech. in Biomed. 13(3): 341-350), systemic sclerosis (Sozzani et al. (2010), Autoimmunity 43(3): 196-203), alopecia areata (Ghoreishi et al. (2010), Br. J. Dermatol. 163: 57-62), Graves' disease (Ruiz-Riol et al. (2011), J. Autoimmunity 36: 189-200), immune-ossious dysplasia spondyloenchondrodysplasia (SPENCD) (Briggs et al. (2011), Nat. Gen. 43(2): 127-132), Degos disease (Magro et al. (2011), Am. J. Clin. Pathol. 135: 599-610), Sjogren's syndrome (Sozzani et al. (2010), Autoimmunity 43(3): 196-203; Emamian et al. (2009), Genes Immun. 10: 285-296), antiphospholipid syndrome (Armañanzas et al. (2009), IEEE Transactions on Inform. Tech. in Biomed. 13(3): 341-350), inflammatory bowel diseases including Crohn's disease and ulcerative colitis (see, e.g., U.S. Patent 6,558,661), rheumatoid arthritis (Dawidowicz et al. (2011), Ann. Rheum. Dis. 70: 117-121), Chagas disease cardiomyopathy (Cunha-Neto (2010), Autoimmunity Rev. 10: 163-165), psoriasis (Pietrzak et al. (2008), Clin. Chim. Acta 394: 7-21), multiple sclerosis (van Baarsen et al. (2006), Genes and Immunity 7: 522-531), dermatomyositis (Somani et al. (2008), Arch. Dermatol. 145(4): 1341-1349), polimyositis (Sozzani et al. (2010), Autoimmunity 43(3): 196-203) panniculitis-like T-cell lymphoma (Maliniemi et al. (2010), J. Invest, Dermatol. 130; S54 (abstract 320)), type I diabetes (Reynier et al. (2010), Genes Immun. 11: 269-278), sarcoidosis (Lee et al. 2011, Ann. Dermatol. 23(2): 239-241; Kriegova et al. (2011), Eur. Respir. J. 38: 1136-1144), and hemophagocytic lymphohistiocytosis (HLH; Schmid et al. (2009), EMBO Molec. Med. 1(2): 112-124).

SLE is an autoimmune disease of unknown etiology marked by autoreactivity to nuclear self antigens. Its clinical manifestations are so diverse that it is questionable whether it is truly a single disease or a group of related conditions (Kotzin (1996) Cell 85:303; Rahman et al. (2008) N. Engl. J. Med. 358:929). Symptoms can include the following: constitutional symptoms such as malaise, fatigue, fevers, anorexia, and weight loss; diverse skin symptoms including acute, transient facial rashes in adults, bullous disease, and chronic and disfiguring rashes of the head and neck; arthritis; muscle pain and/or weakness; cardiovascular symptoms such as mitral valve thickening, vegetations, regurgitation, stenosis, pericarditis, and ischemic heart disease, some of which can culminate in stroke, embolic disease, heart failure, infectious endocarditis, or valve failure; nephritis, which is the major cause of morbidity in SLE; neurological symptoms including cognitive dysfunction, depression, psychosis, coma, seizure disorders, migraine, and other headache syndromes, aseptic meningitis, chorea, stroke, and cranial neuropathies ; hemotologic symptoms including leucopenia, thrombocytopenia, serositis, anemia, coagulation abnormalities, splenomegaly, and lymphadenopathy, various gastrointestinal abnormalities, and even death (Vratsanos et al., “Systemic Lupus Erythematosus,” Chapter 39 in Samter’s Immunological Diseases, 6th Edition, Austen et al., eds., Lippincott Williams & Wilkins, Philadelphia, PA, 2001). In one embodiment, the compositions and/or methods of the present invention are used to treat, reduce, ameliorate, eliminate or prevent one or more of these symptoms in a patient thought to have SLE.

Severity of symptoms varies widely, as does the course of the disease. The disease activity of SLE patients can be rated using an instrument such as the Systemic Lupus Erythrmatosus Disease Activity Index (SELDAI), which provides a score for disease activity based on a score that takes into consideration the following symptoms, which are weighted according to clinicians’ opinion of their importance: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leucopenia (Bombardier et al. (1992), Arthr. & Rheum. 35:630), the relevant portions of which are incorporated herein by reference. The treatments described herein can be useful in lessening or eliminating symptoms of SLE as measured by SELDAI.

Another method for assessing disease activity in SLE is British Isles Lupus Assessment Group (BILAG) index, which is a disease activity assessment system for SLE patients based on the principle of the physician's intention to treat (Stoll et al. (1996) Ann. Rheum Dis. 55: 756-760; Hay et al. (1993) Q. J. Med. 86:447). The portions of these references describing the BILAG are incorporated herein by reference. A BILAG score is assigned by giving separate numeric or alphabetic disease activity scores in each of eight organ-based systems, general (such as fever and fatigue), mucocutaneous (such as rash and alopecia, among many other symptoms), neurological (such as seizures, migraine headaches, and psychosis, among many other symptoms), musculoskeletal (such as arthritis), cardiorespiratory (such as cardiac failure and decreased pulmonary function), vasculitis and thrombosis, renal (such as nephritis), and hematological. The compositions and/or methods described herein can be useful in lessening or eliminating symptoms of SLE as measured by the BILAG index.

Discoid lupus is a particular form of chronic cutaneous lupus in which the patient has circular lesions that occur most commonly in sun-exposed areas. The lesions can leave disfiguring scars. Up to about 25% of SLE patients develop discoid lupus lesions at some point in the course of their disease. These lesions may occur in patients that have no other symptoms of SLE. The symptoms that relate specifically to skin in cutaneous forms of lupus can be scored using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), which takes into consideration both disease activity (including erythema, scaling, and hypertrophy of the skin in various areas, as well as mucus membrane lesions and alopecia) and disease-related damage (including dyspigmentation, scarring, atrophy, and panniculitis of the skin as well as scarring of the scalp). Such symptoms can be affected by a treatment for discoid lupus with an IL-21 receptor inhibitor. The CLASI is described in detail by Albrecht et al. (2005) J. Invest. Dermatol. 125:889. The portions of this article that describe what the CLASI is, what symptoms are included in it, and how to use it are incorporated herein by reference. The treatments described herein can be useful for lessening or eliminating symptoms of discoid lupus as measured by the CLASI.

Another cutaneous disease that can be mediated by IL-21 receptor is psoriasis. Symptoms of psoriasis include itchy, dry skin that can be pink/red in color, thickened and covered with flakes. It is a common condition and is episodic in nature, that is, patients can experience flares and periods of remission. There are five type of psoriasis: erythrodermic, guttate, inverse, plaque, and pustular. Plaque psoriasis is the most common type.

The severity of disease in psoriasis patients can be measured in a variety of ways. One way disease activity is commonly measured in clinical trials the PASI score. A PASI score can range from 0 to 72, with 72 being the most severe disease. For purposes of PASI assessment, the body is considered to consist of four sections, legs, torso (that is, stomach, chest, back, etc.), arms, and head, which are considered to have 40%, 30%, 20%, and 10% of a person’s skin, respectively. For each section, the percent of the area of skin affected is estimated and transformed into a grade of from 0 to 6, with 0 being no affected skin and 6 being 90-100% of the skin of the body section in question being affected. The severity of disease is scored by separately considering three features of the affected skin, redness (erythema), scaling, and thickness, and assigning a severity score of from 0 to 4 for each feature for each body section. The sum of the severity scores for all three features for each body section is calculated, and this sum is multiplied by the weight of the respective section as determined by how much of the total skin that body section contains and by the percent of the body section affected. After this number is calculated for each body section, these numbers are added to yield the PASI score. Thus, the PASI score can be expressed as follows:

PASI= 0.1(score for percent of the head affected)(sum of 3 severity scores for the head) +

0.2(score for percent of the arms affected)(sum of 3 severity scores for the arms) +

0.3(score for percent of the torso affected)(sum of 3 severity scores for the torso) +

0.4(score for percent of the legs affected)(sum of 3 severity scores for the legs)

The descriptions of PASI scores in the following two references are incorporated by reference herein: Feldman et al. (2005) Ann. Rheum. Dis. 64:68 and Langley et al. (2004), J. Am. Acad. Dermatol. 51:563.

Many clinical trials refer to changes in PASI score over the course of the study. For example, a PASI 75 at a particular time point in a clinical trial means that the PASI score of a patient has decreased by 75% as compared to that patient's PASI score at baseline. Similarly a PASI 50 or a PASI 90 denotes a 50% or 90% reduction in PASI score.

Another commonly used measure of psoriasis severity in clinical trials is the static Physicians Global Assessment (sPGA). The sPGA is typically a six category scale rating ranging from 0=none to 5=severe. ENBREL® (etanercept; Amgen Inc., Thousand Oaks, CA), Package Insert, 2008. A sPGA score of "clear" or "minimal" (sometimes alternately referred to as "almost clear") requires no or minimal elevation of plaques, no or only very faint redness, and no scaling or minimal scaling over <5% of the area of the plaques. ENBREL® (etanercept), Package Insert, 2008. The individual elements of psoriasis plaque morphology or degree of body surface area involvement are not quantified. Nonetheless, sPGA scores correlate to some extent with PASI scores (Langley et al. (2004), J. Am. Acad. Dermatol. 51:563). In one embodiment, methods and/or compositions described herein lessen, eliminate or prevent psoriasis symptoms as measured by a PASI or an sPGA score.

Multiple sclerosis (MS) is an autoimmune disease characterized by damage to the myelin sheath that surrounds nerves, which leads to inhibition or total blockage of nerve impulses. The disease is very heterogeneous in clinical presentation, and there is a wide variation in response to treatment as well (van Baarsen et al. (2006) Genes and Immunity 7:522). Environmental factors, possibly viral infection, as well as genetic susceptibility, are thought to play a role in causing MS. Symptoms can include loss of balance, muscle spasms, tremors, weakness, loss of ability to walk, loss of coordination, various bowel and bladder problems, numbness, pain, tingling, slurred speech, difficulty chewing and swallowing, double vision, loss of vision, uncontrollable eye movements, and depression, among many other possible symptoms. In many patients episodes in which symptoms occur are interspersed with long periods of remission. The methods described herein can lessen, eliminate or prevent one or more symptoms of MS.

Type I diabetes is an autoimmune disease resulting in the destruction of insulin-producing β-cells in the pancreas, which leads to a lack of insulin. Antibodies against β-cell epitopes are detected in the sera of pre-diabetic patients, suggesting that there is an autoimmune process in progress during a long asymptomatic period that precedes the onset of clinical symptoms (Reynier et al. (2010) Genes and Immunity 11:269). The lack of insulin leads to high glucose levels in the blood and urine causing a variety of symptoms including frequent urination, increased hunger and thirst, fatigue, and weight loss. It is generally treated with insulin, a treatment that must be continued indefinitely. The causes of type I diabetes are not completely clear, but are thought to include a genetic component. About thirty percent of non-diabetic siblings of diabetic patients are found to express high levels of RNAs encoded by a group genes activated by type I interferon, although diabetic patients do not overexpress these RNAs. Such overexpression may be an indication of future disease. The methods described herein may be useful to treat or prevent type I diabetes before and/or after the onset of clinical symptoms.

IL-21 receptor activity is also implicated in Inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis. Crohn's disease is chronic and debilitating inflammatory bowel disease that is thought to reflect a overly-active TH1-mediated immune response to the flora of the gut. The lesions of Crohn's disease can appear anywhere in the bowel and occasionally elsewhere in the gastrointestinal tract. Ulcerative colitis lesions, on the other hand, usually appear in the colon. The nature of the lesions is also different, but the diseases are sufficiently similar that is sometimes difficult to distinguish them clinically. See, e.g., U.S. Pat. No. 6,558,661.

Evidence indicates that IL-21 receptor plays a role in IBDs. Elevated IL-21 and IL-21 receptor levels were found in biopsies taken from IBD patients and IL-21 was found to promote expression of inflammatory mediators in inflamed tissue explants cultures (Monteleone, 2005, Gastroenterology 128:687; Monteleone, 2006, Gut 55:1774). The compositions and methods described herein can be used to treat IBD patients, and/or reduce, prevent, or eliminate one or more symptoms of IBD.

Sarcoidosis is a systemic granulomatous disease that can affect essentially any tissue, but it primarily affects the lung and lymphatic systems. It is characterized by the presence of noncaseating epithelioid cell granulomas in more than one organ system. Most commonly the granulomas are found in lung, lymph nodes, skin, liver, and/or spleen, among other possible sites. It can be fatal. For example, fibrosis of the lungs can lead to fatality (Carter and Hunninghake, "Sarcoidosis," Chapter 47 in Samter's Immunological Diseases, 6th Edition, Austen et al., eds., Lippincott Williams & Wilkins, Philadelphia, PA, 2001). The compositions and/or methods described herein can be used to treat sarcoidosis patients, and/or to reduce, eliminate, or prevent symptoms of sarcoidosis.

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal disease having clinical manifestations including fever, hepatosplenomegaly, lymphadenopathy, jaundice and rash. Laboratory findings associated with HLH include lymphocytosis and histiocytosis and the pathologic finding of hemophagocytosis. Pancytopenia, elevated serum ferritin levels, and abnormal liver enzymes are also frequently present. The compositions and/or methods described herein can be used to treat HLH patients and/or to reduce, eliminate, or prevent symptoms of HLH.

Rheumatoid arthritis (RA) is a common inflammatory disease of synovial joints and is characterized by the productin of pro-inflammaatory cytokines/mediators by immune cells that infiltrate synovium. This causes proliferation of synovial fibroblasts, further release cytokine inflammatory molecules and formation of pannus tissue that eventually degrades cartilage and subchondral bone, leading to joint destructin, pain and disability. The compositions and/or methods described herein can be used to treat RA patients and/or to reduce, eliminate, or prevent symptoms of RA.

Therapeutic methods and administration of antigen binding proteins

In one aspect, the present invention provides methods of treating a subject. The method can, for example, have a generally salubrious effect on the subject, e.g., it can increase the subject's expected longevity. Alternatively, the method can, for example, treat, prevent, cure, relieve, or ameliorate ("treat") a disease, disorder, condition, or illness ("a condition"). Among the conditions to be treated in accordance with the present invention are conditions characterized by inappropriate expression or activity of IL-21 receptor and/or IL-21. In some such conditions, the expression or activity level is too high, and the treatment comprises administering an IL-21 receptor antagonist as described herein. In other such conditions, the expression or activity level is too low, and the treatment comprises administering an IL-21 receptor agonist as described herein. In other such conditions, the levels of IL-21 receptor and/or IL-21 activity are not necessarily elevated, but the subject is more sensitive to them.

In another aspect, the present invention provides methods of identifying subjects who are more likely to benefit from treatment using the compositions and/or methods of treatment of the present invention. Such methods can enable a caregiver to better tailor a therapeutic regimen to a particular subject's needs and reduce the likelihood of an ineffective or counterproductive course of treatment. In one embodiment, the present invention provides a method of determining whether a subject is a candidate for treatment using a composition or method as described herein comprising determining whether a target cell type in the subject expresses IL-21 receptor, wherein if the target cell type expresses IL-21 receptor, then the subject is a candidate for treatment. In another embodiment, the method comprises determining the approximate average number of IL-21 receptor molecules per target cell, wherein 10^2, 10^3, 10^4, 10^5, or 10^6 IL-21 receptor per cell indicates that the subject is a candidate for treatment. The approximate average number of IL-21 receptor molecules per target cell can be determined using any technique known in the art, for example, by staining a sample comprising cells of the target cell type with an IL-21 receptor binding molecule, and detecting the amount of IL-21 receptor binding molecule bound to the sample, where the amount of IL-21 receptor binding molecule detected is proportional to the average number of IL-21 receptor molecules in the sample. In another embodiment, the method comprises comparing the approximate average number of IL-21 receptor molecules per target cell to a reference standard, wherein if the approximate average number of IL-21 receptor molecules per target cell is greater than the reference standard, then the subject is more likely to benefit from treatment using the compositions and/or methods of treatment of the present invention. In another aspect, the method comprises determining whether IL-21 is present at elevated levels in the tissue of interest, e.g., in the vicinity of immune cells expressing IL-21 receptor. In another aspect, the method comprises determining whether a molecule downstream of IL-21 receptor is altered or activated in an IL-21 receptor-dependent fashion. Examples of such downstream molecules are STAT3, STAT1, STAT5, JAK1, and JAK3.

Certain methods provided herein comprise administering an IL-21 receptor binding antigen binding protein to a subject, thereby reducing an IL-21-induced biological response that plays a role in a particular condition. In particular embodiments, methods of the invention involve contacting endogenous IL-21 receptor with an IL-21 receptor binding antigen binding protein, e.g., via administration to a subject or in an ex vivo procedure.

The term “treatment” encompasses alleviation or prevention of at least one symptom or other aspect of a disorder, or reduction of disease severity, and the like. An antigen binding protein need not effect a complete cure, or eradicate every symptom or manifestation of a disease, to constitute a viable therapeutic agent. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur or worsen in a subject, is sufficient. One embodiment of the invention is directed to a method comprising administering to a patient an IL-21 receptor antagonist in an amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

As is understood in the pertinent field, pharmaceutical compositions comprising the molecules of the invention are administered to a subject in a manner appropriate to the indication. Pharmaceutical compositions may be administered by any suitable technique, including but not limited to parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes, by bolus injection, or continuous infusion. Localized administration, e.g. at a site of disease or injury is contemplated, as are transdermal delivery and sustained release from implants. Delivery by inhalation includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments.

Use of antigen binding proteins in ex vivo procedures also is contemplated. For example, a patient's blood or other bodily fluid may be contacted with an antigen binding protein that binds IL-21 receptor ex vivo. The antigen binding protein may be bound to a suitable insoluble matrix or solid support material.

Advantageously, antigen binding proteins are administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents, for example, a second IL-21 receptor-inhibiting substance, an anti-inflammatory substance, an anti-angiogenic substance, a chemotherapeutic substance, or an analgesic substance. In various particular embodiments, the composition comprises one, two, three, four, five, or six physiologically active agents in addition to an IL-21 receptor binding antigen binding protein.

In one embodiment, the pharmaceutical composition comprise an antigen binding protein of the invention together with one or more substances selected from the group consisting of a buffer, an antioxidant such as ascorbic acid, a low molecular weight polypeptide (such as those having fewer than 10 amino acids), a protein, an amino acid, a carbohydrate such as glucose, sucrose or dextrins, a chelating agent such as EDTA, glutathione, a stabilizer, and an excipient. Neutral buffered saline or saline mixed with conspecific serum albumin are examples of appropriate diluents. In accordance with appropriate industry standards, preservatives such as benzyl alcohol may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in Remington's Pharmaceutical Sciences, 16th Ed. (1980) and 20th Ed. (2000), Mack Publishing Company, Easton, PA.

Kits for use by medical practitioners include an IL-21 receptor-inhibiting substance of the invention and a label or other instructions for use in treating any of the conditions discussed herein. In one embodiment, the kit includes a sterile preparation of one or more IL-21 receptor binding antigen binding proteins, which may be in the form of a composition as disclosed above, and may be in one or more vials.

Dosages and the frequency of administration may vary according to such factors as the route of administration, the particular antigen binding proteins employed, the nature and severity of the disease to be treated, whether the condition is acute or chronic, and the size and general condition of the subject. Appropriate dosages can be determined by procedures known in the pertinent art, e.g. in clinical trials that may involve dose escalation studies.

An IL-21 receptor inhibiting substance of the invention may be administered, for example, once or more than once, e.g., at regular intervals over a period of time. In particular embodiments, an antigen binding protein is administered over a period of at least a month or more, e.g., for one, two, or three months or even indefinitely. For treating chronic conditions, long-term treatment is generally most effective. However, for treating acute conditions, administration for shorter periods, e.g. from one to six weeks, may be sufficient. In general, the antigen binding protein is administered until the patient manifests a medically relevant degree of improvement over baseline for the chosen indicator or indicators.

Particular embodiments of the present invention involve administering to a subject an antigen binding protein at a dosage of from about 1 ng of antigen binding protein per kg of subject's weight per day ("1ng/kg/day") to about 100 mg/kg/day, from about 500 ng/kg/day to about 50 mg/kg/day, from about 5 μg/kg/day to about 20 mg/kg/day, and from about 5 mg/kg/day to about 20 mg/kg/day to a subject. In additional embodiments, an antigen binding protein is administered to adults one time per week, two times per week, three times per week, four times per week, five times per week, six times per week, or seven or more times per week, to treat an IL-21 receptor mediated disease, condition or disorder, e.g., a medical disorder disclosed herein. If injected, the effective amount of antigen binding protein per adult dose may range from, for example, 1-20 mg/m^2, or from about 5-12 mg/m^2. Alternatively, a flat dose may be administered; the amount may range from 1-300 mg/dose. One range for a flat dose is about 20-30 mg per dose. In one embodiment of the invention, a flat dose of 25 mg/dose is repeatedly administered by injection. If a route of administration other than injection is used, the dose is appropriately adjusted in accordance with standard medical practices. One example of a therapeutic regimen involves injecting a dose of about 20-30 mg of antigen binding protein to one to three times per week over a period of at least three weeks, though treatment for longer periods may be necessary to induce the desired degree of improvement. For pediatric subjects (age 4-17), one exemplary suitable regimen involves the subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of antigen binding protein administered two or three times per week.

Particular embodiments of the methods provided herein involve subcutaneous injection of from 0.5 mg to 10 mg, preferably from 3 to 5 mg, of an antigen binding protein, once or twice per week. Another embodiment is directed to pulmonary administration (e.g., by nebulizer) of 3 or more mg of antigen binding protein once a week.

Examples of therapeutic regimens provided herein comprise subcutaneous injection of an antigen binding protein once a week, at a dose of 1.5 to 3 mg, to treat a condition in which IL-21 receptor signaling plays a role. Examples of such conditions are provided herein and are known in the art. Administration of antigen binding protein can be continued until a desired result is achieved, e.g., the subject's symptoms subside. Treatment may resume as needed, or, alternatively, maintenance doses may be administered.

Other examples of therapeutic regimens provided herein comprise subcutaneous or intravenous administration of a dose of 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 15, or 20 milligrams of an IL-21 receptor inhibitor of the present invention per kilogram body mass of the subject (mg/kg). The dose can be administered once to the subject, or more than once at a certain interval, for example, once a day, three times a week, twice a week, once a week, once every two weeks, once every three weeks, three times a month, twice a month, once a month, once every two months, once every three months, once every six months, or once a year. The duration of the treatment, and any changes to the dose and/or frequency of treatment, can be altered or varied during the course of treatment in order to meet the particular needs of the subject.

In another embodiment, an antigen binding protein is administered to the subject in an amount and for a time sufficient to maintain the concentration of the antigen binding protein at or above a desired level, to maintain the amount, concentration, or other state of a biomarker at a desired level, or to induce an improvement, preferably a sustained improvement, in at least one symptom or other indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the subject's illness, disease or condition may be assessed for determining whether the amount and time of the treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease severity, symptoms, or manifestations of the disorder in question. In one embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four weeks. The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, biopsies, or other test results, and who may also employ questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease.

Combination Therapies

Treatments exist for most IL-21 receptor mediated diseases, even though many of these treatments are effective only to a limited extent or for only a subset of patients, and/or have substantial toxicities that limit patient tolerance of treatment. The IL-21 receptor inhibitors described herein can be combined with other existing therapies for IL-21 receptor-mediated diseases.

In particular, an SLE patient can be treated concurrently with another therapy for SLE plus an IL-21 receptor-inhibitor such as an anti- IL-21 receptor antibody as described herein. Existing therapies for SLE include glucocorticoids, such as prednisone, prednisolone, and methylprednisolone, antimalarials such as hydroxychloroquine, quinacrine, and chloroquine, retinoic acid, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), cyclophosphamide, dehydroepiandrosterone, mycophenolate mofetil, azathioprine, chlorambucil, methotrexate, tacrolimus, dapsone, thalidomide, leflunomide, cyclosporine, anti-CD20 antibodies such as rituximab, BLyS inhibitors such as belimumab, anti-IFN-γ antibodies, and fusion proteins such as abatacept.

In other embodiments a patient suffering from an inflammatory bowel disease (IBD), such as Crohn's disease or ulcerative colitis, can be concurrently treated with a therapy for IBD plus an anti-IL-21 receptor antibody as described herein. Existing therapies for IBD include sulfasalazine, 5-aminosalicylic acid and its derivatives (such as olsalazine, balsalazide, and mesalamine), anti-IFN-γ antibodies, anti-TNF antibodies (including infliximab, adalimumab, golimumab, and certolizumab pegol), corticosteroids for oral or parenteral administration (including prednisone, methylprednisone, budesonide, or hydrocortisone), adrenocorticotropic hormone, antibiotics (including metronidazole, ciprofloxacin, or rifaximin), azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, and thalidomide.

In other embodiments, a patient suffering from rheumatoid arthritis can be concurrently treated with a drug used for RA therapy plus an anti-IL-21 receptor antibody as described herein. Therapies for rheumatoid arthritis (RA) include non-steroidal anti-inflammatory drugs (NSAIDs) (such aspirin and cyclooxygenase-2 (COX-2) inhibitors), disease modifying anti-inflammatory drugs (DMARDs)(such as methotrexate, leflunomide, and sulfasalazine), anti-malarials (such as hydroxychloroquine), cyclophosphamide, D-penicillamine, azathioprine, gold salts, tumor necrosis factor inhibitors (such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol), CD20 inhibitors such as rituximab, IL-1 antagonists such as anakinra, IL-6 inhibitors such as tocilizumab, inhibitors of Janus kinases (JAK)(such as tofacitinib), abatacept, and glucocorticoids, among others.

In another embodiment, a patient suffering from sarcoidosis can be concurrently treated with a drug used for sarcoidosis therapy plus an anti-IL-21 receptor antibody as described herein. Therapies for sarcoidosis include corticosteroids (may be topical or parenteral, depending on symptoms), salicylates (such as aspirin), anti-IFN-γ antibodies, and colchicine. Choroquine has been reported to be helpful with cutaneous symptoms. Methotrexate, cyclophosphamide, azathioprine, and nonsteroidal anti-inflammatory drugs have also been used in sarcoidosis. Various other treatment strategies can be helpful for some of the many different symptoms of sarcoidosis. For example, heart arrhythmias can be treated with antiarrhythmics or a pacemaker. Hypercalcemia can be treated with hydration, reduction in calcium and vitamin D intake, avoidance of sunlight, or ketoconazole. Skin lesions can be treated with hydroxychloroquine, methotrexate, or thalidomide.

In another embodiment, a patient suffering from HLH can be concurrently treated with a drug used for HLH therapy plus an anti-IL-21 receptor antibody as described herein. Therapies for HLH include corticosteroids, intravenous immunoglobulin, IL-1 inhibiting agents such as anakinra, VP-16, etoposide, cyclosporine A, dexamethasone, various other chemotherapeutics, bone marrow transplant or stem cell transplant, anti-IFN-γ antibodies,and antiviral and/or antibacterial agents.

Examples

EXAMPLE 1: LEAD CANDIDATE SELECTION

This example provides a method of screening for anti-IL-21 receptor antibodies.

Primary Screening

Two forms of human IL-21 receptor were used as antigens for XENOMOUSE™ (Amgen Inc., Thousand Oaks, CA; transgenic mice engineered to generate human antibodies) immunization. One form was a soluble human Fc-fusion (“IL-21R.Fc”) and the other was a full-length wild-type form. Both proteins were expressed using transient 293T cells. Hybridomas were generated using standard procedures using two pools of mice: IL-21R.Fc alone, designated as campaign #3 (harvest 5) and

IL-21R/CHO stables, designated as campaign #4 (harvest 6). For campaign #3, the anti-IL-21R specific binders were identified by FMAT using full length wild-type IL-21R expressed on the surface of stable CHO cells. For campaign #4, the antigen-specific binders were identified by FMAT using IL-21R/293 transient cells. These primary screens resulted in the identification of 692 (campaign #3) and 128 (campaign #4) antigen-specific binders. These panels were then tested for binding to endogenous human IL-21R on RAMOS cells by FACs. In this screen, 384 of the original 692 campaign #3 binders and 58 of the original 128 campaign #4 binders showed some degree of detectable binding to the RAMOS cells. The combined panel of 442 IL-21R specific binders was advanced to additional characterization screens.

The primary selection criterion for antibodies with antagonist activity was a flow cytometry-based receptor-ligand blocking assay using RAMOS cells and labeled IL-21 ligand. The secondary selection criterion was cross-reactive binding to cyno IL-21R. This assay was also run by flow cytometry using full length cyno IL-21R transiently expressed on the surface of 293Ts. These two selection criteria resulted in the identification of 26 hybridomas of interest to advance to subcloning and scale up.

Three antibodies with functional antagonism and cross-reactive binding to cyno IL-21R were subcloned as full IgG constructs and sequence analyzed. These antibodies were 34H7, which was derived from the soluble immunogen, and 30G3 and 29G8, which were derived from the cell based immunogen.

Cloning and Sequence Analysis

The 30G3 light and heavy chain variable regions were PCR amplified from independent sub-clones derived from hybridomas and then DNA sequenced. The light chain variable region was cloned onto a kappa light constant region. The gamma chain variable region was cloned onto an IgG2 constant region. 30G3 was determined by sequence analysis to be composed of a VK3 | L27 | JK4 kappa light chain variable region and a VH4|4-59 | JH4 gamma variable region. The heavy chain constant region (CH2) of 30G3 contained one N-linked glycosylation consensus site. The theoretical pI of the full molecule was calculated to be 8.6 (with processed termini) and empirically determined to be 8.76. 34H7 and 29G8 were cloned and sequence analyzed in a similar manner.

The table below lists salient features.

Table 1

Sequence Parameter	34H7	29G8	30G3
HC isotype	huIgG2	huIgG2	huIgG2
LC type	huKappa	huKappa	huKappa
Non germ line framework residues	Non germ line residue / Germ line residue L 12 V_VH R 30 S_VH H 94 S_VH V 98 A_VH S 108 R_VH S 90 T_VL	Non germ line residue / Germ line residue S 143 T_VH T 102 A_VL	Non germ line residue / Germ line residue A 48 P_VH M 80 I_VH V 2 I_VL F 57 Y_VL N 94 S_VL L 103 V_VL
Uncommon framework residues *	Same as above	Same as above	Same as above
Freq. VH / VL subtype **	82.29% / 18.75%	6.57% / 5.68%	21.53% / 55.36%
VH /VL domain subtype	VH5|5-51 / VK3|L2	VH3|3-33 / VK1|L5	VH4|4-59 / VK3|A27
Consensus N-glycosylation sites	HC: NST at 412 (CH2)	HC: NST at 412 (CH2)	HC: NST at 412 (CH2)
Number of residues in HC CDR3	12	14	7
Whole molecule theoretical pI (pI with processed N- and C-terminal residues	8.55	8.67	8.6
Immunogenicity (number predicted agretopes)	1	1	0

*Uncommon residues are defined as being represented at less than 10% positional frequency within their respective family in the IMGT/Kabat database.

**The subtype frequency within a family in the IMGT/Kabat database.

EXAMPLE 2: FUNCTIONAL SCREENING

Several assays were used to test antibody activity. The primary assay for ranking potency was the B/T cell co-culture described above because it involved inhibition of native IL-21 produced by T cells in close proximity to responding B cells. Exogenous IL-21 assays were also used to measure antibody potency. IL-21 + CD40L stimulation was used to stimulate IgA from B cells. IL-21 alone was used to stimulate IFN-γ production in CD8 T cells. Lastly, STAT3 phosphorylation was measured in IL-21-

stimulated whole blood. For affinity measurements with recombinant IL-21R, both Biacore and KinExA were used. Affinity measurements were also conducted on whole cells by flow cytometry, using an IL-21R-expressing cell line. The results of these assays for three mAbs are shown in Table 2. The values indicate concentration in pM (picomolar) at which IL-21 activity is inhibited by 50% (IC-50). Lower values represent more potent inhibition. For affinity measurements, lower values also represent higher affinity.

Table 2 Potency and affinity of IL-21R mAbs

	IC-50 (pM)													K_D (pM)			
	B/T co-culture (IgA)[1]					B cell (IgA)[2]		CD8 T (IFNγ)[3]		hu pSTAT3[4]		cyno pSTAT3		Biacore		Kinexa	On cells[5]
Clone	exp1	exp2	exp3	exp4	exp5	exp1	exp2	exp1	exp2	B	T	B	T	hu	cyno	hu	
34H7	16	9	11	17	10	18	49	79	27	14	8	4	13	35	43	6	15
29G8	29	8	17	17	14	22	47	139	48	137	33	65	286	78	166	26	16
30G3	44	31	24	24	19	58	31	203	35	36	10	9	33	16	78	15	33

Assay protocols

[1] *B/T co-culture.* Mitomicin C-treated human T cells were cultured with B cells in anti-CD3 antibody pre-coated 96-well plates as described in Kuchen et al. (2007) J Immunol 179:5886, incorporated herein by reference in its entirety. Supernatants were collected for IgA ELISA on day 6.

[2] *B cell IgA production.* Negatively selected human peripheral blood B cells were cultured *in vitro* with IL-21 and CD40L. On day 6, supernatants were collected for human IgG ELISA analysis.

[3] *CD8 IFN-γ production.* Purified human CD8 T cells were cultured with IL-21. IFN-γ was measured in the supernatant on day 3.

[4] *Whole blood pSTAT3 stimulation.* Human or cynomolgus monkey whole blood was pre-incubated with IL-21R mAbs titrations at 37°C for 1 hr and stimulated with IL-21. Cells were fixed, permeabilized and stained for pSTAT3 and cell surface markers.

[5] *Cell based K_D measurement.* Ramos cells (Human Burkitt's lymphoma) were incubated with a titration of IL-21R mAbs and bound antibody was detected with anti-huIgG by flow cytometry.

EXAMPLE 3: CROSS-COMPETITION BINDING ASSAY

This example provides an assay for determining whether two antibodies cross-compete for binding to the extracellular domain of human IL-21 receptor.

A cross-competition binding assay is performed using the BIACORE™ 3000 instrument (Biacore International AB, Uppsala, Sweden and Piscataway, N.J), following the manufacturer's protocols. A recombinant human IL-21 receptor::FC chimera is immobilized onto the dextran layer of a CM5 biosensor chip using amine coupling. Chips are prepared using 10 mM acetate buffer pH 5.0 as the immobilization buffer at a protein density of 940 RU. Deactivation of unreacted N-hydroxysuccinimide esters is performed using 1 M ethanolamine hydrochloride, pH 8.5. Purified antibodies or antibody fragments are diluted to a concentration of 50 nM in HBS-EP running buffer (0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% Polysorbate 20). A first anti-IL-21 receptor antibody is chosen and then injected across the flow cell for 600 seconds at a rate of 10 μ L/min. After the injection is complete, a second anti-IL-21 receptor antibody is chosen and injected across the same flow cell for 600 seconds at a rate of 10 μ L/min. (As a positive control for cross-competition, the first and second antibody can be the same antibody. As a negative control for cross-competition, the first antibody can be an antibody that does not specifically bind to human IL-21 receptor.) The sensor surface is regenerated by a 12 second injection of 100 mM H_3PO_4 (25 μL/min). After regeneration, the second antibody is now injected across the flow cell for 600 seconds at a rate of 10 μ L/min. After the injection is complete, the first antibody is injected across the same flow cell for 600 seconds at a rate of 10 μ L/min. The first and second antibodies are said to cross-compete for binding to human IL-21 receptor if each reduces the binding of the other in this assay by at least 80%.

CLAIMS

WHAT IS CLAIMED IS:

1. An isolated anti-IL-21 receptor antigen binding protein, wherein said antigen binding protein comprises either:

    a. the heavy chain variable domain and the light chain variable domain of antibody 30G3; or

    b. CDR1, CDR2, and CDR3 of the light chain variable domain sequence of antibody 30G3, and CDR1, CDR2, and CDR3 of the heavy chain variable domain sequence of antibody 30G3; or

    c. a heavy chain variable domain selected from the 30G3 group of Figure 12E, and a light chain variable domain selected from the corresponding group of Figure 13C.

2. The anti-IL-21 receptor antigen binding protein of claim 1, comprising:

    a. the heavy chain variable domain sequence of antibody 30G3 disclosed in Figure 2; or

    b. the light chain variable domain sequence of antibody 30G3 disclosed in Figure 4; or

    c. the heavy chain variable domain sequence of antibody 30G3 disclosed in Figure 2 and the light chain variable domain sequence of antibody 30G3 disclosed in Figure 4; or

    d. the CDR1, CDR2, and CDR3 sequences of the heavy chain sequence of antibody 30G3 disclosed in Figure 2; or

    e. the CDR1, CDR2, and CDR3 sequences of a light chain sequence of antibody 30G3 disclosed in Figure 4; or

    f. the CDR1, CDR2, and CDR3 sequences of a heavy chain sequence of antibody 30G3 disclosed in Figure 2 and the CDR1, CDR2, and CDR3 sequences of a light chain sequence of antibody 30G3 disclosed in Figure 4; or

    g. the heavy chain constant region disclosed in Figure 7; or

    h. the lambda light chain constant region disclosed in Figure 7; or

    i. the kappa light chain constant region disclosed in Figure 7; or

    j. the heavy chain constant region disclosed in Figure 7 and either the lambda light constant region disclosed in Figure 7 or the kappa light chain constant region disclosed in Figure 7; or

    k. a heavy chain sequence of antibody 30G3 disclosed in Figure 8B; or

    l. a light chain sequence of antibody 30G3 disclosed in Figure 9B; or

m. a heavy chain sequence disclosed in Figure 8B and a light chain sequence disclosed in Figure 9B, wherein said heavy chain and said light chain sequence are from the same antibody 30G3; or

n. a heavy chain sequence of antibody 30G3 disclosed in Figure 10B; or

o. a light chain sequence of antibody 30G3 disclosed in Figure 11B; or

p. a heavy chain sequence disclosed in Figure 10B and a light chain sequence disclosed in Figure 11B, wherein said heavy chain and said light chain sequence are from the same antibody 30G3.

3. The isolated anti-IL-21 receptor antigen binding protein of claim 1, wherein said antigen binding protein competes for binding to a human IL-21 receptor with antibody 30G3.

4. The isolated IL-21 receptor antigen binding protein of any one of claims 1 through 3, wherein said antigen binding protein comprises:

a. a human antibody;

b. a humanized antibody;

c. a chimeric antibody;

d. a monoclonal antibody;

e. a polyclonal antibody;

f. a recombinant antibody;

g. an antigen-binding antibody fragment;

h. a single chain antibody;

i. a diabody;

j. a triabody;

k. a tetrabody;

l. a Fab fragment;

m. a F(ab')2 fragment;

n. a domain antibody;

o. an IgD antibody;

p. an IgE antibody;

q. an IgM antibody;

r. an IgG1 antibody;

s. an IgG2 antibody;

t. an IgG3 antibody;

u. an IgG4 antibody; or

v. an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

5. The isolated anti-IL-21 receptor antigen binding protein of any one of claims 1 through 4, wherein:

a. said antigen binding protein inhibits binding of IL-21 to IL-21 receptor; or

b. said antigen binding protein shows activity in the B/T co-culture assay, the B cell IgA production assay, the CD8 IFN-γ production assay, or the whole blood pSTAT3 stimulation assay, of Example 3; or

c. said antigen binding protein of (b) has a potency about equal to or greater than the potency shown in Table 2 for antibodies 34H7 or 29G8 in the B/T co-culture assay, the B cell IgA production assay, the CD8 IFN-γ production assay, or the whole blood pSTAT3 stimulation assay of Example 3.

6. An isolated polynucleotide comprising a sequence that encodes the light and heavy chain of said isolated anti-IL-21 receptor antigen binding protein of any one of claims 1 through 5.

7. The isolated polynucleotide of claim 6, wherein said isolated polynucleotide comprises a light chain variable domain nucleic acid sequence of antibody 30G3 of Figure 5B and a heavy chain variable domain nucleic acid sequence of antibody 30G3 of Figure 3B.

8. A plasmid comprising said polynucleotide of claim 7.

9. The plasmid of claim 8, wherein said plasmid is an expression vector.

10. An isolated cell comprising said polynucleotide of claim 6 or 7.

11. The isolated cell of claim 10, wherein a chromosome of said cell comprises said polynucleotide.

12. The isolated cell of claim 10 or 11, wherein an expression vector comprises said polynucleotide.

13. The isolated cell of any one of claims 10 to 12, wherein said cell is:
a. a hybridoma;
b. a CHO cell;
c. a bacterial cell;
d. an E. coli cell;
e. a yeast cell;
f. an animal cell; or
g. a human cell.

14. A method of making an anti-IL-21 receptor antigen binding protein, comprising incubating said cell of any one of claims 10 to 13 under conditions that allow it to express said antigen binding protein.

15. A pharmaceutical composition comprising the anti-IL-21 receptor antigen binding protein of any one of claims 1 through 5.

16. A method of treating a condition in a subject, comprising administering to said subject the anti-IL-21 receptor antigen binding protein of any one of claims 1 through 5 or the pharmaceutical composition of claim 15, wherein said condition is treated or prevented by a reduction in IL-21 receptor activity.

17. Use of the anti-IL-21 receptor antigen binding protein of any one of claims 1 through 5 or the pharmaceutical composition of claim 15, in the preparation of a medicament for the treatment of a condition in a subject, wherein said condition is treated or prevented by a reduction in IL-21 receptor activity.

18. The method of claim 16, wherein:

a. about 15 milligrams to about 300 milligrams, about 30 milligrams to about 200 milligrams, about 50 milligrams to about 150 milligrams, or about 75 milligrams to about 125 milligrams of said antigen binding protein is administered to said patient; or

b. wherein said administration of said antigen binding protein is repeated three times per day, twice per day, once per day, once every two days, once every three days, once per week, twice per week, three times per week, four times per month, three times per month, twice per month, once per month,

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once every two months, once every three months, once every four months, once every six months, or once per year; or

c. wherein a dose and a frequency of administration of said antigen binding protein are used such as to maintain serum levels of said antigen binding protein in said patient at or above a desired level.

19. The method of claim 16 or use of claim 17, wherein said condition is:

a. an infectious, inflammatory, or autoimmune condition; or

b. Acquired Immune Deficiency Syndrome (AIDS), rheumatoid arthritis including juvenile rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, Addison's disease, diabetes (type I), epididymitis, glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hemolytic anemia, systemic lupus erythematosus (SLE), lupus nephritis, myasthenia gravis, pemphigus, psoriasis, psoriatic arthritis, atherosclerosis, erythropoietin resistance, graft versus host disease, transplant rejection, autoimmune hepatitis-induced hepatic injury, biliary cirrhosis, alcohol-induced liver injury, alcoholic cirrhosis, rheumatic fever, sarcoidosis, scleroderma, Sjogren's syndrome, a spondyloarthropathy, ankylosing spondylitis, thyroiditis, vasculitis, atherosclerosis, coronary artery disease, or heart disease.

20. The method of claim 16, further comprising administering to said subject a second treatment.

21. The method of claim 20, wherein said second treatment is an anti-inflammatory, anti-infectious disease, or anti-autoimmune disorder treatment.

22. The method of claim 16, wherein said antigen binding protein or pharmaceutical composition is administered subcutaneously or intravenously.

FIGURE 1A

Human IL-21 receptor
GenBank Accession Number Q9HBE5

```
1    mprgwaapll llllqggwgc pdlvcytdyl qtvicilemw nlhpstltlt wqdqyeelkd
61   eatscslhrs ahnathatyt chmdvfhfma ddifsvnitd qsgnysqecg sfllaesikp
121  appfnvtvtf sgqyniswrs dyedpafyml kgklqyelqy rnrgdpwavs prrklisvds
181  rsvsllplef rkdssyelqv ragpmpgssy qgtwsewsdp vifqtqseel kegwnphlll
241  llllvivfip afwslkthpl wrlwkkiwav psperffmpl ykgcsgdfkk wvgapftgss
301  lelgpwspev pstlevysch pprspakrlq ltelqepael vesdgvpkps fwptaqnsgg
361  sayseerdrp yglvsidtvt vldaegpctw pcsceddgyp aldldaglep spgledplld
421  agttvlscgc vsagspglgg plgslldrlk ppladgedwa gglpwggrsp ggvseseags
481  plagldmdtf dsgfvgsdcs spvecdftsp gdegpprsyl rqwvvipppl sspgpqas
```

FIGURE 1B

Murine IL-21 receptor
GenBank Accession Number Q9JHX3

```
1    mprgpvaall llilhgawsc ldltcytdyl wtitcvletr spnpsilslt wqdeyeelqd
61   qetfcslhrs ghntthiwyt chmrlsqfls devfivnvtd qsgnnsqecg sfvlaesikp
121  applnvtvaf sgrydiswds aydepsnyvl rgklqyelqy rnlrdpyavr pvtklisvds
181  rnvsllpeef hkdssyqlqv raapqpgtsf rgtwsewsdp vifqtqagep eagwdphmll
241  llavliivlv fmglkihlpw rlwkkiwapv ptpesffqpl yrehsgnfkk wvntpftass
301  ielvpqsstt tsalhlslyp akekkfpglp gleeqlecdg msepghwcii plaagqavsa
361  yseerdrpyg lvsidtvtvg daeglcvwpc sceddgypam nldagresgp nsedlllvtd
421  paflscgcvs gsglrlggsp gslldrlrls fakegdwtad ptwrtgspgg gseseagspp
481  gldmdtfdsg fagsdcgspv etdegpprsy lrqwvvrtpp pvdsgaqss
```

FIGURE 2

10C2
QVQLVESGGGVVQPGRSLRLSCAASGFTFS**SYGMH**WVRQAPGKGLEWVA**VIWYDGSNKYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDRAVYYCAR**EGWDRYYGLD**
VWGQGTTVTVSS

8B9
QVQLQESGPGLVKPSETLSLTCTVSGGSIN**SYYWS**WIRQSAGKGLEWIG**RIYTSGSTSYNPSLKS**RVTMSVDTSKNQFSLKLRSVTAADTAVYYCAR**ESYWYFDL**WGR
GTLVIVSS

8B9.13
QVQLQESGPGLVKPSETLSLTCTVSGGSIN**SYYWS**WIRQSAGKGLEWIG**RIYTSGSTSYNPSLKS**RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR**ESYWYFDL**WGR
GTLVIVSS

29G8
QVQLVESGGGVVQPGRSLRLSCAASGFTFS**SYGMH**WVRQAPGKGLEWVA**VIWYDGSNKYYVDSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**DRGYYDSGSY**
YMDYWGQGSLVTVSS

31C5
QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQPAGKGLEWLG**RSYSSGSTYYNPSLKS**RVTMSIDTSKNQFSLKLSSVTAADTAVYYCAR**GREIFDI**WGQG
TMVTVSS

29G2
QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQPAGKGLEWIG**RIYTSGSTYFNPSLKS**RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR**GRELLDY**WGQG
TLVTVSS

31E7
QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQTAGKGLEWLG**RIYTSGSTNYNPSLKR**RVTMSVDTSRNQFSLKLSSVTAADTAVYYCAR**GREILDY**WGQG
TLVTVSS

34H7
EVQLVQSGAELKKPGESLKISCKGSGYRFT**SYWIG**WVRQMPGKGLEWMG**IIYPGDSDTRYSPSFQG**QVTISADKSISTAYLQWHSLKVSDTAMYYCAS**PGYSTRWYHF**
DYWGQGTLVTVSS

30G3
QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQPAGKGLEWIG**RIYTSGSTYFNPSLKS**RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR**GRELLDY**WGQG
TLVTVSS

37G3
QVQLVQSGAEVKKPGASVKVSCKASGYTFT**GYYLH**WVRQAPGQGLEWMG**WLNPNRGGTNSAQKFQG**RVTMARDTSISTAYMELSGLKSDDTAVYYCAR**RGYGDPLDY**W
GQGTLVTVSS

FIGURE 3A

10C2_VH
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTC
TCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCT
CCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTAT
GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGAGAGCCGAGGACAGGGCTGTGTATTACTGTGCGAGAGAGGGG
TGGGACCGGTACTACGGTCTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

8B9_VH
CAAGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAATAGTTACTACTGGAGCTGGATCCGGCAGTCC
GCCGGGAAGGGACTGGAGTGGATTGGGCGTATCTATACCAGTGGGAGCACCAGCTACAAC
CCCTCCCTCAAGAGTCGCGTCACCATGTCAGTAGACACGTCCAAGAACCAGTTCTCCCTG
AAGCTGCGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGAATCCTAC
TGGTATTTCGATCTCTGGGGCCGTGGCACCCTAGTCATTGTCTCCTCA

8B9.13_VH
CAAGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTT
CGGAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAATAGT
TACTACTGGAGCTGGATCCGGCAGTCCGCCGGGAAGGGACTGGAGTGGAT
TGGGCGTATCTATACCAGTGGGAGCACCAGCTACAACCCCTCCCTCAAGA
GTCGCGTCACCATGTCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAG
CTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGA
ATCCTACTGGTATTTCGATCTCTGGGGCCGTGGCACCCTAGTCATTGTCT
CCTCA

29G8_VH
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTC
TCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCT
CCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTAT
GTAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAATAGCCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGATCGG
GGATACTATGATTCGGGGAGTTATTATATGGACTACTGGGGCCAGGGATCCCTGGTCACC
GTCTCCTCA

31C5_VH
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGCCC
GCCGGGAAGGGACTGGAGTGGCTTGGGCGTTCCTATAGTAGTGGGAGCACCTACTACAAC
CCCTCCCTCAAGAGTCGAGTCACCATGTCAATAGACACGTCCAAGAACCAGTTCTCCCTG
AAGCTGAGTTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGGAAGGGAG
ATTTTCGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

FIGURE 3B

29G2_VH
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGCCC
GCCGGGAAGGGACTGGAGTGGATTGGGCGTATCTATACCAGTGGGAGCACCTACTTCAAC
CCCTCCCTCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGAACCAGTTCTCCCTG
AAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGGGAGGGAG
TTACTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

31E7_VH
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGACC
GCCGGGAAGGGACTGGAGTGGCTTGGGCGTATCTATACCAGTGGGAGCACCAACTACAAC
CCCTCCCTCAAGCGTCGAGTCACCATGTCAGTAGACACGTCCAGGAACCAGTTCTCCCTG
AAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTATTGTGCGAGAGGGCGCGAA
ATTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

34H7_VH
GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGCTGAAAAAGCCCGGGGAGTCTCTGAAGATC
TCCTGTAAGGGTTCTGGATACAGGTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATG
CCCGGGAAAGGCCTGGAGTGGATGGGTATCATCTATCCTGGTGACTCTGATACCAGATAC
AGCCCGTCCTTCCAAGGCCAAGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTAC
CTGCAGTGGCACAGCCTGAAGGTCTCGGACACCGCCATGTACTACTGTGCGAGCCCCGGG
TATAGCACTAGGTGGTACCATTTTGACTACTGGGGCCAGGGAACCCTAGTCACCGTCTCC
TCA

30G3_VH
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTGGATCCGGCAGCCC
GCCGGGAAGGGACTGGAGTGGATTGGGCGTATCTATACCAGTGGGAGCACCTACTTCAAC
CCCTCCCTCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGAACCAGTTCTCCCTG
AAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGGGAGGGAG
TTACTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

37G3_VH
CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATTTGCACTGGGTGCGACAGGCC
CCTGGACAGGGGCTTGAGTGGATGGGATGGCTCAACCCTAACAGAGGTGGCACAAACTCT
GCCCAGAAGTTTCAGGGCAGGGTCACCATGGCCAGGGACACGTCCATCAGCACAGCCTAC
ATGGAGCTGAGCGGGCTGAAATCTGACGACACGGCCGTGTATTACTGTGCGAGACGGGGG
TACGGTGACCCCCTTGATTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

FIGURE 4

10C2
SYELTQPPSVSVSPGQTARITC**SGDALPKKYAY**WYQQKSGQAPVLVIY**EDSKRPS**GIPERFSGSSSGTMATLTISGAQMEDEADYYC**YSKDSSGNHRV**FGGGTKLTVLG

8B9
EIVLTQSPGTLSLSPGERATLSC**RASQSFSSNYLA**WYQQRPGQAPRLLIS**DVSSRAA**GIPDRFSGSGSGADFTLTISRLEPEDFAVYYC**QQYSRSPRT**FGQGTKVEIKR

8B9.13
EIVLTQSPGTLSLSPGERATLSC**RASQSFSSNYLA**WYQQRPGQAPRLLIY**DVSSRAA**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYSRSPRT**FGQGTKVEIKR

29G8
DIQMTQSPSSVSASVGDRVTITC**RASQGISTWLA**WYQQKPGKAPKLLIY**AASILQR**GVPSRFSGSGSGTDFTLTISSLQPEDFTTYYC**QQANSFPRT**FGQGTKVEIKR

31C5
EIVLTQSPGTLSLSPGERATLSC**RASQSFSSTYLA**WYQLKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFVVFYC**QQYSRSPLT**FGGGTKVEIRR

29G2
EIVLTQSPGTLSLSPGERVTLSC**RASQSFSSSYLA**WYQQKPGQAPRLLIF**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGRSPLT**FGGGTKVEIKR

31E7
EIVLTQSPGTLSLSPGERATLSC**RASQSMSSSYLA**WYQQKPGQAPRLLIY**GVSSRAT**GIPDRFSGSGSGADFTLTISRLEPEDFAVYYC**QQYGRSPLT**FGGGTQVEIKR

34H7
EIVMTQSPATLSVSPGERATLSC**RASQSISSSLV**WYQQKPGQAPRLLIY**GASTRAT**GIPARFSGSGSGTEFSLTISSLQSEDFAVYYC**QQYNNWPLLT**FGPGTKVDIKR

30G3
EVVLTQSPGTLSLSPGERATLSC**RASQSFSSSYLA**WYQQKPGQAPRLLIF**GASSRAT**GIPDRFSGSGSGTDFTLTINRLEPEDFALYYC**QQYGRSPLT**FGGGTKVEIKR

37G3
QSVLTQPPSVSAAPGQKVTISC**SGSSSNIGNNFVS**WYQQLPGTAPKLLIY**DNNKRPS**GIPDRFSGSKSGTSATLAITGLLTGDEADYYC**GSWDSSLRAVV**FGGGTKLTV
LG

FIGURE 5A

10C2_VL

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAAACGGCCAGGATC
ACCTGCTCTGGAGATGCATTGCCAAAAAAATATGCTTATTGGTACCAGCAGAAGTCAGGC
CAGGCCCCTGTGCTGGTCATCTATGAGGACAGCAAACGACCCTCCGGGATCCCTGAGAGA
TTCTCTGGCTCCAGTTCAGGGACAATGGCCACCCTGACTATCAGTGGGGCCCAGATGGAG
GATGAAGCTGACTACTACTGTTACTCAAAAGACAGCAGTGGTAATCATAGGGTGTTCGGC
GGAGGGACCAAGCTGACCGTCCTAGGT

8B9_VL

GAGATTGTGTTGACACAGTCTCCAGGCACCCTGTCTCTCTCCCCAGGGGAAAGAGCCACC
CTCTCCTGCAGGGCCAGTCAGAGTTTTAGCAGCAACTACTTAGCCTGGTACCAGCAGAGA
CCTGGCCAGGCTCCCAGGCTCCTCATCTCTGATGTATCCAGCAGGGCCGCTGGCATCCCC
GACAGGTTCAGTGGCAGTGGGTCTGGGGCAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATAGTAGGTCACCTCGGACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAACGT

8B9.13_VL

GAGATTGTGTTGACACAGTCTCCAGGCACCCTGTCTCTCT
CCCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTTTTAGC
AGCAACTACTTAGCCTGGTACCAGCAGAGACCTGGCCAGGCTCCCAGGCT
CCTCATCTATGATGTATCCAGCAGGGCCGCTGGCATCCCCGACAGGTTCA
GTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATAGTAGGTCACCTCG
GACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGT

29G8_VL

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGTCGGGCGAGTCAGGGTATTAGCACCTGGTTAGCCTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAACTCCTGATCTATGCTGCTTCCATTTTGCAAAGAGGGGTCCCATCA
AGGTTCAGCGGCAGTGGATCTGGAACAGATTTCACTCTCACCATCAGCAGCCTACAGCCT
GAAGATTTTACAACTTACTATTGTCAACAGGCTAACAGTTTCCCGCGGACGTTCGGCCAA
GGGACCAAGGTGGAAATCAAACGA

31C5_VL

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
CTCTCGTGCAGGGCCAGTCAGAGTTTTAGCAGCACCTACTTAGCCTGGTACCAGCTGAAA
CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA
GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGTAGTGTTTTACTGTCAGCAGTATAGTAGGTCACCTCTCACTTTCGGC
GGAGGGACCAAGGTGGAGATCAGACGA

FIGURE 5B

29G2_VL

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGTCACC
CTCTCCTGCAGGGCCAGTCAGAGTTTTAGCAGCAGCTATTTAGCCTGGTACCAGCAGAAA
CCTGGCCAGGCTCCCAGACTCCTCATCTTTGGTGCATCCAGCAGGGCCACTGGCATCCCA
GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAATATGGTAGGTCACCGCTCACTTTCGGC
GGAGGGACCAAGGTGGAGATCAAACGA

31E7_VL

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGTAGGGCCAGTCAGAGTATGAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAA
CCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGTTTCCAGCAGGGCCACTGGCATCCCA
GACAGGTTCAGTGGCAGTGGGTCTGGGGCAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTCGCTCACCTCTCACTTTCGGC
GGAGGGACCCAGGTGGAGATCAAGCGA

34H7_VL

GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGCAGGGCCAGTCAGAGTATTAGTAGCAGCTTGGTCTGGTACCAGCAGAAACCT
GGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCACCAGGGCCACTGGTATCCCAGCC
AGGTTCAGTGGCAGTGGGTCTGGGACAGAATTCAGTCTCACCATCAGCAGCCTGCAGTCT
GAAGATTTTGCAGTTTATTACTGTCAGCAGTATAATAACTGGCCTCTACTCACTTTCGGC
CCTGGGACCAAAGTGGATATCAAA

30G3_VL

GAAGTTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGCAGGGCCAGTCAGAGTTTTAGCAGCAGCTATTTAGCCTGGTACCAGCAGAAA
CCTGGCCAGGCTCCCAGACTCCTCATCTTTGGTGCATCCAGCAGGGCCACTGGCATCCCA
GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAACAGACTGGAG
CCTGAAGATTTTGCATTGTATTACTGTCAGCAATATGGTAGGTCACCGCTCACTTTCGGC
GGAGGGACCAAGGTGGAGATCAAACGA

37G3_VL

CAGTCTGTATTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCACCATC
TCCTGCTCTGGAAGCAGCTCCAACATTGGGAATAATTTTGTATCCTGGTACCAGCAGCTC
CCAGGAACAGCCCCCAAACTCCTCATTTATGACAATAATAAGCGACCCTCAGGGATTCCT
GACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGCCATCACCGGACTCCTG
ACTGGGGACGAGGCCGATTATTACTGCGGATCATGGGATAGCAGCCTGAGAGCTGTGGTT
TTCGGCGGAGGGACCAAGCTGACCGTCCTAGGT

FIGURE 6

	CDR1	CDR2	CDR3
37G3_HC	G-----YYLH	WLNPN---RGGTNSAQKFQG	RGYG---------------------DPLDY
29G8_HC	S-----YGMH	VIWYD---GSNKYYVDSVKG	DRGYYD----------------SGSYYMDY
10C2_HC	S-----YGMH	VIWYD---GSNKYYADSVKG	EGWDR-------------------YYGLDV
8B9_HC	S-----YYWS	RIYT----SGSTSYNPSLKS	ESY----------------------WYFDL
31C5_HC	S-----YYWS	RSYS----SGSTYYNPSLKS	GRE-----------------------IFDI
29G2_HC	S-----YYWS	RIYT----SGSTYFNPSLKS	GRE-----------------------LLDY
31E7_HC	S-----YYWS	RIYT----SGSTNYNPSLKR	GRE-----------------------ILDY
30G3_HC	S-----YYWS	RIYT----SGSTYFNPSLKS	GRE-----------------------LLDY
34H7_HC	S-----YWIG	IIYPG---DSDTRYSPSFQG	PGYST------------------RWYHFDY
8B9.13_HC	S-----YYWS	RIYT----SGSTSYNPSLKS	ESY----------------------WYFDL

	CDR1	CDR2	CDR3
37G3_LC	SGSS-SNIGN-----NFVS	D--------NNKRPS	GSWDSS------------------LRAVV
29G8_LC	RAS--QGIS------TWLA	A--------ASILQR	QQANS--------------------FPRT
10C2_LC	SGD---ALPK-----KYAY	E--------DSKRPS	YSKDSS------------------GNHRV
8B9_LC	RAS--QSFSS-----NYLA	D--------VSSRAA	QQYSR--------------------SPRT
31C5_LC	RAS--QSFSS-----TYLA	G--------ASSRAT	QQYSR--------------------SPLT
29G2_LC	RAS--QSFSS-----SYLA	G--------ASSRAT	QQYGR--------------------SPLT
31E7_LC	RAS--QSMSS-----SYLA	G--------VSSRAT	QQYGR--------------------SPLT
30G3_LC	RAS--QSFSS-----SYLA	G--------ASSRAT	QQYGR--------------------SPLT
34H7_LC	RAS--QSIS------SSLV	G--------ASTRAT	QQYNNW-------------------PLLT
8B9.13_LC	RAS--QSFSS-----NYLA	D--------VSSRAA	QQYSR--------------------SPRT

FIGURE 7

>Protein_Constant_HC
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK

>DNA_Constant_HC
GCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACA
CCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGC
ACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTG
TGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACA
CCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTC
AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCG
TGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
GCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC
CCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGC
CGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

>Protein_Constant_Lambda Light Chain
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTP
EQWKSHRSYSCQVTHEGSTVEKTVAPTECS

>DNA_Constant_Lambda Light Chain
CAGCCCAAGGCGGCGCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAG
GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCC
GTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGC
CTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAG
ACAGTGGCCCCTACAGAATGTTCA

>Protein_Constant_Kappa Light Chain
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>DNA_Constant_Kappa Light Chain
ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACT
GCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC
CAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG
ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCC
GTCACAAAGAGCTTCAACAGGGGAGAGTGT

FIGURE 8A

10C2_HC
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK

8B9_HC
QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYN
PSLKSRVTMSVDTSKNQFSLKLRSVTAADTAVYYCARESYWYFDLWGRGTLVIVSSASTK
GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSV
LTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSC
SVMHEALHNHYTQKSLSLSPGK

8B9.13_HC
QVQLQESGPGLVKPSETLSLTCTVSGGSINS
YYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLK
LSSVTAADTAVYYCARESYWYFDLWGRGTLVIVSSASTKGPSVFPLAPCS
RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVA
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI
SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK

29G8_HC
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYY
VDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYYDSGSYYMDYWGQGSLVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNS
TFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK

31C5_HC
QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWLGRSYSSGSTYYN
PSLKSRVTMSIDTSKNQFSLKLSSVTAADTAVYYCARGREIFDIWGQGTMVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVL
TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK

FIGURE 8B

29G2_HC
QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWIGRIYTSGSTYFN
PSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARGRELLDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVL
TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK

31E7_HC
QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQTAGKGLEWLGRIYTSGSTNYN
PSLKRRVTMSVDTSRNQFSLKLSSVTAADTAVYYCARGREILDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVL
TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK

34H7_HC
EVQLVQSGAELKKPGESLKISCKGSGYRFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY
SPSFQGQVTISADKSISTAYLQWHSLKVSDTAMYYCASPGYSTRWYHFDYWGQGTLVTVS
SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF
RVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK

30G3_HC
QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWIGRIYTSGSTYFN
PSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARGRELLDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVL
TVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK

37G3_HC
QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYLHWVRQAPGQGLEWMGWLNPNRGGTNS
AQKFQGRVTMARDTSISTAYMELSGLKSDDTAVYYCARRGYGDPLDYWGQGTLVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVV
SVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGK

FIGURE 9A

10C2_LC
SYELTQPPSVSVSPGQTARITCSGDALPKKYAYWYQQKSGQAPVLVIYEDSKRPSGIPER
FSGSSSGTMATLTISGAQMEDEADYYCYSKDSSGNHRVFGGGTKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYL
SLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

8B9_LC
EIVLTQSPGTLSLSPGERATLSCRASQSFSSNYLAWYQQRPGQAPRLLISDVSSRAAGIP
DRFSGSGSGADFTLTISRLEPEDFAVYYCQQYSRSPRTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

8B9.13_LC
EIVLTQSPGTLSLSPGERATLSCRASQSFS
SNYLAWYQQRPGQAPRLLIYDVSSRAAGIPDRFSGSGSGTDFTLTISRLE
PEDFAVYYCQQYSRSPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

29G8_LC
DIQMTQSPSSVSASVGDRVTITCRASQGISTWLAWYQQKPGKAPKLLIYAASILQRGVPS
RFSGSGSGTDFTLTISSLQPEDFTTYYCQQANSFPRTFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

31C5_LC
EIVLTQSPGTLSLSPGERATLSCRASQSFSSTYLAWYQLKPGQAPRLLIYGASSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFVVFYCQQYSRSPLTFGGGTKVEIRRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

29G2_LC
EIVLTQSPGTLSLSPGERVTLSCRASQSFSSSYLAWYQQKPGQAPRLLIFGASSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGRSPLTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

31E7_LC
EIVLTQSPGTLSLSPGERATLSCRASQSMSSSYLAWYQQKPGQAPRLLIYGVSSRATGIP
DRFSGSGSGADFTLTISRLEPEDFAVYYCQQYGRSPLTFGGGTQVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

34H7_LC
EIVMTQSPATLSVSPGERATLSCRASQSISSSLVWYQQKPGQAPRLLIYGASTRATGIPA
RFSGSGSGTEFSLTISSLQSEDFAVYYCQQYNNWSTHFGPGTKVDIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 9B

30G3_LC
EVVLTQSPGTLSLSPGERATLSCRASQSFSSSYLAWYQQKPGQAPRLLIFGASSRATGIP
DRFSGSGSGTDFTLTINRLEPEDFALYYCQQYGRSPLTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

37G3_LC
QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLLIYDNNKRPSGIP
DRFSGSKSGTSATLAITGLLTGDEADYYCGSWDSSLRAVVFGGGTKLTVLGQPKAAPSVT
LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASS
YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 10A

10C2_HC
MELGLCWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGS
NKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSSASTKGPSVFPL
APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD
HKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK*

8B9_HC
MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGS
TSYNPSLKSRVTMSVDTSKNQFSLKLRSVTAADTAVYYCARESYWYFDLWGRGTLVIVSSASTKGPSVFPLAPCS
RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPS
NTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK*

8B9.13_HC
MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGS
TSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYWYFDLWGRGTLVIVSSASTKGPSVFPLAPCS
RSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPS
NTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK

29G8_HC
MELGLSWVFLVALLRGVQCQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGS
NKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYYDSGSYYMDYWGQGSLVTVSSASTKGPSV
FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC
NVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV
DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK

31C5_HC
MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWLGRSYSSGS
TYYNPSLKSRVTMSIDTSKNQFSLKLSSVTAADTAVYYCARGREIFDIWGQGTMVTVSSASTKGPSVFPLAPCSR
STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSN
TKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK

FIGURE 10B

31E7_HC
MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQTAGKGLEWLGRIYTSGS
TNYNPSLKRRVTMSVDTSRNQFSLKLSSVTAADTAVYYCARGREILDYWGQGTLVTVSSASTKGPSVFPLAPCSR
STSSTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNT
KVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

34H7_HC
MGSTAILALLLAVLQGVCAEVQLVQSGAELKKPGESLKISCKGSGYRFTSYWIGWVRQMPGKGLEWMGIIYPGDS
DTRYSPSFQGQVTISADKSISTAYLQWHSLKVSDTAMYYCASPGYSTRWYHFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV
DHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

30G3_HC
MKHLWFFLLLVAAPRWVLSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWIGRIYTSGS
TYFNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARGRELLDYWGQGTLVTVSSASTKGPSVFPLAPCSR
STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSN
TKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK

37G3_HC
MDWTWRILFLVAAATGAHSQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYLHWVRQAPGQGLEWMGWLNPNRG
GTNSAQKFQGRVTMARDTSISTAYMELSGLKSDDTAVYYCARRGYGDPLDYWGQGTLVTVSSASTKGPSVFPLAP
CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHK
PSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK

FIGURE 11A

10C2_LC
MAWALLLLTLLTQDTGSWASYELTQPPSVSVSPGQTARITCSGDALPKKYAYWYQQKSGQAPVLVIYEDS
KRPSGIPERFSGSSSGTMATLTISGAQMEDEADYYCYSKDSSGNHRVFGGGTKLTVLGQPKAAPSVTLFP
PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR
SYSCQVTHEGSTVEKTVAPTECS

8B9_LC
METPAQLLFLLLLWLPDTTGEIVLTQSPGTLSLSPGERATLSCRASQSFSSNYLAWYQQRPGQAPRLLIS
DVSSRAAGIPDRFSGSGSGADFTLTISRLEPEDFAVYYCQQYSRSPRTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

8B9.13_LC
METPAQLLFLLLLWLPDTTGEIVLTQSPGTLSLSPGERATLSCRASQSFSSNYLAWYQQRPGQAPRLLIY
DVSSRAAGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSRSPRTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

29G8_LC
MDMRVPAQLLGLLLLWFPGSRCDIQMTQSPSSVSASVGDRVTITCRASQGISTWLAWYQQKPGKAPKLLI
YAASILQRGVPSRFSGSGSGTDFTLTISSLQPEDFTTYYCQQANSFPRTFGQGTKVEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
HKVYACEVTHQGLSSPVTKSFNRGEC

31C5_LC
MEAPAQLLFLLLLWLPDTTGEIVLTQSPGTLSLSPGERATLSCRASQSFSSTYLAWYQLKPGQAPRLLIY
GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFVVFYCQQYSRSPLTFGGGTKVEIRRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

29G2_LC
MEAPAQLLFLLLLWLPDTTGEIVLTQSPGTLSLSPGERVTLSCRASQSFSSSYLAWYQQKPGQAPRLLIF
GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGRSPLTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

31E7_LC
MEAPAQLLFLLLLWLPDTTGEIVLTQSPGTLSLSPGERATLSCRASQSMSSSYLAWYQQKPGQAPRLLIY
GVSSRATGIPDRFSGSGSGADFTLTISRLEPEDFAVYYCQQYGRSPLTFGGGTQVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

34H7_LC
MEAPAQLLFLLLLWLPDTTGEIVMTQSPATLSVSPGERATLSCRASQSISSSLVWYQQKPGQAPRLLIYG
ASTRATGIPARFSGSGSGTEFSLTISSLQSEDFAVYYCQQYNNWPLLTFGPGTKVDIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 11B

30G3_LC
MEAPAQLLFLLLLWLPDTTGEVVLTQSPGTLSLSPGERATLSCRASQSFSSSYLAWYQQKPGQAPRLLIF
GASSRATGIPDRFSGSGSGTDFTLTINRLEPEDFALYYCQQYGRSPLTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC

37G3_LC
MDMRVPAQLLGLLLLWLRGARCQSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLL
IYDNNKRPSGIPDRFSGSKSGTSATLAITGLLTGDEADYYCGSWDSSLRAVVFGGGTKLTVLGGQPKAAP
SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPE
QWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 12A

10C2 Group Heavy Chain Variable Domains

10C2

QVQLVESGGGVVQPGRSLRLSCAASGFTFS**SYGMH**WVRQAPGKGLEWVA**VIWYDGSNKYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDRAVYYCAR**EGWDRYYGLDV**WGQGTTVTVSS

C54703

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS

C54704

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYEGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS

C54706

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYAESVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS

C54707

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIHWVRQAPGKGLEWVAVIWYEGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS

C54708

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIHWVRQAPGKGLEWVAVIWYDGSNKYYAESVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS

C54709

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYEGSNKYYAESVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS

C54710

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGIHWVRQAPGKGLEWVAVIWYEGSNKYYAESVKGRFTISRDNSKNTLYLQMNSLRAEDRAVYYCAREGWDRYYGLDVWGQGTTVTVSS

8B9 Group Heavy Chain Variable Domains

8B9

QVQLQESGPGLVKPSETLSLTCTVSGGSIN**SYYWS**WIRQSAGKGLEWIG**RIYTSGSTSYNPSLKS**RVTMSVDTSKNQFSLKLRSVTAADTAVYYCAR**ESYWYFDL**WGRGTLVIVSS

8B9.13

QVQLQESGPGLVKPSETLSLTCTVSGGSIN**SYYWS**WIRQSAGKGLEWIG**RIYTSGSTSYNPSLKS**RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR**ESYWYFDL**WGRGTLVIVSS

FIGURE 12B

C53005

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYWYFDLWGRGTLVTVSS

C53007

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLRSVTAADTAVYYCARESYWYFDLWGRGTLVTVSS

C53008

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLRSVTAADTAVYYCARESYWYFDLWGQGTLVIVSS

C53010

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLRSVTAADTAVYYCARESYWYFDLWGRGTLVIVSS

C53011

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLRSVTAADTAVYYCARESYWYFDLWGRGTLVIVSS

C53012

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLRSVTAADTAVYYCARESYWYFDLWGRGTLVIVSS

C53004

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYWYFDLWGRGTLVTVSS

C53003

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYWYFDLWGQGTLVTVSS

C53002

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYWYFDLWGRGTLVTVSS

C53001

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYWYFDLWGQGTLVTVSS

C54423

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYAYFDLWGRGTLVIVSS

FIGURE 12C

C54424

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYAYFDLWGRGTLVTVSS

C54425

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYAYFDLWGQGTLVTVSS

C54426

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYGYFDLWGRGTLVIVSS

C54427

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYGYFDLWGRGTLVTVSS

C54428

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYGYFDLWGQGTLVTVSS

C54429

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYFYFDLWGRGTLVIVSS

C54430

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYFYFDLWGRGTLVTVSS

C54431

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQPPGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYFYFDLWGQGTLVTVSS

C59144

QVQLQESGPGLVKPSETLSLTCTVSGGSINSYYWSWIRQSAGKGLEWIGRIYTSGSTSYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVYYCARESYWYFDLWGQGTLVIVSS

29G8 Group Heavy Chain Variable Domains

29G8

QVQLVESGGGVVQPGRSLRLSCAASGFTFS**SYGMH**WVRQAPGKGLEWVA**VIWYDGSNKYYVDSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**DRGYYDSGSYYMDY**WGQGSLVTVSS

C62625

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYEGSNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYYDSGSYYMDYWGQGSLVTVSS

FIGURE 12D

C62626

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYYESGSYYMDYWGQGSLVTVSS

31C5 Group Heavy Chain Variable Domains

31C5

QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQPAGKGLEWLG**RSYSSGSTYYNPSLKS**RVTMSIDTSKNQFSLKLSSVTAADTAVYYCAR**GREIFDI**WGQGTMVTVSS

C62627

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWLGRSYSSGSTYYNTSLKSRVTMSIDTSKNQFSLKLSSVTAADTAVYYCARGREIFDIWGQGTMVTVSS

29G2 Group Heavy Chain Variable Domain

29G2

QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQPAGKGLEWIG**RIYTSGSTYFNPSLKS**RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR**GRELLDY**WGQGTLVTVSS

31E7 Group Heavy Chain Variable Domains

31E7

QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQTAGKGLEWLG**RIYTSGSTNYNPSLKR**RVTMSVDTSRNQFSLKLSSVTAADTAVYYCAR**GREILDY**WGQGTLVTVSS

C62628

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWLGRIYTSGSTNYNPSLKRRVTMSVDTSRNQFSLKLSSVTAADTAVYYCARGREILDYWGQGTLVTVSS

C62629

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWLGRIYTSGSTNYNPSLKRRVTMSVDTSRNQFSLKLSSVTAADTAVYYCARGREILDYWGQGTLVTVSS

34H7 Group Heavy Chain Variable Domains

34H7

EVQLVQSGAELKKPGESLKISCKGSGYRFT**SYWIG**WVRQMPGKGLEWMG**IIYPGDSDTRYSPSFQG**QVTISADKSISTAYLQWHSLKVSDTAMYYCAS**PGYSTRWYHFDY**WGQGTLVTVSS

C62630

EVHLVQSGAELKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWHSLKVSDTAMYYCASPGYSTRWYHFDYWGQGTLVTVSS

FIGURE 12E

C62631

EVHLVQSGAELKKPGESLKISCKGSGYRFTSYWIGWVRQMPGKGLEWMGIIYPGDSETRYSPSFQGQVTISADKSISTAYLQWHSLKVSDTAMYYCASPGYSTRWYHFDYWGQGTLVTVSS

C62632

EVHLVQSGAELKKPGESLKISCKGSGYRFTSYWIGWVRQMPGKGLEWMGIIYPGESDTRYSPSFQGQVTISADKSISTAYLQWHSLKVSDTAMYYCASPGYSTRWYHFDYWGQGTLVTVSS

C62633

EVHLVQSGAELKKPGESLKISCKGSGYRFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKVSDTAMYYCASPGYSTRWYHFDYWGQGTLVTVSS

C62634

EVQLVQSGAELKKPGESLKISCKGSGYRFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKVSDTAMYYCARPGYSTRWYHFDYWGQGTLVTVSS

C60585

EVHLVQSGAELKKPGESLKISCKGSGYRFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWHSLKVSDTAMYYCASPGYSTRWYHFDYWGQGTLVTVSS

30G3 Group Heavy Chain Variable Domain

30G3

QVQLQESGPGLVKPSETLSLTCTVSGGSIS**SYYWS**WIRQPAGKGLEWIG**RIYTSGSTYFNPSLKS**RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAR**GRELLDY**WGQGTLVTVSS

37G3 Group Heavy Chain Variable Domains

37G3

QVQLVQSGAEVKKPGASVKVSCKASGYTFT**GYYLH**WVRQAPGQGLEWMG**WLNPNRGGTNSAQKFQG**RVTMARDTSISTAYMELSGLKSDDTAVYYCAR**RGYGDPLDY**WGQGTLVTVSS

C62635

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYLHWVRQAPGQGLEWMGWLNPNRGGTQSAQKFQGRVTMARDTSISTAYMELSGLKSDDTAVYYCARRGYGDPLDYWGQGTLVTVSS

C62636

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYLHWVRQAPGQGLEWMGWLNPNRGGTNSAQKFQGRVTMARDTSISTAYMELSGLKSDDTAVYYCARRGYGEPLDYWGQGTLVTVSS

FIGURE 13A

10C2 Group Light Chain Variable Domain

10C2

SYELTQPPSVSVSPGQTARITC**SGDALPKKYAY**WYQQKSGQAPVLVIY**EDSKRPS**GIPERFSGSSSGTMATLTISGAQMEDEADYYC**YSKDSSGNHRV**FGGGTKLTVLG

8B9 Group Light Chain Variable Domains

8B9

EIVLTQSPGTLSLSPGERATLSC**RASQSFSSNYLA**WYQQRPGQAPRLLIS**DVSSRAA**GIPDRFSGSGSGADFTLTISRLEPEDFAVYYC**QQYSRSPRT**FGQGTKVEIKR

8B9.13

EIVLTQSPGTLSLSPGERATLSC**RASQSFSSNYLA**WYQQRPGQAPRLLIY**DVSSRAA**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYSRSPRT**FGQGTKVEIKR

C52999

EIVLTQSPGTLSLSPGERATLSCRASQSFSSNYLAWYQQRPGQAPRLLISDVSSRAAGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSRSPRTFGQGTKVEIKR

C53000

EIVLTQSPGTLSLSPGERATLSCRASQSFSSNYLAWYQQRPGQAPRLLIYDVSSRAAGIPDRFSGSGSGADFTLTISRLEPEDFAVYYCQQYSRSPRTFGQGTKVEIKR

C59142

EIVLTQSPGTLSLSPGERATLSCRASQSFSSNYLAWYQQRPGQAPRLLIYAVSSRAAGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSRSPRTFGQGTKVEIKR

C59143

EIVLTQSPGTLSLSPGERATLSCRASQSFSSNYLAWYQQRPGQAPRLLIYGVSSRAAGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSRSPRTFGQGTKVEIKR

FIGURE 13B

29G8 Group Light Chain Variable Domains

29G8

DIQMTQSPSSVSASVGDRVTITC**RASQGISTWLA**WYQQKPGKAPKLLIY**AASILQR**GVPSRFSGSGSGTDFTLTISSLQPEDFTTYYC**QQANSFPRT**FGQGTKVEIKR

C62651

DIQMTQSPSSVSASVGDRVTITCRASQGISTWLAWYQQKPGKAPKLLIYAASILQRGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVEIKR

31C5 Group Light Chain Variable Domain

31C5

EIVLTQSPGTLSLSPGERATLSC**RASQSFSSTYLA**WYQLKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFVVFYC**QQYSRSPLT**FGGGTKVEIRR

29G2 Group Light Chain Variable Domain

29G2

EIVLTQSPGTLSLSPGERVTLSC**RASQSFSSSYLA**WYQQKPGQAPRLLIF**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGRSPLT**FGGGTKVEIKR

31E7 Group Light Chain Variable Domains

31E7

EIVLTQSPGTLSLSPGERATLSC**RASQSMSSSYLA**WYQQKPGQAPRLLIY**GVSSRAT**GIPDRFSGSGSGADFTLTISRLEPEDFAVYYC**QQYGRSPLT**FGGGTQVEIKR

C62653

EIVLTQSPGTLSLSPGERATLSCRASQSMSSSYLAWYQQKPGQAPRLLIYGVSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGRSPLTFGGGTKVEIKR

C62654

EIVLTQSPGTLSLSPGERATLSCRASQSMSSSYLAWYQQKPGQAPRLLIYGVSSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGRSPLTFGQGTKVEIKR

FIGURE 13C

34H7 Group Light Chain Variable Domains

34H7

EIVMTQSPATLSVSPGERATLSC**RASQSISSSLV**WYQQKPGQAPRLLIY**GASTRAT**GIPARFSGSGSGTEFSLTISSLQSEDFAVYYC**QQYNNWPLLT**FGPGTKVDIKR

C62655

EIVMTQSPATLSVSPGERATLSCRASQSISSSLVWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFSLTISSLQSEDFAVYYCQQYNNWPLLTFGQGTKVDIKR

C62656

EIVMTQSPATLSVSPGERATLSCRASQSISSSLVWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFSLTISSLEPEDFAVYYCQQYNNWPLLTFGQGTKVDIKR

30G3 Group Light Chain Variable Domains

30G3

EVVLTQSPGTLSLSPGERATLSC**RASQSFSSSYLA**WYQQKPGQAPRLLIF**GASSRAT**GIPDRFSGSGSGTDFTLTINRLEPEDFALYYC**QQYGRSPLT**FGGGTKVEIKR

C62652

EVVLTQSPGTLSLSPGERATLSCRASQSFSSSYLAWYQQKPGQAPRLLIFGASSRATGIPDRFSGSGSGTDFTLTINRLEPEDFALYYCQQYGRSPLTFGQGTKVEIKR

37G3 Group Light Chain Variable Domains

37G3

QSVLTQPPSVSAAPGQKVTISC**SGSSSNIGNNFVS**WYQQLPGTAPKLLIY**DNNKRPS**GIPDRFSGSKSGTSATLAITGLLTGDEADYYC**GSWDSSLRAVV**FGGGTKLTV
LG

C62657

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLAITGLLTGDEADYYCGSWESSLRAVVFGGGTKLTV
LG

SEQUENCE LISTING

<110> Amgen Inc.

<120> METHODS AND COMPOSITIONS RELATING TO ANTI-IL-21 RECEPTOR
       ANTIBODIES

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<140>
<141> 2013-10-14

<150> US 13/830,844
<151> 2013-03-14

<150> US 61/715,156
<151> 2012-10-17

<160> 184

<170> PatentIn version 3.5

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 1

Asp Tyr Lys Asp Asp Asp Asp Lys
1   5

<210> 2
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 2

Cys Pro Ser Cys Pro
1   5

<210> 3
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 3

Cys Pro Pro Cys Pro
1   5

<210> 4
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic 6xHis tag

<400> 4

His His His His His His
1   5

<210> 5
<211> 538
<212> PRT
<213> Homo sapiens

<400> 5

Met Pro Arg Gly Trp Ala Ala Pro Leu Leu Leu Leu Leu Leu Gln Gly
1   5   10   15

Gly Trp Gly Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr
            20   25   30

Val Ile Cys Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr
        35   40   45

Leu Thr Trp Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser
    50   55   60

Cys Ser Leu His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr
65   70   75   80

Cys His Met Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val
                85   90   95

Asn Ile Thr Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe
            100   105   110

Leu Leu Ala Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val
        115   120   125

Thr Phe Ser Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp
    130   135   140

Pro Ala Phe Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr
145   150   155   160

Arg Asn Arg Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile
                165   170   175

Ser Val Asp Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys
            180   185   190

Asp Ser Ser Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser
        195   200   205

```
Ser Tyr Gln Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln
    210                 215                 220

Thr Gln Ser Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu
225                 230                 235                 240

Leu Leu Leu Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys
                245                 250                 255

Thr His Pro Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser
            260                 265                 270

Pro Glu Arg Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe
        275                 280                 285

Lys Lys Trp Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly
    290                 295                 300

Pro Trp Ser Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His
305                 310                 315                 320

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

Pro Ala Glu Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp
            340                 345                 350

Pro Thr Ala Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp
        355                 360                 365

Arg Pro Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala
    370                 375                 380

Glu Gly Pro Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro
385                 390                 395                 400

Ala Leu Asp Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp
                405                 410                 415

Pro Leu Leu Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser
            420                 425                 430

Ala Gly Ser Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg
        435                 440                 445

Leu Lys Pro Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro
    450                 455                 460

Trp Gly Gly Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser
465                 470                 475                 480
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Pro Leu Ala Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly
                485                 490                 495


Ser Asp Cys Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp
            500                 505                 510


Glu Gly Pro Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro
        515                 520                 525


Pro Leu Ser Ser Pro Gly Pro Gln Ala Ser
    530                 535


<210>  6
<211>  529
<212>  PRT
<213>  Mus musculus

<400>  6

Met Pro Arg Gly Pro Val Ala Ala Leu Leu Leu Leu Ile Leu His Gly
1               5                   10                  15


Ala Trp Ser Cys Leu Asp Leu Thr Cys Tyr Thr Asp Tyr Leu Trp Thr
            20                  25                  30


Ile Thr Cys Val Leu Glu Thr Arg Ser Pro Asn Pro Ser Ile Leu Ser
        35                  40                  45


Leu Thr Trp Gln Asp Glu Tyr Glu Glu Leu Gln Asp Gln Glu Thr Phe
    50                  55                  60


Cys Ser Leu His Arg Ser Gly His Asn Thr Thr His Ile Trp Tyr Thr
65                  70                  75                  80


Cys His Met Arg Leu Ser Gln Phe Leu Ser Asp Glu Val Phe Ile Val
                85                  90                  95


Asn Val Thr Asp Gln Ser Gly Asn Asn Ser Gln Glu Cys Gly Ser Phe
            100                 105                 110


Val Leu Ala Glu Ser Ile Lys Pro Ala Pro Pro Leu Asn Val Thr Val
        115                 120                 125


Ala Phe Ser Gly Arg Tyr Asp Ile Ser Trp Asp Ser Ala Tyr Asp Glu
    130                 135                 140


Pro Ser Asn Tyr Val Leu Arg Gly Lys Leu Gln Tyr Glu Leu Gln Tyr
145                 150                 155                 160


Arg Asn Leu Arg Asp Pro Tyr Ala Val Arg Pro Val Thr Lys Leu Ile
                165                 170                 175
```

```
Ser Val Asp Ser Arg Asn Val Ser Leu Leu Pro Glu Glu Phe His Lys
            180                 185                 190

Asp Ser Ser Tyr Gln Leu Gln Val Arg Ala Ala Pro Gln Pro Gly Thr
        195                 200                 205

Ser Phe Arg Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln
    210                 215                 220

Thr Gln Ala Gly Glu Pro Glu Ala Gly Trp Asp Pro His Met Leu Leu
225                 230                 235                 240

Leu Leu Ala Val Leu Ile Ile Val Leu Val Phe Met Gly Leu Lys Ile
                245                 250                 255

His Leu Pro Trp Arg Leu Trp Lys Lys Ile Trp Ala Pro Val Pro Thr
            260                 265                 270

Pro Glu Ser Phe Phe Gln Pro Leu Tyr Arg Glu His Ser Gly Asn Phe
        275                 280                 285

Lys Lys Trp Val Asn Thr Pro Phe Thr Ala Ser Ser Ile Glu Leu Val
    290                 295                 300

Pro Gln Ser Ser Thr Thr Thr Ser Ala Leu His Leu Ser Leu Tyr Pro
305                 310                 315                 320

Ala Lys Glu Lys Lys Phe Pro Gly Leu Pro Gly Leu Glu Glu Gln Leu
                325                 330                 335

Glu Cys Asp Gly Met Ser Glu Pro Gly His Trp Cys Ile Ile Pro Leu
            340                 345                 350

Ala Ala Gly Gln Ala Val Ser Ala Tyr Ser Glu Glu Arg Asp Arg Pro
        355                 360                 365

Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Gly Asp Ala Glu Gly
    370                 375                 380

Leu Cys Val Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro Ala Met
385                 390                 395                 400

Asn Leu Asp Ala Gly Arg Glu Ser Gly Pro Asn Ser Glu Asp Leu Leu
                405                 410                 415

Leu Val Thr Asp Pro Ala Phe Leu Ser Cys Gly Cys Val Ser Gly Ser
            420                 425                 430

Gly Leu Arg Leu Gly Gly Ser Pro Gly Ser Leu Leu Asp Arg Leu Arg
        435                 440                 445
```

Leu Ser Phe Ala Lys Glu Gly Asp Trp Thr Ala Asp Pro Thr Trp Arg
    450   455   460

Thr Gly Ser Pro Gly Gly Gly Ser Glu Ser Glu Ala Gly Ser Pro Pro
465   470   475   480

Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Ala Gly Ser Asp Cys
                485   490   495

Gly Ser Pro Val Glu Thr Asp Glu Gly Pro Pro Arg Ser Tyr Leu Arg
            500   505   510

Gln Trp Val Val Arg Thr Pro Pro Pro Val Asp Ser Gly Ala Gln Ser
        515   520   525

Ser

<210> 7
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 7

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 8
<211> 116

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 8

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

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

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

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

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

Ile Val Ser Ser
        115
```

<210> 9
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 9

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

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

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

```
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


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


Ile Val Ser Ser
        115


<210>  10
<211>  123
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  10

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


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


Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60


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


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


Ala Arg Asp Arg Gly Tyr Tyr Asp Ser Gly Ser Tyr Tyr Met Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser
        115                 120


<210>  11
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  11

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

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


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


Gly Arg Ser Tyr Ser Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60


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


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


Arg Gly Arg Glu Ile Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  12
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  12

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


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


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


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


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


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


Arg Gly Arg Glu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110
```

Val Ser Ser
        115

<210> 13
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 13

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

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

Tyr Trp Ser Trp Ile Arg Gln Thr Ala Gly Lys Gly Leu Glu Trp Leu
        35   40   45

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

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

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

Arg Gly Arg Glu Ile Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 14
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 14

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
            20   25   30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

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

Leu Gln Trp His Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 15
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 15

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

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

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

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

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

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

Arg Gly Arg Glu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 16
<211> 118
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 16

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

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

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

Gly Trp Leu Asn Pro Asn Arg Gly Gly Thr Asn Ser Ala Gln Lys Phe
    50                  55                  60

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

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

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

Leu Val Thr Val Ser Ser
        115
```

<210> 17
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 17

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caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc       60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct      120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat      180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240

ctgcaaatga acagcctgag agccgaggac agggctgtgt attactgtgc gagagagggg      300

tgggaccggt actacggtct ggacgtctgg ggccaaggga ccacggtcac cgtctcctca      360
```

<210> 18
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 18

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caagtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc       60
```

acctgcactg tctctggtgg ctccatcaat agttactact ggagctggat ccggcagtcc 120

gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac cagctacaac 180

ccctccctca agagtcgcgt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

aagctgcgct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agaatcctac 300

tggtatttcg atctctgggg ccgtggcacc ctagtcattg tctcctca 348

<210> 19
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 19
caagtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcaat agttactact ggagctggat ccggcagtcc 120

gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac cagctacaac 180

ccctccctca agagtcgcgt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agaatcctac 300

tggtatttcg atctctgggg ccgtggcacc ctagtcattg tctcctca 348

<210> 20
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 20
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga atagcctgag agccgaagac acggctgtgt attactgtgc gagagatcgg 300

ggatactatg attcggggag ttattatatg gactactggg gccagggatc cctggtcacc 360

gtctcctca 369

<210> 21
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 21
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

gccgggaagg gactggagtg gcttgggcgt tcctatagta gtgggagcac ctactacaac 180

ccctccctca agagtcgagt caccatgtca atagacacgt ccaagaacca gttctccctg 240

aagctgagtt ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag aggaagggag 300

attttcgata tctggggcca agggacaatg gtcaccgtct cttca 345

<210> 22
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 22
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac ctacttcaac 180

ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agggagggag 300

ttactggact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 23
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 23
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagacc 120

gccgggaagg gactggagtg gcttgggcgt atctatacca gtgggagcac caactacaac 180

ccctccctca agcgtcgagt caccatgtca gtagacacgt ccaggaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt attgtgcgag agggcgcgaa 300

attctggact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 24
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 24
gaggtgcagc tggtgcagtc tggagcagag ctgaaaaagc ccggggagtc tctgaagatc 60

tcctgtaagg gttctggata caggtttacc agctactgga tcggctgggt gcgccagatg 120 cccgggaaag gcctggagtg gatgggtatc atctatcctg gtgactctga taccagatac 180

agcccgtcct tccaaggcca agtcaccatc tcagccgaca agtccatcag caccgcctac 240

ctgcagtggc acagcctgaa ggtctcggac accgccatgt actactgtgc gagccccggg 300

tatagcacta ggtggtacca ttttgactac tggggccagg gaaccctagt caccgtctcc 360

tca 363

<210> 25
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 25
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac ctacttcaac 180

ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agggagggag 300

ttactggact actggggcca gggaaccctg gtcaccgtct cctca 345

<210> 26
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 26
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc ggctactatt tgcactgggt gcgacaggcc 120

cctggacagg ggcttgagtg gatgggatgg ctcaacccta acagaggtgg cacaaactct 180

gcccagaagt ttcagggcag ggtcaccatg gccagggaca cgtccatcag cacagcctac 240

atggagctga gcgggctgaa atctgacgac acggccgtgt attactgtgc gagacggggg 300

tacggtgacc cccttgatta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 27
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 27

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

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala
            20   25   30

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

Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Met Glu
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Lys Asp Ser Ser Gly Asn His
                85   90   95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100   105

<210> 28
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 28

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Ser Asp Val Ser Ser Arg Ala Ala Gly Ile Pro Asp Arg Phe Ser
    50   55   60

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

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

<210> 29
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

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

<210> 30
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 30

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

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

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

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

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

Glu Asp Phe Thr Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Arg
                85   90   95

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

<210> 31
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 31

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Thr
            20   25   30

Tyr Leu Ala Trp Tyr Gln Leu Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

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

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

Pro Glu Asp Phe Val Val Phe Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Arg Arg
            100   105

<210> 32
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 32

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

Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Phe Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60

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


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


Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100                 105


<210>  33
<211>  109
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  33

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


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Met Ser Ser Ser
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


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


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


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


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


<210>  34
<211>  109
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  34

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


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
            20                  25                  30
```

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

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
                85   90   95

Leu Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
            100   105

<210> 35
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 35

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Phe Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60

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

Pro Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Pro
                85   90   95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 36
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 36

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

Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20   25   30

Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35   40   45

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

Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Ala Ile Thr Gly Leu Leu
65   70   75   80

Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ser Ser Leu
                85   90   95

Arg Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100   105   110

<210> 37
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 37
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc   60

acctgctctg gagatgcatt gccaaaaaaa tatgcttatt ggtaccagca gaagtcaggc   120

caggcccctg tgctggtcat ctatgaggac agcaaacgac cctccgggat ccctgagaga   180

ttctctggct ccagttcagg gacaatggcc accctgacta tcagtggggc ccagatggag   240

gatgaagctg actactactg ttactcaaaa gacagcagtg gtaatcatag ggtgttcggc   300

ggagggacca agctgaccgt cctaggt   327

<210> 38
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 38
gagattgtgt tgacacagtc tccaggcacc ctgtctctct ccccagggga aagagccacc   60

ctctcctgca gggccagtca gagttttagc agcaactact tagcctggta ccagcagaga   120

cctggccagg ctcccaggct cctcatctct gatgtatcca gcagggccgc tggcatcccc   180

gacaggttca gtggcagtgg gtctggggca gacttcactc tcaccatcag cagactggag   240

cctgaagatt ttgcagtgta ttactgtcag cagtatagta ggtcacctcg gacgttcggc   300 caagggacca aggtggaaat caaacgt 327

<210> 39
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 39
gagattgtgt tgacacagtc tccaggcacc ctgtctctct ccccagggga aagagccacc 60

ctctcctgca gggccagtca gagttttagc agcaactact tagcctggta ccagcagaga 120

cctggccagg ctcccaggct cctcatctat gatgtatcca gcagggccgc tggcatcccc 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag cagtatagta ggtcacctcg gacgttcggc 300

caagggacca aggtggaaat caaacgt 327

<210> 40
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 40
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc acctggttag cctggtatca gcagaaacca 120

gggaaagccc ctaaactcct gatctatgct gcttccattt tgcaaagagg ggtcccatca 180

aggttcagcg gcagtggatc tggaacagat ttcactctca ccatcagcag cctacagcct 240

gaagatttta caacttacta ttgtcaacag gctaacagtt tcccgcggac gttcggccaa 300

gggaccaagg tggaaatcaa acga 324

<210> 41
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 41
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

ctctcgtgca gggccagtca gagttttagc agcacctact tagcctggta ccagctgaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgtagtgtt ttactgtcag cagtatagta ggtcacctct cactttcggc 300

ggagggacca aggtggagat cagacga 327

<210> 42
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 42
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagtcacc   60

ctctcctgca gggccagtca gagttttagc agcagctatt tagcctggta ccagcagaaa   120

cctggccagg ctcccagact cctcatcttt ggtgcatcca gcagggccac tggcatccca   180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag   240

cctgaagatt ttgcagtgta ttactgtcag caatatggta ggtcaccgct cactttcggc   300

ggagggacca aggtggagat caaacga   327

<210> 43
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 43
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc   60

ctctcctgta gggccagtca gagtatgagc agcagctact tagcctggta ccagcagaaa   120

cctggccagg ctcccaggct cctcatctat ggtgtttcca gcagggccac tggcatccca   180

gacaggttca gtggcagtgg gtctggggca gacttcactc tcaccatcag cagactggag   240

cctgaagatt ttgcagtgta ttactgtcag cagtatggtc gctcacctct cactttcggc   300

ggagggaccc aggtggagat caagcga   327

<210> 44
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 44
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc   60

ctctcctgca gggccagtca gagtattagt agcagcttgg tctggtacca gcagaaacct   120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc   180

aggttcagtg gcagtgggtc tgggacagaa ttcagtctca ccatcagcag cctgcagtct   240

gaagattttg cagtttatta ctgtcagcag tataataact ggcctctact cactttcggc   300

cctgggacca aagtggatat caaa   324

<210> 45
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 45
gaagttgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc   60

ctctcctgca gggccagtca gagttttagc agcagctatt tagcctggta ccagcagaaa   120

cctggccagg ctcccagact cctcatcttt ggtgcatcca gcagggccac tggcatccca   180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcaa cagactggag   240

cctgaagatt ttgcattgta ttactgtcag caatatggta ggtcaccgct cactttcggc   300

ggagggacca aggtggagat caaacga   327

<210> 46
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 46
cagtctgtat tgacgcagcc gccctcagtg tctgcggccc caggacagaa ggtcaccatc   60

tcctgctctg gaagcagctc caacattggg aataattttg tatcctggta ccagcagctc   120

ccaggaacag cccccaaact cctcatttat gacaataata agcgaccctc agggattcct   180

gaccgattct ctggctccaa gtctggcacg tcagccaccc tggccatcac cggactcctg   240

actggggacg aggccgatta ttactgcgga tcatgggata gcagcctgag agctgtggtt   300

ttcggcggag ggaccaagct gaccgtccta ggt   333

<210> 47
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 47

Gly Tyr Tyr Leu His
1   5

<210> 48
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 48

Ser Tyr Gly Met His
1   5

<210> 49
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 49

Ser Tyr Tyr Trp Ser
1   5

<210> 50
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 50

Ser Tyr Trp Ile Gly
1   5

<210> 51
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 51

Trp Leu Asn Pro Asn Arg Gly Gly Thr Asn Ser Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 52
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 52

Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val Lys
1   5   10   15

Gly

<210> 53
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 53

Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 54
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 54

Arg Ile Tyr Thr Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu Lys Ser
1   5   10   15

<210> 55
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 55

Arg Ser Tyr Ser Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1   5   10   15

<210> 56
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 56

Arg Ile Tyr Thr Ser Gly Ser Thr Tyr Phe Asn Pro Ser Leu Lys Ser
1   5   10   15

<210> 57
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 57

Arg Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Arg
1   5   10   15

<210> 58
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 58

Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1   5   10   15

Gly

<210> 59
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 59

Arg Gly Tyr Gly Asp Pro Leu Asp Tyr
1   5

<210> 60
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 60

Asp Arg Gly Tyr Tyr Asp Ser Gly Ser Tyr Tyr Met Asp Tyr
1   5   10

<210> 61
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 61

Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val
1   5   10

<210> 62
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 62

Glu Ser Tyr Trp Tyr Phe Asp Leu
1   5

<210> 63
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 63

Gly Arg Glu Ile Phe Asp Ile
1   5

<210> 64
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 64

Gly Arg Glu Leu Leu Asp Tyr
1   5

<210> 65
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 65

Gly Arg Glu Ile Leu Asp Tyr
1   5

<210> 66
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 66

Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr
1   5   10

<210> 67
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 67

Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Phe Val Ser
1   5   10

<210> 68
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 68

Arg Ala Ser Gln Gly Ile Ser Thr Trp Leu Ala
1   5   10

<210> 69
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 69

Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala Tyr
1   5   10

<210> 70
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 70

Arg Ala Ser Gln Ser Phe Ser Ser Asn Tyr Leu Ala
1   5   10

<210> 71
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 71

Arg Ala Ser Gln Ser Phe Ser Ser Thr Tyr Leu Ala
1   5   10

<210> 72
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 72

Arg Ala Ser Gln Ser Phe Ser Ser Ser Tyr Leu Ala
1   5   10

<210> 73
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 73

Arg Ala Ser Gln Ser Met Ser Ser Ser Tyr Leu Ala
1   5   10

<210> 74
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 74

Arg Ala Ser Gln Ser Ile Ser Ser Ser Leu Val
1   5   10

<210> 75
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 75

Asp Asn Asn Lys Arg Pro Ser
1   5

<210> 76
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 76

Ala Ala Ser Ile Leu Gln Arg
1   5

<210> 77
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 77

Glu Asp Ser Lys Arg Pro Ser
1   5

<210> 78
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 78

Asp Val Ser Ser Arg Ala Ala
1   5

<210> 79
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 79

Gly Ala Ser Ser Arg Ala Thr
1   5

<210> 80
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 80

Gly Val Ser Ser Arg Ala Thr
1   5

<210> 81
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 81

Gly Ala Ser Thr Arg Ala Thr
1   5

<210> 82
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 82

Gly Ser Trp Asp Ser Ser Leu Arg Ala Val Val
1   5   10

<210> 83
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 83

Gln Gln Ala Asn Ser Phe Pro Arg Thr
1   5

<210> 84
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 84

Tyr Ser Lys Asp Ser Ser Gly Asn His Arg Val
1   5   10

<210> 85
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 85

Gln Gln Tyr Ser Arg Ser Pro Arg Thr
1   5

<210> 86
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 86

Gln Gln Tyr Ser Arg Ser Pro Leu Thr
1   5

<210> 87
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 87

Gln Gln Tyr Gly Arg Ser Pro Leu Thr
1   5

<210> 88
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 88

Gln Gln Tyr Asn Asn Trp Pro Leu Leu Thr
1   5   10

<210> 89
<211> 326
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 89

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Leu Ser Pro Gly Lys
                325


<210>  90
<211>  978
<212>  DNA
<213>  Artificial Sequence

<220>
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<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 90
gctagcacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag   60

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg   120

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca   180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc   240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc   300

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc   360

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc   420

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc   480

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt   540

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc   600

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg   660

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac   720

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg   780

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac   840

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   900

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   960

tccctgtctc cgggtaaa   978

<210> 91
<211> 105
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 91

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

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
            20   25   30

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
        35   40   45

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
    50   55   60

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
65   70   75   80

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
                85   90   95

Lys Thr Val Ala Pro Thr Glu Cys Ser
            100   105

<210> 92
<211> 315
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 92
cagcccaagg cggcgccctc ggtcactctg ttcccgccct cctctgagga gcttcaagcc   60

aacaaggcca cactggtgtg tctcataagt gacttctacc cgggagccgt gacagtggcc   120

tggaaggcag atagcagccc cgtcaaggcg ggagtggaga ccaccacacc ctccaaacaa   180

agcaacaaca agtacgcggc cagcagctat ctgagcctga cgcctgagca gtggaagtcc   240

cacagaagct acagctgcca ggtcacgcat gaagggagca ccgtggagaa gacagtggcc   300

cctacagaat gttca   315

<210> 93
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 93

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

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

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

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

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

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

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

<210> 94
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 94
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga   60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg   120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc   180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa   240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc   300

ttcaacaggg gagagtgt   318

<210> 95
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 95

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
            100   105   110

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

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

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

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

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

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

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

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

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

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

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

Lys Thr 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 Met 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> 96
<211> 442
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 96

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

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

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

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

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

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

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

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
    210   215   220

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

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

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
            260   265   270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275   280   285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
    290   295   300

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

Lys Gly Leu Pro Ala 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 Ala 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> 97
<211> 442
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 97

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

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

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

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

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

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

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

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
    210   215   220

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

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

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
            260   265   270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275   280   285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
    290   295   300

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

Lys Gly Leu Pro Ala 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 Ala 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> 98
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 98

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

```
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60

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

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

Ala Arg Asp Arg Gly Tyr Tyr Asp Ser Gly Ser Tyr Tyr Met Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

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

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

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

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

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

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

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
225                 230                 235                 240

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

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

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

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

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

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

Thr Ile Ser Lys Thr 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 Met 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> 99
<211> 441
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 99

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

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

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

Gly Arg Ser Tyr Ser Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
    50   55   60

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

```
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Gly Arg Glu Ile Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
            100                 105                 110

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

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

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

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

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

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

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225                 230                 235                 240

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

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
            260                 265                 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        275                 280                 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
    290                 295                 300

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

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

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

```
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
        355                 360                 365

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

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

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

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

Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440


<210>  100
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  100

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

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

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

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

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

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

Arg Gly Arg Glu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

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

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140
```

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

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

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

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

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225                 230                 235                 240

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

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
            260                 265                 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        275                 280                 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
    290                 295                 300

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

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

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

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
        355                 360                 365

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

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

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

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

Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435   440

<210> 101
<211> 441
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 101

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

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

Tyr Trp Ser Trp Ile Arg Gln Thr Ala Gly Lys Gly Leu Glu Trp Leu
        35   40   45

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

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

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

Arg Gly Arg Glu Ile Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

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

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

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

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

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

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

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225                 230                 235                 240

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

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
            260                 265                 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        275                 280                 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
    290                 295                 300

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

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

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

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
        355                 360                 365

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

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

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

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

Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440

<210>  102
<211>  447
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 102

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
            20                  25                  30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60

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

Leu Gln Trp His Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100                 105                 110

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

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

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

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

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

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

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

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
225                 230                 235                 240

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

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

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

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

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

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

Ser Lys Thr 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 Met Leu Asp Ser
385 390 395 400

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> 103
<211> 441
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 103

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

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

```
Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

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

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

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

Arg Gly Arg Glu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

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

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

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

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

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

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

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225                 230                 235                 240

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

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
            260                 265                 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        275                 280                 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
    290                 295                 300
```

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

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

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

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

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

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

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

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

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 104
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 104

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

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

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

Gly Trp Leu Asn Pro Asn Arg Gly Gly Thr Asn Ser Ala Gln Lys Phe
50 55 60

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

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

```
Ala Arg Arg Gly Tyr Gly Asp Pro 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 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 Ala 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>  105
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  105

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

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala
            20                  25                  30

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

Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Met Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Lys Asp Ser Ser Gly Asn His
                85                  90                  95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140
```

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145   150   155   160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165   170   175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180   185   190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195   200   205

Ala Pro Thr Glu Cys Ser
    210

<210> 106
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 106

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Ser Asp Val Ser Ser Arg Ala Ala Gly Ile Pro Asp Arg Phe Ser
    50   55   60

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

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

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

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

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

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

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180   185   190

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

Ser Phe Asn Arg Gly Glu Cys
    210   215

<210> 107
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 107

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

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

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

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

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

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

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180   185   190

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

Ser Phe Asn Arg Gly Glu Cys
    210   215

<210> 108
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 108

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

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

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

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

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

Glu Asp Phe Thr Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Arg
                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

<210> 109
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 109

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Thr
            20   25   30

Tyr Leu Ala Trp Tyr Gln Leu Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

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

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

Pro Glu Asp Phe Val Val Phe Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

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

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

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

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

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

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

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

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 110
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 110

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

Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Phe Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

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

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

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

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

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

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

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

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

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


Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  111
<211>  215
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  111

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


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Met Ser Ser Ser
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


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


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


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


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


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


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


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


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


Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190
```

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

Ser Phe Asn Arg Gly Glu Cys
    210   215

<210> 112
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 112

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
            20   25   30

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

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Ser Thr
                85   90   95

His Phe Gly Pro Gly Thr Lys Val Asp 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

<210> 113
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 113

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Phe Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

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

Pro Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Pro
                85                  90                  95

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

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

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

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

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

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

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

Ser Phe Asn Arg Gly Glu Cys
    210   215

<210> 114
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 114

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

Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20   25   30

Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35   40   45

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

Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Ala Ile Thr Gly Leu Leu
65   70   75   80

Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ser Ser Leu
                85   90   95

Arg Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100   105   110

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

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130   135   140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145   150   155   160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165   170   175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180   185   190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195   200   205

Thr Val Ala Pro Thr Glu Cys Ser
    210   215

<210> 115
<211> 465
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 115

```
Met Glu Leu Gly Leu Cys Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Arg Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val
        115                 120                 125

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
    210                 215                 220
```

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225   230   235   240

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245   250   255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260   265   270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275   280   285

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290   295   300

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305   310   315   320

Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
                325   330   335

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
            340   345   350

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355   360   365

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370   375   380

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385   390   395   400

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                405   410   415

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            420   425   430

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435   440   445

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450   455   460

Lys
465

<210> 116
<211> 461
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 116

```
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1               5                   10                  15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35                  40                  45

Asn Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu
    50                  55                  60

Glu Trp Ile Gly Arg Ile Tyr Thr Ser Gly Ser Thr Ser Tyr Asn Pro
65                  70                  75                  80

Ser Leu Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln
                85                  90                  95

Phe Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Ala Arg Glu Ser Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly
        115                 120                 125

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

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145                 150                 155                 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
                165                 170                 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            180                 185                 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        195                 200                 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
    210                 215                 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
                245                 250                 255
```

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            260   265   270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
        275   280   285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    290   295   300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305   310   315   320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                325   330   335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340   345   350

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        355   360   365

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    370   375   380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385   390   395   400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
                405   410   415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            420   425   430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        435   440   445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450   455   460

<210> 117
<211> 461
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 117

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1   5   10   15

```
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35                  40                  45

Asn Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu
    50                  55                  60

Glu Trp Ile Gly Arg Ile Tyr Thr Ser Gly Ser Thr Ser Tyr Asn Pro
65                  70                  75                  80

Ser Leu Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln
                85                  90                  95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Ala Arg Glu Ser Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly
        115                 120                 125

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

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145                 150                 155                 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
                165                 170                 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            180                 185                 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        195                 200                 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
    210                 215                 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
                245                 250                 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            260                 265                 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
        275                 280                 285
```

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    290   295   300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305   310   315   320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                325   330   335

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340   345   350

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        355   360   365

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    370   375   380

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385   390   395   400

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
                405   410   415

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            420   425   430

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        435   440   445

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450   455   460

<210> 118
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 118

Met Glu Leu Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1   5   10   15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20   25   30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35   40   45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50   55   60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Val
65   70   75   80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85   90   95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100   105   110

Tyr Tyr Cys Ala Arg Asp Arg Gly Tyr Tyr Asp Ser Gly Ser Tyr Tyr
        115   120   125

Met Asp Tyr Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala Ser
    130   135   140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145   150   155   160

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

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180   185   190

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

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
    210   215   220

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
225   230   235   240

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
                245   250   255

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260   265   270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275   280   285

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    290   295   300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305   310   315   320

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                325   330   335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
340 345 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
355 360 365

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
370 375 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385 390 395 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
405 410 415

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
420 425 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
435 440 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
450 455 460

Ser Pro Gly Lys
465

<210> 119
<211> 460
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 119

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
35 40 45

Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu
50 55 60

Glu Trp Leu Gly Arg Ser Tyr Ser Ser Gly Ser Thr Tyr Tyr Asn Pro
65 70 75 80

```
Ser Leu Lys Ser Arg Val Thr Met Ser Ile Asp Thr Ser Lys Asn Gln
                85                  90                  95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Ala Arg Gly Arg Glu Ile Phe Asp Ile Trp Gly Gln Gly Thr
        115                 120                 125

Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
    130                 135                 140

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
145                 150                 155                 160

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
                165                 170                 175

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
            180                 185                 190

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
        195                 200                 205

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
    210                 215                 220

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
225                 230                 235                 240

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
                245                 250                 255

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
            260                 265                 270

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
        275                 280                 285

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
    290                 295                 300

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
305                 310                 315                 320

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
                325                 330                 335

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
            340                 345                 350
```

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
        355   360   365

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
    370   375   380

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385   390   395   400

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
                405   410   415

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
            420   425   430

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
        435   440   445

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450   455   460

<210> 120
<211> 459
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 120

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1   5   10   15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20   25   30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35   40   45

Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Thr Ala Gly Lys Gly Leu
    50   55   60

Glu Trp Leu Gly Arg Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro
65   70   75   80

Ser Leu Lys Arg Arg Val Thr Met Ser Val Asp Thr Ser Arg Asn Gln
                85   90   95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100   105   110

Tyr Cys Ala Arg Gly Arg Glu Ile Leu Asp Tyr Trp Gly Gln Gly Thr
        115   120   125

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Ser Thr Ala Ala Leu Gly Cys
145                 150                 155                 160

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
                165                 170                 175

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
            180                 185                 190

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn
        195                 200                 205

Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
    210                 215                 220

Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
225                 230                 235                 240

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
                245                 250                 255

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
            260                 265                 270

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
        275                 280                 285

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
    290                 295                 300

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
305                 310                 315                 320

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
                325                 330                 335

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
            340                 345                 350

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
        355                 360                 365

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
    370                 375                 380

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385                 390                 395                 400
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Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
                405                 410                 415


Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
            420                 425                 430


Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
        435                 440                 445


Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455


<210>  121
<211>  466
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  121

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


Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Leu Lys Lys
            20                  25                  30


Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe
        35                  40                  45


Thr Ser Tyr Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser
65                  70                  75                  80


Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser
                85                  90                  95


Thr Ala Tyr Leu Gln Trp His Ser Leu Lys Val Ser Asp Thr Ala Met
            100                 105                 110


Tyr Tyr Cys Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp
        115                 120                 125


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


Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160
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Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

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

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430
```

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435   440   445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450   455   460

Gly Lys
465

<210> 122
<211> 460
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 122

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1   5   10   15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20   25   30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35   40   45

Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu
    50   55   60

Glu Trp Ile Gly Arg Ile Tyr Thr Ser Gly Ser Thr Tyr Phe Asn Pro
65   70   75   80

Ser Leu Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln
                85   90   95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100   105   110

Tyr Cys Ala Arg Gly Arg Glu Leu Leu Asp Tyr Trp Gly Gln Gly Thr
        115   120   125

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
145   150   155   160

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
                165   170   175

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
            180   185   190

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
        195   200   205

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
    210   215   220

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
225   230   235   240

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
                245   250   255

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
            260   265   270

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
        275   280   285

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
    290   295   300

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
305   310   315   320

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
                325   330   335

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
            340   345   350

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
        355   360   365

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
    370   375   380

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385   390   395   400

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
                405   410   415

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
            420   425   430

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
        435   440   445

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450   455   460

<210> 123
<211> 463
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 123

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Gly Tyr Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Leu Asn Pro Asn Arg Gly Gly Thr Asn Ser Ala
65                  70                  75                  80


Gln Lys Phe Gln Gly Arg Val Thr Met Ala Arg Asp Thr Ser Ile Ser
                85                  90                  95


Thr Ala Tyr Met Glu Leu Ser Gly Leu Lys Ser Asp Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Arg Gly Tyr Gly Asp Pro Leu Asp Tyr Trp Gly
        115                 120                 125


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


Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
145                 150                 155                 160


Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175


Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190


Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205


Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
    210                 215                 220
```

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
225   230   235   240

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                245   250   255

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260   265   270

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        275   280   285

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290   295   300

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
305   310   315   320

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                325   330   335

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            340   345   350

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        355   360   365

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    370   375   380

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385   390   395   400

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                405   410   415

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            420   425   430

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        435   440   445

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450   455   460

<210> 124
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 124

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Asp Thr Gly
1   5   10   15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20   25   30

Pro Gly Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys
        35   40   45

Lys Tyr Ala Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu
    50   55   60

Val Ile Tyr Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65   70   75   80

Ser Gly Ser Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala
                85   90   95

Gln Met Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Lys Asp Ser Ser
            100   105   110

Gly Asn His Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
        115   120   125

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
    130   135   140

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145   150   155   160

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
                165   170   175

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
            180   185   190

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
        195   200   205

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
    210   215   220

Lys Thr Val Ala Pro Thr Glu Cys Ser
225   230

<210> 125
<211> 235
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 125

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1   5   10   15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20   25   30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35   40   45

Phe Ser Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala
    50   55   60

Pro Arg Leu Leu Ile Ser Asp Val Ser Ser Arg Ala Ala Gly Ile Pro
65   70   75   80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
                85   90   95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100   105   110

Ser Arg Ser Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115   120   125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130   135   140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145   150   155   160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165   170   175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180   185   190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195   200   205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210   215   220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225   230   235

<210> 126
<211> 235
<212> PRT
<213> Artificial Sequence

```
<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  126

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15


Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30


Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45


Phe Ser Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala
    50                  55                  60


Pro Arg Leu Leu Ile Tyr Asp Val Ser Ser Arg Ala Ala Gly Ile Pro
65                  70                  75                  80


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95


Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100                 105                 110


Ser Arg Ser Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190


Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  127
<211>  236
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 127

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1   5   10   15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20   25   30

Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35   40   45

Gln Gly Ile Ser Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50   55   60

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ile Leu Gln Arg Gly Val
65   70   75   80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85   90   95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Thr Thr Tyr Tyr Cys Gln Gln
            100   105   110

Ala Asn Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115   120   125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130   135   140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145   150   155   160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165   170   175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180   185   190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195   200   205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210   215   220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225   230   235

<210> 128
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 128

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
20 25 30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Phe Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Leu Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Arg Leu Glu Pro Glu Asp Phe Val Val Phe Tyr Cys Gln Gln Tyr
100 105 110

Ser Arg Ser Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Arg
115 120 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 129
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 129

```
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30

Leu Ser Pro Gly Glu Arg Val Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

Phe Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100                 105                 110

Gly Arg Ser Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220
```

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 130
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 130

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
20 25 30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Met Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr Gly Val Ser Ser Arg Ala Thr Gly Ile Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
85 90 95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
100 105 110

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

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 131
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 131

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Ile Ser Ser Ser Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60

Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser
85 90 95

Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn
100 105 110

Asn Trp Pro Leu Leu Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
115 120 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210   215   220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225   230   235

<210> 132
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 132

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1   5   10   15

Asp Thr Thr Gly Glu Val Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20   25   30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35   40   45

Phe Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50   55   60

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85   90   95

Asn Arg Leu Glu Pro Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr
            100   105   110

Gly Arg Ser Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115   120   125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130   135   140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145   150   155   160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165   170   175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180   185   190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195   200   205

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Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  133
<211>  239
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  133

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Gln Ser Val Leu Thr Gln Pro Pro Ser Val
            20                  25                  30


Ser Ala Ala Pro Gly Gln Lys Val Thr Ile Ser Cys Ser Gly Ser Ser
        35                  40                  45


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


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


Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu
                85                  90                  95


Ala Ile Thr Gly Leu Leu Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly
            100                 105                 110


Ser Trp Asp Ser Ser Leu Arg Ala Val Val Phe Gly Gly Gly Thr Lys
        115                 120                 125


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


Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val
145                 150                 155                 160


Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys
                165                 170                 175


Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser
            180                 185                 190
```

Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr
        195   200   205

Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His
    210   215   220

Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225   230   235

<210> 134
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 134

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 135
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 135

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 136
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 136

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val
    50   55   60

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 137
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 137

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


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


Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 138
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 138

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


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


Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60
```

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 139
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 139

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val
50 55 60

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 140
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 140

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Glu Ser Val
    50   55   60

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

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

Ala Arg Glu Gly Trp Asp Arg Tyr Tyr Gly Leu Asp Val Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 141
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 141

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Thr Val Ser Ser
115

<210> 142
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 142

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
35 40 45

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

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

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

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

Thr Val Ser Ser
115

<210> 143
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 143

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

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

```
Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


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


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


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


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


Ile Val Ser Ser
        115


<210>  144
<211>  116
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  144

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


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


Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


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


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


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


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


Ile Val Ser Ser
        115


<210>  145
<211>  116
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<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 145

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Ile Val Ser Ser
        115

<210> 146
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 146

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

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

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

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

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

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

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

Ile Val Ser Ser
115

<210> 147
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 147

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

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

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

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

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

Thr Val Ser Ser
115

<210> 148
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 148

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

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

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

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

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

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

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

Thr Val Ser Ser
        115

<210> 149
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 149

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Thr Val Ser Ser
115

<210> 150
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 150

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

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

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

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

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

Thr Val Ser Ser
115

<210> 151
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 151

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
35 40 45

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

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

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

Arg Glu Ser Tyr Ala Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu Val
            100   105   110

Ile Val Ser Ser
        115

<210> 152
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 152

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

Arg Glu Ser Tyr Ala Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser
        115

<210> 153
<211> 116
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 153

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Thr Val Ser Ser
        115

<210> 154
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 154

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Ile Val Ser Ser
        115

<210> 155
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 155

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Thr Val Ser Ser
        115

<210> 156
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 156

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Thr Val Ser Ser
        115

<210> 157
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 157

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Ile Val Ser Ser
        115

<210> 158
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 158

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Thr Val Ser Ser
        115

<210> 159
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 159

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Thr Val Ser Ser
        115

<210> 160
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 160

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

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

Tyr Trp Ser Trp Ile Arg Gln Ser Ala Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

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

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

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

Ile Val Ser Ser
        115

<210> 161
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 161

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
    50   55   60

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

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

Ala Arg Asp Arg Gly Tyr Tyr Asp Ser Gly Ser Tyr Tyr Met Asp Tyr
            100   105   110

Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser
        115   120

<210> 162
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 162

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
    50   55   60

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

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

Ala Arg Asp Arg Gly Tyr Tyr Glu Ser Gly Ser Tyr Tyr Met Asp Tyr
            100   105   110

Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser
        115   120

<210> 163
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 163

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

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

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

Gly Arg Ser Tyr Ser Ser Gly Ser Thr Tyr Tyr Asn Thr Ser Leu Lys
    50   55   60

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

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

Arg Gly Arg Glu Ile Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
            100   105   110

Val Ser Ser
        115

<210> 164
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 164

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

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

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

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

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

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

Arg Gly Arg Glu Ile Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 165
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 165

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35   40   45

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

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

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

Arg Gly Arg Glu Ile Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 166
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 166

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

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

Leu Gln Trp His Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 167
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 167

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
            20   25   30

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

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

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

Leu Gln Trp His Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 168
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 168

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
            20   25   30

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

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

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

Leu Gln Trp His Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 169
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 169

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
            20   25   30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

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

Leu Gln Trp Ser Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 170
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 170

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
            20   25   30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

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

Leu Gln Trp Ser Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Arg Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 171
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 171

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
            20   25   30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

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

Leu Gln Trp His Ser Leu Lys Val Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Ser Pro Gly Tyr Ser Thr Arg Trp Tyr His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 172
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 172

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

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

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

Gly Trp Leu Asn Pro Asn Arg Gly Gly Thr Gln Ser Ala Gln Lys Phe
    50   55   60

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

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

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

Leu Val Thr Val Ser Ser
115

<210> 173
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 173

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

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

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

Gly Trp Leu Asn Pro Asn Arg Gly Gly Thr Asn Ser Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Arg Gly Tyr Gly Glu Pro Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 174
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 174

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Ser Asp Val Ser Ser Arg Ala Ala Gly Ile Pro Asp Arg Phe Ser
    50   55   60

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

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

<210> 175
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 175

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85   90   95

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

<210> 176
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 176

```
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


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


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


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
                85                  90                  95


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

<210> 177
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 177

```
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Asn
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


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


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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Ser Pro
85 90 95

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

<210> 178
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 178

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

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

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

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

Ser Gly 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 Ala Asn Ser Phe Pro Arg
85 90 95

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

<210> 179
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 179

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Met Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

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

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

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

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 180
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 180

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Met Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

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

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

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

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

<210> 181
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 181

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
            20   25   30

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

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
                85   90   95

Leu Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg
            100   105

<210> 182
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 182

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
            20   25   30

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

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
                85   90   95

Leu Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg
            100   105

<210> 183
<211> 109
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 183

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Phe Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

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

Pro Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Pro
                85                  90                  95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105
```

<210> 184
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 184

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

Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30

Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

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

Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Ala Ile Thr Gly Leu Leu
65                  70                  75                  80

Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Glu Ser Ser Leu
                85                  90                  95

Arg Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
```