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(54) Title: SOLUBLE HETERODIMERIC CYTOKINE RECEPTOR

(57) **Abrégé/Abstract:**

A soluble receptor that binds to IL-20 having two polypeptide subunits, IL-22R and IL-20RB. The two subunits are preferably linked together. In one embodiment one subunit is fused to the constant region of the light chain of an immunoglobulin, and the other subunit is fused to the constant region of the heavy chain of the immunoglobulin. The light chain and the heavy chain are connected via a disulfide bond.



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(54) Title: SOLUBLE HETERODIMERIC CYTOKINE RECEPTOR

(57) Abstract: A soluble receptor that binds to IL-20 having two polypeptide subunits, IL-22R and IL-20RB. The two subunits are preferably linked together. In one embodiment one subunit is fused to the constant region of the light chain of an immunoglobulin, and the other subunit is fused to the constant region of the heavy chain of the immunoglobulin. The light chain and the heavy chain are connected via a disulfide bond.



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5 SOLUBLE HETERODIMERIC CYTOKINE RECEPTOR

BACKGROUND OF THE INVENTION

The teachings of all of the references cited herein are incorporated in their entirety herein by reference.

10 Cytokines are soluble proteins that influence the growth and differentiation of many cell types. Their receptors are composed of one or more integral membrane proteins that bind the cytokine with high affinity and transduce this binding event to the cell through the cytoplasmic portions of the certain receptor subunits. Cytokine receptors have been grouped into several classes on the basis of similarities in
15 their extracellular ligand binding domains. For example, the receptor chains responsible for binding and/or transducing the effect of interferons (IFNs) are members of the type II cytokine receptor family (CRF2), based upon a characteristic 200 residue extracellular domain. The demonstrated *in vivo* activities of these interferons illustrate the enormous clinical potential of, and need for, other cytokines, cytokine agonists, and
20 cytokine antagonists. Some cytokines are involved in the inflammatory cascade and can promote such diseases as rheumatoid arthritis, Crohn's disease, psoriasis, heart disease etc. Thus, there is a need to discover cytokines and their receptors that are involved in inflammation. One can then use the isolated soluble receptors of the cytokine to inhibit the cytokine-mediated inflammation.

25

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES 1-8 are schematic representations of different embodiments of the soluble receptor of the present invention

30 DESCRIPTION OF THE INVENTION

The present invention fills this need by providing a newly discovered soluble receptor that binds to Interleukin-20 (IL-20). The soluble receptor can be used to down-regulate IL-20 and thus treat inflammatory diseases such as psoriasis and inflammatory lung diseases.

35

IL-20 was formally called 'Zcyto10', (International Patent Publication No. WO 99/27103) and has the amino acid sequences of SEQ ID NOs: 1-9. A heterodimeric receptor that binds to IL-20 is comprised of two chains, an alpha chain

and a beta chain. The alpha chain is referred to as IL-22R (formerly called Zcytor11). See U.S. Patent No. 5,965,704. The beta chain, hereinafter referred to as IL-20RB, was formally called DIRS1. See International Patent Application No. PCT/US99/03735. The present invention is a soluble receptor comprised of the extracellular domain of IL-22R and the extracellular domain of IL-20RB.

The present invention encompasses an isolated soluble receptor comprised of a 'IL-22R' subunit and an 'IL-20RB' subunit, wherein the IL-22R subunit is comprised of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 12 and 13, and the IL-20RB subunit is comprised of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14-23. The IL-22R and IL-20RB subunits are generally linked together by a polypeptide linker. The linking can be by any means but generally by a peptide bond or a disulfide bond between a polypeptide connected to the IL-22R subunit and a polypeptide connected to the IL-20RB subunit. The present invention is also directed towards isolated polynucleotides that encode the novel IL-22R and IL-20RB polypeptides of the present invention.

In one embodiment the IL-22R subunit is fused to the constant region of the heavy chain of an immunoglobulin (Ig) molecule or a portion thereof and the IL-20RB subunit is fused to the constant region of the light chain of an Ig molecule such that the constant region of the light chain is disulfide bonded to the constant region of the heavy chain, generally to a cysteine residue on the hinge region of the heavy chain. Also the opposite can occur, the IL-22R subunit can be fused to the constant region of the light chain of an Ig molecule and the IL-20RB subunit can be fused to the constant region of the heavy chain of an Ig molecule.

In one embodiment of the soluble receptor of the present invention, the IL-22R subunit fused to the constant region of the heavy chain is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 25, 26, 31 and 32 and the IL-20RB subunit fused to the constant region of the light chain of the Ig molecule is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 28 and 29.

The present invention is further directed to a method for inhibiting interleukin-20 (IL-20) comprising administering to an individual a soluble IL-22R/IL-20RB heterodimeric polypeptide.

The present invention is also directed to a method for inhibiting IL-20
5 comprising administering to an antibody that binds to IL-22R.

The present invention is further directed to a polynucleotide encoding for the extracellular domain of IL-22R and the extracellular domain of IL-20RB. An example of such a polynucleotide is a vector or plasmid containing a polynucleotide that encodes for IL-22R and IL-20RB.

10

Definitions

Prior to setting forth the invention in more detail, it may be helpful to the understanding thereof to define the following terms.

The terms “amino-terminal” and “carboxyl-terminal” are used herein to
15 denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete
20 polypeptide.

As used herein, the term “antibody fusion protein” refers to a recombinant molecule that comprises an antibody component and a therapeutic agent. Examples of therapeutic agents suitable for such fusion proteins include immunomodulators (“antibody-immunomodulator fusion protein”) and toxins
25 (“antibody-toxin fusion protein”).

The term “complement/anti-complement pair” denotes non-identical moieties that form a non-covalently associated, stable pair under appropriate conditions. For instance, biotin and avidin (or streptavidin) are prototypical members of a complement/anti-complement pair. Other exemplary complement/anti-complement
30 pairs include receptor/ligand pairs, antibody/antigen (or hapten or epitope) pairs, sense/antisense polynucleotide pairs, and the like. Where subsequent dissociation of the complement/anti-complement pair is desirable, the complement/anti-complement pair preferably has a binding affinity of $<10^9 \text{ M}^{-1}$.

The term “complements of a polynucleotide molecule” is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence.

5 The term “contig” denotes a polynucleotide that has a contiguous stretch of identical or complementary sequence to another polynucleotide. Contiguous sequences are said to “overlap” a given stretch of polynucleotide sequence either in their entirety or along a partial stretch of the polynucleotide.

10 The term “degenerate nucleotide sequence” denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons contain different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

15 The term “expression vector” is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

20 The term “isolated”, when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78 (1985)).

30 An “isolated” polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide is substantially free of other polypeptides, particularly other polypeptides of animal origin. It is preferred to provide the polypeptides in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term “isolated” does not exclude the presence of the same polypeptide in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

The term "operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, *e.g.*, transcription initiates in the promoter and proceeds through the coding segment to the terminator.

5 A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides
10 ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length
15 and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nucleotides in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10
20 amino acid residues are commonly referred to as "peptides".

The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

25 A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures;
30 substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

The term "receptor" denotes a cell-associated protein that binds to a bioactive molecule (*i.e.*, a ligand) and mediates the effect of the ligand on the cell. Membrane-bound receptors are characterized by a multi-domain structure comprising
35 an extracellular ligand-binding domain and an intracellular effector domain that is typically involved in signal transduction. Binding of ligand to receptor results in a conformational change in the receptor that causes an interaction between the effector

domain and other molecule(s) in the cell. This interaction in turn leads to an alteration in the metabolism of the cell. Metabolic events that are linked to receptor-ligand interactions include gene transcription, phosphorylation, dephosphorylation, increases in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. In general, receptors can be membrane bound, cytosolic or nuclear, monomeric (*e.g.*, thyroid stimulating hormone receptor, beta-adrenergic receptor) or multimeric (*e.g.*, PDGF receptor, growth hormone receptor, IL-3 receptor, GM-CSF receptor, G-CSF receptor, erythropoietin receptor and IL-6 receptor).

10 The term "secretory signal sequence" denotes a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

15 The term "splice variant" is used herein to denote alternative forms of RNA transcribed from a gene. Splice variation arises naturally through use of alternative splicing sites within a transcribed RNA molecule, or less commonly between separately transcribed RNA molecules, and may result in several mRNAs transcribed from the same gene. Splice variants may encode polypeptides having altered amino acid sequence. The term splice variant is also used herein to denote a protein encoded by a splice variant of an mRNA transcribed from a gene.

20 Molecular weights and lengths of polymers determined by imprecise analytical methods (*e.g.*, gel electrophoresis) will be understood to be approximate values. When such a value is expressed as "about" X or "approximately" X, the stated value of X will be understood to be accurate to $\pm 10\%$.

25 As was stated above, IL-20 (formally called Zcyto10) is defined and methods for producing it and antibodies to IL-20 are contained in International Patent Application No. PCT/US98/25228, publication no. WO 99/27103, published November 25, 1998 and U.S. Patent Application No. 09/313,458 filed May 17, 1999. The polynucleotide and polypeptide of human IL-20 are represented by SEQ ID NOs: 1 - 4, and mouse IL-20 by SEQ ID NOs: 5-9.

30 A receptor that binds to IL-20 has been discovered and is a heterodimer comprised of the polypeptide termed 'IL-22R' and a polypeptide termed 'IL-20RB'. The IL-22R, also called ZcytoR11, polypeptide, nucleic acid that encodes it, antibodies to IL-22R, and methods for producing it are disclosed in U.S. Patent No. 5,965,704 issued October 12, 1999. SEQ ID NOs: 10 - 12 are the IL-22R polynucleotides and

polypeptides. The extracellular domain of the human IL-22R is comprised of either SEQ ID NO: 12 or SEQ ID NO: 13.

The extracellular domain of IL-20RB (SEQ ID NOs: 14-15, and a variant SEQ ID NOs: 22 and 23) is comprised of a polypeptide selected from the group consisting of SEQ ID NOs: 16-21. Preferably, the extracellular domain of the IL-22R polypeptide and the extracellular domain of the IL-20RB polypeptide are covalently linked together. In a preferred embodiment one extracellular subunit polypeptide has a constant region of a heavy chain of an immunoglobulin fused to its carboxy terminus and the other extracellular subunit has a constant light chain of an immunoglobulin (Ig) fused to its carboxy terminus such that the two polypeptides come together to form a soluble receptor and a disulfide bond is formed between the heavy and the light Ig chains. In another embodiment, a peptide linker could be fused to the two carboxy-termini of the polypeptides to form a covalently bonded soluble receptor.

SEQ ID NOs: 24 and 25 are constructs of the extracellular domain of IL-22R fused to a mutated human immunoglobulin gamma 1 constant region. SEQ ID NO: 26 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 27 and 28 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region. SEQ ID NO: 29 is the predicted mature sequence without the signal sequence. Figure 1 is a schematic representation of the heterotetramer.

SEQ ID NOs: 30 and 31 are constructs of the extracellular domain of IL-22R fused to a mutated human immunoglobulin gamma 1 constant region. SEQ ID NO: 32 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 33 and 34 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region produced according to the procedure of example 12. SEQ ID NO: 35 is the predicted mature sequence without the signal sequence. The resultant heterotetramer does not have a polypeptide linker between the extracellular domains and the beginning of the Ig constant regions, 22 in Figure 1. Hereinafter, the term "extracellular domain of a receptor" means the extracellular domain of the receptor or a portion of the extracellular domain that is necessary for binding to its ligand, in this case the ligand being IL-20.

One can link together the extracellular domains of IL-22R and IL-20RB in a number of ways such that the resultant soluble receptor can bind to IL-20. Figures 1-8 illustrate a representative number of embodiments of the present invention. Common elements in each of the drawings are given the same number. Figure 1 represents the embodiment of the present invention of SEQ ID NOs: 24, 25, 26, 27, 28 and 29. The soluble receptor construct, designated 10, is comprised of two IL-20

binding site polypeptide chains designated 12 and 14. Each binding site is comprised of the extracellular domain of IL-22R, designated 16, and the extracellular domain of IL-20RB designated 18.

5 The extracellular domain, 16, of IL-22R is linked to the constant heavy one (CH1) domain, 20, of the human immunoglobulin gamma 1 heavy chain constant region via linker 22, which is SEQ ID NO: 36. The CH1 domain, 20, is then linked to the CH2 domain, 24, via hinge region 23. The CH2 domain, 24, is linked to the CH3 domain, 26, via hinge region 25.

10 Comparing the construct of Figure 1 with SEQ ID NO:25, the mature extracellular domain, 16, of IL-22R extends from amino acid residues 18, a proline, to and including amino acid residue 228, a threonine of SEQ ID NO:25. Polypeptide linker, 22, extends from amino acid residue 229, a glycine to and including amino acid residue 243, a serine, of SEQ ID NO:25. The CH1 domain, 22 of Figure 1, extends from amino acid residue 244, an alanine, to and including amino acid residue 341, a
15 valine, of SEQ ID NO: 25. Hinge region 23 of Figure 1 extends from amino acid residue 342, a glutamic acid to and including amino acid residue 356, a proline, of SEQ ID NO: 25. Chains 12 and 14 are disulfide-bonded together by means of disulfide bonds 28 and 30. The disulfide bonds are formed between the heavy chains by the cysteine residues at positions 352 and 356 of SEQ ID NO: 25 of each of the two heavy chains.

20 Extracellular domain, 18, of IL-20RB is linked to the constant region of the human kappa light chain (CL), 34 of Figure 1 via polypeptide linker 32, which is the polypeptide SEQ ID NO: 36. The extracellular domain, 18, of IL-20RB extends from amino acid residue 30, a valine, to and including amino acid residue 230, an alanine, of SEQ ID NO: 28. Polypeptide linker, 32, extends from amino acid residue 231, a
25 glycine, to and including amino acid residue 245, a serine, of SEQ ID NO: 28. The kappa constant light region, 34, extends from amino acid residue 246, an arginine, to and including the final amino acid residue 352, a cysteine, of SEQ ID NO: 28. The cysteine at position 352 of SEQ ID NO: 28 forms a disulfide bond, 36 in Figure 1, with the cysteine at position 346 of SEQ ID NO: 25. The constant light chain 34 is thus
30 linked to the hinge region, 23, by disulfide bond, 36. In this way, the extracellular domain, 16, of IL-22R is linked to the extracellular domain, 18, of IL-20RB to form a soluble receptor.

If the cysteine residues at positions 352 and 356 of SEQ ID NO: 25 were changed to different amino acid residues, the two IL-20 binding polypeptides, 12 and
35 14, would not be disulfide bonded together and would form a construct shown in Figure 2 having hinge region, 27.

Figure 3 shows a very simple soluble receptor 38 of the present invention wherein extracellular domain, 16, of IL-22R is connected to the extracellular domain, 18, of IL-20RB by means of a polypeptide linker, 40. The polypeptide linker extends from the amino terminus of extracellular domain, 16, of IL-22R and is
5 connected to the carboxyl terminus of the extracellular domain, 18, of IL-20RB. The polypeptide linker should be between 100-240 amino acids in length, preferably about 170 amino acid residues in length. A suitable linker would be comprised of glycine and serine residues. A possible linker would be multiple units of SEQ ID NO: 36, preferably about 12.

10 Figure 4 shows an embodiment that has the extracellular domain, 16, of IL-22R linked to the extracellular domain, 18, of IL-20RB by means of linker 40, as in Figure 3. While the extracellular domain, 16, of IL-22R is linked to the CH1 domain, 20, as in Figure 1 by means of polypeptide linker 42, which should be about 30 amino acid residues in length. An ideal linker would be comprised of glycine and serine as in
15 SEQ ID NO: 72, and the hinge sequence, 23 of Figure 1.

Figure 5 shows another possible embodiment of the present invention. In this embodiment, a polypeptide linker 44 of about 15 amino acid residue, *e.g.* SEQ ID NO: 36, links the carboxyl terminus of the extracellular domain, 18, of IL-20RB with the amino terminus of the extracellular domain, 16, of IL-22R. A polypeptide linker 46
20 of about 30 amino acid residues extends from the carboxy terminus of the extracellular domain, 16, of IL-22R to the CH2 domain. The carboxyl terminus of linker 46 would preferably be comprised of the hinge region extending from amino acid residue 342, a glutamic acid to and including amino acid residue 356, a proline, of SEQ ID NO: 25. Nonetheless, polypeptide linker 46 would ideally have at least one cysteine residue at
25 its carboxyl terminus so a disulfide bond could be formed.

The soluble IL-20 receptor of Figure 6 is identical to that of Figure 1 except for the CH3 domain, 26 of Figure 1, is not present on the embodiment of Figure 6. The CH3 region begins at amino acid residue 467, a glycine, and extends to the last residue 573 of SEQ ID NO: 25.

30 Figure 7 shows a soluble IL-20 receptor construct that is identical to the construct of Figure 1 except both the CH2, and CH3 domains are absent. The CH2 and CH3 domains run from amino acid residue 357, an alanine, to the end of the polypeptide sequence of SEQ ID NO: 25.

Figure 8 shows a construct wherein both IL-22R, 16, and IL-20RB have
35 a polypeptide linker, 48, fused to their respective carboxyl termini. Each polypeptide linker has two cysteine residues such that when they are expressed the cysteines form two disulfide bonds, 50 and 52. In this case the polypeptide linker is comprised of the

hinge region, 23 in Figure 1. The hinge region is comprised of amino acid residues 342, a glutamic acid, to and including amino acid residue 356 of SEQ ID NO: 25.

In another aspect of the invention, a method is provided for producing a soluble receptor comprised of extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-22R and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a transcriptional promoter operatively linked to a second secretory signal followed downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-20RB and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the secretion of a fusion protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region.

In an alternative embodiment, a method is provided for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-20RB and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a transcriptional promoter operatively linked to a second secretory signal followed downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-22R and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the production of a dimerized heterodimeric fusion protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the dimerized polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the

hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region. (See U.S. Patent No. 5,843,725.)

5 In another embodiment, a method is provided for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a DNA construct containing a DNA construct that encodes the extracellular portion of IL-20RB and a DNA construct of the extracellular portion of IL-22R, (b) growing the host cell in an appropriate medium under physiological
10 conditions to allow the production of the extracellular domain of IL-22R and the extracellular domain of IL-20RB; and (d) isolating the polypeptides from the host cell.

Other aspects of the present invention include host cells transformed or transfected with a DNA construct that encodes the extracellular domain of IL-22RB and a DNA construct that encodes the extracellular domain of IL-20RB. Both constructs can
15 be on one vector or on separate vectors.

A polynucleotide, generally a cDNA sequence, encodes the described polypeptides herein. A cDNA sequence that encodes a polypeptide of the present invention is comprised of a series of codons, each amino acid residue of the polypeptide being encoded by a codon and each codon being comprised of three nucleotides. The
20 amino acid residues are encoded by their respective codons as follows.

Alanine (Ala) is encoded by GCA, GCC, GCG or GCT.
Cysteine (Cys) is encoded by TGC or TGT.
25 Aspartic acid (Asp) is encoded by GAC or GAT.
Glutamic acid (Glu) is encoded by GAA or GAG.
Phenylalanine (Phe) is encoded by TTC or TTT.
Glycine (Gly) is encoded by GGA, GGC, GGG or GGT.
Histidine (His) is encoded by CAC or CAT.
30 Isoleucine (Ile) is encoded by ATA, ATC or ATT.
Lysine (Lys) is encoded by AAA, or AAG.
Leucine (Leu) is encoded by TTA, TTG, CTA, CTC, CTG or CTT.
Methionine (Met) is encoded by ATG.
Asparagine (Asn) is encoded by AAC or AAT.
35 Proline (Pro) is encoded by CCA, CCC, CCG or CCT.
Glutamine (Gln) is encoded by CAA or CAG.
Arginine (Arg) is encoded by AGA, AGG, CGA, CGC, CGG or CGT.

Serine (Ser) is encoded by AGC, AGT, TCA, TCC, TCG or TCT.

Threonine (Thr) is encoded by ACA, ACC, ACG or ACT.

Valine (Val) is encoded by GTA, GTC, GTG or GTT.

Tryptophan (Trp) is encoded by TGG.

5 Tyrosine (Tyr) is encoded by TAC or TAT.

It is to be recognized that according to the present invention, when a polynucleotide is claimed as described herein, it is understood that what is claimed are both the sense strand, the anti-sense strand, and the DNA as double-stranded having both the sense and anti-sense strand annealed together by their respective hydrogen bonds. Also claimed is the messenger RNA (mRNA) that encodes the polypeptides of the present invention, and which mRNA is encoded by the cDNA described herein. Messenger RNA (mRNA) will encode a polypeptide using the same codons as those defined herein, with the exception that each thymine nucleotide (T) is replaced by a uracil nucleotide (U).

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One of ordinary skill in the art will also appreciate that different species can exhibit "preferential codon usage." In general, see, Grantham, *et al.*, *Nuc. Acids Res.* 8:1893-1912 (1980); Haas, *et al.* *Curr. Biol.* 6:315-324 (1996); Wain-Hobson, *et al.*, *Gene* 13:355-364 (1981); Grosjean and Fiers, *Gene* 18:199-209 (1982); Holm, *Nuc. Acids Res.* 14:3075-3087 (1986); Ikemura, *J. Mol. Biol.* 158:573-597 (1982). As used herein, the term "preferential codon usage" or "preferential codons" is a term of art referring to protein translation codons that are most frequently used in cells of a certain species, thus favoring one or a few representatives of the possible codons encoding each amino acid. For example, the amino acid Threonine (Thr) may be encoded by ACA, ACC, ACG, or ACT, but in mammalian cells ACC is the most commonly used codon; in other species, for example, insect cells, yeast, viruses or bacteria, different Thr codons may be preferential. Preferential codons for a particular species can be introduced into the polynucleotides of the present invention by a variety of methods known in the art. Introduction of preferential codon sequences into recombinant DNA can, for example, enhance production of the protein by making protein translation more efficient within a particular cell type or species. Sequences containing preferential codons can be tested and optimized for expression in various species, and tested for functionality as disclosed herein.

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Methods for synthesizing amino acids and aminoacylating tRNA are known in the art. Transcription and translation of plasmids containing nonsense mutations is carried out in a cell-free system comprising an *E. coli* S30 extract and

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commercially available enzymes and other reagents. Proteins are purified by chromatography. See, for example, Robertson *et al.*, *J. Am. Chem. Soc.* 113:2722 (1991); Ellman *et al.*, *Methods Enzymol.* 202:301 (1991); Chung *et al.*, *Science* 259:806-809 (1993); and Chung *et al.*, *Proc. Natl. Acad. Sci. USA* 90:10145-1019 (1993). In a
5 second method, translation is carried out in *Xenopus* oocytes by microinjection of mutated mRNA and chemically aminoacylated suppressor tRNAs, Turcatti *et al.*, *J. Biol. Chem.* 271:19991-19998 (1996). Within a third method, *E. coli* cells are cultured in the absence of a natural amino acid that is to be replaced (*e.g.*, phenylalanine) and in the presence of the desired non-naturally occurring amino acid(s) (*e.g.*, 2-
10 azaphenylalanine, 3-azaphenylalanine, 4-azaphenylalanine, or 4-fluorophenylalanine). The non-naturally occurring amino acid is incorporated into the protein in place of its natural counterpart. See, Koide *et al.*, *Biochem.* 33:7470-7476 (1994). Naturally occurring amino acid residues can be converted to non-naturally occurring species by *in vitro* chemical modification. Chemical modification can be combined with site-
15 directed mutagenesis to further expand the range of substitutions, Wynn and Richards, *Protein Sci.* 2:395-403 (1993).

A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, non-naturally occurring amino acids, and unnatural amino acids may be substituted for amino acid residues.

20 Essential amino acids in the polypeptides of the present invention can be identified according to procedures known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis, Cunningham and Wells, *Science* 244: 1081-1085 (1989); Bass *et al.*, *Proc. Natl. Acad. Sci. USA* 88:4498-502 (1991). In the latter technique, single alanine mutations are introduced at every residue in the molecule, and
25 the resultant mutant molecules are tested for biological activity as disclosed below to identify amino acid residues that are critical to the activity of the molecule. See also, Hilton *et al.*, *J. Biol. Chem.* 271:4699-708, 1996. Sites of ligand-receptor interaction can also be determined by physical analysis of structure, as determined by such techniques as nuclear magnetic resonance, crystallography, electron diffraction or
30 photoaffinity labeling, in conjunction with mutation of putative contact site amino acids. See, for example, de Vos *et al.*, *Science* 255:306-312 (1992); Smith *et al.*, *J. Mol. Biol.* 224:899-904 (1992); Wlodaver *et al.*, *FEBS Lett.* 309:59-64 (1992).

Multiple amino acid substitutions can be made and tested using known methods of mutagenesis and screening, such as those disclosed by Reidhaar-Olson and
35 Sauer, *Science* 241:53-57 (1988) or Bowie and Sauer, *Proc. Natl. Acad. Sci. USA* 86:2152-2156 (1989). Briefly, these authors disclose methods for simultaneously randomizing two or more positions in a polypeptide, selecting for functional

polypeptide, and then sequencing the mutagenized polypeptides to determine the spectrum of allowable substitutions at each position. Other methods that can be used include phage display, *e.g.*, Lowman *et al.*, *Biochem.* 30:10832-10837 (1991); Ladner *et al.*, U.S. Patent No. 5,223,409; Huse, WIPO Publication WO 92/06204) and region-
5 directed mutagenesis, Derbyshire *et al.*, *Gene* 46:145 (1986); Ner *et al.*, *DNA* 7:127 (1988).

Variants of the disclosed *IL-20*, *IL-22R* and *IL-20RB* DNA and polypeptide sequences can be generated through DNA shuffling as disclosed by Stemmer, *Nature* 370:389-391, (1994), Stemmer, *Proc. Natl. Acad. Sci. USA* 91:10747-
10 10751 (1994) and WIPO Publication WO 97/20078. Briefly, variant DNAs are generated by *in vitro* homologous recombination by random fragmentation of a parent DNA followed by reassembly using PCR, resulting in randomly introduced point mutations. This technique can be modified by using a family of parent DNAs, such as allelic variants or DNAs from different species, to introduce additional variability into
15 the process. Selection or screening for the desired activity, followed by additional iterations of mutagenesis and assay provides for rapid "evolution" of sequences by selecting for desirable mutations while simultaneously selecting against detrimental changes.

Mutagenesis methods as disclosed herein can be combined with high-
20 throughput, automated screening methods to detect activity of cloned, mutagenized polypeptides in host cells. Mutagenized DNA molecules that encode active polypeptides can be recovered from the host cells and rapidly sequenced using modern equipment. These methods allow the rapid determination of the importance of individual amino acid residues in a polypeptide of interest, and can be applied to
25 polypeptides of unknown structure.

PROTEIN PRODUCTION

Polypeptides can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can
30 be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are preferred. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*,
35 2nd ed., (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and Ausubel *et al.*, eds., *Current Protocols in Molecular Biology* (John Wiley and Sons, Inc., NY, 1987).

In general, a DNA sequence encoding a polypeptide is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although
5 those skilled in the art will recognize that within certain systems selectable markers may be provided on separate vectors, and replication of the exogenous DNA may be provided by integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and
10 are available through commercial suppliers.

To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the native polypeptides, or may be derived from another secreted protein (*e.g.*, t-
15 PA) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized polypeptide into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the polypeptide of interest, although certain secretory signal sequences may be
20 positioned elsewhere in the DNA sequence of interest (see, *e.g.*, Welch *et al.*, U.S. Patent No. 5,037,743; Holland *et al.*, U.S. Patent No. 5,143,830).

Alternatively, the secretory signal sequence contained in the polypeptides of the present invention is used to direct other polypeptides into the secretory pathway. The present invention provides for such fusion polypeptides. The
25 secretory signal sequence contained in the fusion polypeptides of the present invention is preferably fused amino-terminally to an additional peptide to direct the additional peptide into the secretory pathway. Such constructs have numerous applications known in the art. For example, these novel secretory signal sequence fusion constructs can direct the secretion of an active component of a normally non-secreted protein, such as
30 a receptor. Such fusions may be used *in vivo* or *in vitro* to direct peptides through the secretory pathway.

Cultured mammalian cells are suitable hosts within the present invention. Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection, Wigler *et al.*, *Cell* 14:725 (1978), Corsaro
35 and Pearson, *Somatic Cell Genetics* 7:603 (1981); Graham and Van der Eb, *Virology* 52:456 (1973), electroporation, Neumann *et al.*, *EMBO J.* 1:841-845 (1982), DEAE-dextran mediated transfection (Ausubel *et al.*, *ibid.*, and liposome-mediated

transfection, Hawley-Nelson *et al.*, *Focus* 15:73 (1993); Ciccarone *et al.*, *Focus* 15:80 (1993), and viral vectors, Miller and Rosman, *BioTechniques* 7:980(1989); Wang and Finer, *Nature Med.* 2:714 (1996). The production of recombinant polypeptides in cultured mammalian cells is disclosed, for example, by Levinson *et al.*, U.S. Patent No. 4,713,339; Hagen *et al.*, U.S. Patent No. 4,784,950; Palmiter *et al.*, U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham *et al.*, *J. Gen. Virol.* 36:59 (1977) and Chinese hamster ovary (*e.g.* CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, *e.g.*, U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and are able to pass the gene of interest to their progeny are referred to as "stable transfectants." A preferred selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. A preferred amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (*e.g.* hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used. Alternative markers that introduce an altered phenotype, such as green fluorescent protein, or cell surface proteins such as CD4, CD8, Class I MHC, placental alkaline phosphatase may be used to sort transfected cells from untransfected cells by such means as FACS sorting or magnetic bead separation technology.

Other higher eukaryotic cells can also be used as hosts, including plant cells, insect cells and avian cells. The use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar *et al.*, *J. Biosci. (Bangalore)* 11:47 (1987). Transformation of insect cells and production of foreign

polypeptides therein is disclosed by Guarino *et al.*, U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463. Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). DNA encoding a polypeptide is inserted into the baculoviral genome in place of the AcNPV polyhedrin gene coding sequence by one of two methods. The first is the traditional method of homologous DNA recombination between wild-type AcNPV and a transfer vector containing the gene flanked by AcNPV sequences. Suitable insect cells, *e.g.* SF9 cells, are infected with wild-type AcNPV and transfected with a transfer vector comprising a polynucleotide operably linked to an AcNPV polyhedrin gene promoter, terminator, and flanking sequences. See, King, L.A. and Possee, R.D., *The Baculovirus Expression System: A Laboratory Guide*, (Chapman & Hall, London); O'Reilly, D.R. *et al.*, *Baculovirus Expression Vectors: A Laboratory Manual* (Oxford University Press, New York, New York, 1994); and, Richardson, C. D., Ed., *Baculovirus Expression Protocols. Methods in Molecular Biology*, (Humana Press, Totowa, NJ 1995). Natural recombination within an insect cell will result in a recombinant baculovirus that contains coding sequences driven by the polyhedrin promoter. Recombinant viral stocks are made by methods commonly used in the art.

The second method of making recombinant baculovirus utilizes a transposon-based system described by Luckow, V.A., *et al.*, *J Virol* 67:4566 (1993). This system is sold in the Bac-to-Bac kit (Life Technologies, Rockville, MD). This system utilizes a transfer vector, pFastBac1™ (Life Technologies) containing a Tn7 transposon to move the DNA encoding the polypeptide into a baculovirus genome maintained in *E. coli* as a large plasmid called a "bacmid." The pFastBac1™ transfer vector utilizes the AcNPV polyhedrin promoter to drive the expression of the gene of interest. However, pFastBac1™ can be modified to a considerable degree. The polyhedrin promoter can be removed and substituted with the baculovirus basic protein promoter (also known as P_{cor}, p6.9 or MP promoter), which is expressed earlier in the baculovirus infection, and has been shown to be advantageous for expressing secreted proteins. See, Hill-Perkins, M.S. and Possee, R.D., *J Gen Virol* 71:971 (1990); Bonning, B.C. *et al.*, *J Gen Virol* 75:1551 (1994); and, Chazenbalk, G.D., and Rapoport, B., *J Biol Chem* 270:1543 (1995). In such transfer vector constructs, a short or long version of the basic protein promoter can be used. Moreover, transfer vectors can be constructed that replace the native secretory signal sequences with secretory signal sequences derived from insect proteins. For example, a secretory signal sequence from Ecdysteroid Glucosyltransferase (EGT), honey bee Melittin (Invitrogen, Carlsbad, CA), or baculovirus gp67 (PharMingen, San Diego, CA) can be used in constructs to replace the native secretory signal sequence. In addition, transfer vectors

can include an in-frame fusion with DNA encoding an epitope tag at the C- or N-terminus of the expressed polypeptide, for example, a Glu-Glu epitope tag, Grussenmeyer, T. *et al.*, *Proc Natl Acad Sci.* 82:7952 (1985). Using a technique known in the art, a transfer vector containing a recombinant gene is transformed into *E. coli*,
5 and screened for bacmids that contain an interrupted lacZ gene indicative of recombinant baculovirus. The bacmid DNA containing the recombinant baculovirus genome is isolated, using common techniques, and used to transfect *Spodoptera frugiperda* cells, *e.g.* Sf9 cells. Recombinant virus that expresses the polypeptide is subsequently produced. Recombinant viral stocks are made by methods commonly
10 used the art.

The recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda*. See, in general, Glick and Pasternak, *Molecular Biotechnology: Principles and Applications of Recombinant DNA* (ASM Press, Washington, D.C., 1994). Another suitable cell line is the High
15 FiveO™ cell line (Invitrogen) derived from *Trichoplusia ni* (U.S. Patent #5,300,435). Commercially available serum-free media are used to grow and maintain the cells. Suitable media are Sf900 II™ (Life Technologies) or ESF 921™ (Expression Systems) for the Sf9 cells; and Ex-cello405™ (JRH Biosciences, Lenexa, KS) or Express FiveO™ (Life Technologies) for the *T. ni* cells. The cells are grown up from an
20 inoculation density of approximately $2-5 \times 10^5$ cells to a density of $1-2 \times 10^6$ cells at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. The recombinant virus-infected cells typically produce the recombinant polypeptide at 12-72 hours post-infection and secrete it with varying efficiency into the medium. The culture is usually harvested 48 hours post-infection.
25 Centrifugation is used to separate the cells from the medium (supernatant). The supernatant containing the polypeptide is filtered through micropore filters, usually 0.45 μ m pore size. Procedures used are generally described in available laboratory manuals (King, L. A. and Possee, R.D., *ibid.*, O'Reilly, D.R. *et al.*, *ibid.*; Richardson, C. D., *ibid.*). Subsequent purification of the polypeptide from the supernatant can be achieved
30 using methods described herein.

Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include *Saccharomyces cerevisiae*, *Pichia pastoris*, and *Pichia methanolica*. Methods for transforming *S. cerevisiae* cells with exogenous DNA and producing recombinant polypeptides
35 therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki *et al.*, U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch *et al.*, U.S. Patent No. 5,037,743; and Murray *et al.*, U.S. Patent No. 4,845,075.

Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in *Saccharomyces cerevisiae* is the *POT1* vector system disclosed by Kawasaki *et al.* (U.S. Patent No. 4,931,373), which
5 allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman *et al.*, U.S. Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and
10 4,661,454. Transformation systems for other yeasts, including *Hansenula polymorpha*, *Schizosaccharomyces pombe*, *Kluyveromyces lactis*, *Kluyveromyces fragilis*, *Ustilago maydis*, *Pichia pastoris*, *Pichia methanolica*, *Pichia guilliermondii* and *Candida maltosa* are known in the art. See, for example, Gleeson *et al.*, *J. Gen. Microbiol.* 132:3459 (1986) and Cregg, U.S. Patent No. 4,882,279. *Aspergillus* cells may be
15 utilized according to the methods of McKnight *et al.*, U.S. Patent No. 4,935,349. Methods for transforming *Acremonium chrysogenum* are disclosed by Sumino *et al.*, U.S. Patent No. 5,162,228. Methods for transforming *Neurospora* are disclosed by Lambowitz, U.S. Patent No. 4,486,533.

The use of *Pichia methanolica* as host for the production of recombinant
20 proteins is disclosed in WIPO Publications WO 97/17450, WO 97/17451, WO 98/02536, and WO 98/02565. DNA molecules for use in transforming *P. methanolica* will commonly be prepared as double-stranded, circular plasmids, which are preferably linearized prior to transformation. For polypeptide production in *P. methanolica*, it is preferred that the promoter and terminator in the plasmid be that of a *P. methanolica*
25 gene, such as a *P. methanolica* alcohol utilization gene (*AUG1* or *AUG2*). Other useful promoters include those of the dihydroxyacetone synthase (DHAS), formate dehydrogenase (FMD), and catalase (CAT) genes. To facilitate integration of the DNA into the host chromosome, it is preferred to have the entire expression segment of the plasmid flanked at both ends by host DNA sequences. A preferred selectable marker
30 for use in *Pichia methanolica* is a *P. methanolica* *ADE2* gene, which encodes phosphoribosyl-5-aminoimidazole carboxylase (AIRC; EC 4.1.1.21), which allows *ade2* host cells to grow in the absence of adenine. For large-scale, industrial processes where it is desirable to minimize the use of methanol, it is preferred to use host cells in which both methanol utilization genes (*AUG1* and *AUG2*) are deleted. For production
35 of secreted proteins, host cells deficient in vacuolar protease genes (*PEP4* and *PRB1*) are preferred. Electroporation is used to facilitate the introduction of a plasmid containing DNA encoding a polypeptide of interest into *P. methanolica* cells. It is

preferred to transform *P. methanolica* cells by electroporation using an exponentially decaying, pulsed electric field having a field strength of from 2.5 to 4.5 kV/cm, preferably about 3.75 kV/cm, and a time constant (t) of from 1 to 40 milliseconds, most preferably about 20 milliseconds.

5 Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art; see, e.g., Sambrook *et al.*, *ibid.*). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the
10 cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the
15 and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding.

20 Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and
25 minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient, which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell. *P. methanolica* cells are cultured in a medium comprising
30 adequate sources of carbon, nitrogen and trace nutrients at a temperature of about 25°C to 35°C. Liquid cultures are provided with sufficient aeration by conventional means, such as shaking of small flasks or sparging of fermentors. A preferred culture medium for *P. methanolica* is YEPD (2% D-glucose, 2% Bacto™ Peptone (Difco Laboratories, Detroit, MI), 1% Bacto™ yeast extract (Difco Laboratories), 0.004% adenine and
35 0.006% L-leucine).

Protein Isolation

It is preferred to purify the polypeptides of the present invention to $\geq 80\%$ purity, more preferably to $\geq 90\%$ purity, even more preferably $\geq 95\%$ purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide is substantially free of other polypeptides, particularly other polypeptides of animal origin.

Expressed recombinant polypeptides (or chimeric polypeptides) can be purified using fractionation and/or conventional purification methods and media. Ammonium sulfate precipitation and acid or chaotrope extraction may be used for fractionation of samples. Exemplary purification steps may include hydroxyapatite, size exclusion, FPLC and reverse-phase high performance liquid chromatography. Suitable chromatographic media include derivatized dextrans, agarose, cellulose, polyacrylamide, specialty silicas, and the like. PEI, DEAE, QAE and Q derivatives are preferred. Exemplary chromatographic media include those media derivatized with phenyl, butyl, or octyl groups, such as Phenyl-Sepharose FF (Pharmacia), Toyopearl butyl 650 (Toso Haas, Montgomeryville, PA), Octyl-Sepharose (Pharmacia) and the like; or polyacrylic resins, such as Amberchrom CG 71 (Toso Haas) and the like. Suitable solid supports include glass beads, silica-based resins, cellulosic resins, agarose beads, cross-linked agarose beads, polystyrene beads, cross-linked polyacrylamide resins and the like that are insoluble under the conditions in which they are to be used. These supports may be modified with reactive groups that allow attachment of proteins by amino groups, carboxyl groups, sulfhydryl groups, hydroxyl groups and/or carbohydrate moieties. Examples of coupling chemistries include cyanogen bromide activation, N-hydroxysuccinimide activation, epoxide activation, sulfhydryl activation, hydrazide activation, and carboxyl and amino derivatives for carbodiimide coupling chemistries. These and other solid media are well known and widely used in the art, and are available from commercial suppliers. Methods for binding receptor polypeptides to support media are well known in the art. Selection of a particular method is a matter of routine design and is determined in part by the properties of the chosen support. See, for example, *Affinity Chromatography: Principles & Methods* (Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988).

Polypeptides can be isolated by exploitation of their properties. For example, immobilized metal ion adsorption (IMAC) chromatography can be used to purify histidine-rich proteins, including those comprising polyhistidine tags. Briefly, a gel is first charged with divalent metal ions to form a chelate, Sulkowski, *Trends in Biochem.* 3:1 (1985). Histidine-rich proteins will be adsorbed to this matrix with differing affinities, depending upon the metal ion used, and will be eluted by

competitive elution, lowering the pH, or use of strong chelating agents. Other methods of purification include purification of glycosylated proteins by lectin affinity chromatography and ion exchange chromatography. A protein fused to the Fc portion of an immunoglobulin can be purified using a 'Protein A column'. *Methods in Enzymol.*,
5 Vol. 182, "Guide to Protein Purification", M. Deutscher, (ed.), page 529-539 (Acad. Press, San Diego, 1990). Within additional embodiments of the invention, a fusion of the polypeptide of interest and an affinity tag (*e.g.*, maltose-binding protein, an immunoglobulin domain) may be constructed to facilitate purification.

As used herein, the term "antibodies" includes polyclonal antibodies,
10 affinity-purified polyclonal antibodies, monoclonal antibodies, and antigen-binding fragments, such as F(ab')₂ and Fab proteolytic fragments. Genetically engineered intact antibodies or fragments, such as chimeric antibodies, Fv fragments, single chain antibodies and the like, as well as synthetic antigen-binding peptides and polypeptides, are also included. Non-human antibodies may be humanized by grafting non-human
15 CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through
20 humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that bind to protein or peptide. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.) (Cold Spring
25 Harbor Laboratory Press, 1988). Representative examples of such assays include: concurrent immunoelectrophoresis, radioimmunoassay, radioimmuno-precipitation, enzyme-linked immunosorbent assay (ELISA), dot blot or Western blot assay, inhibition or competition assay, and sandwich assay.

The soluble receptors of the present invention can be used to down-
30 regulate IL-20, which has been shown to be involved in a number of inflammatory processes. Specifically, IL-20 has been shown to up-regulate IL-8. Inflammatory diseases in which IL-8 plays a significant role, and for which a decrease in IL-8 would be beneficial are, adult respiratory disease (ARD), septic shock, multiple organ failure, inflammatory lung injury such as asthma or bronchitis, bacterial pneumonia, psoriasis,
35 eczema, atopic and contact dermatitis, and inflammatory bowel disease such as ulcerative colitis and Crohn's disease. Thus, the soluble receptor to IL-20 of the present invention can be administered to a patient to treat these diseases.

Biology of IL-20, Its receptor and Its Role in Psoriasis

Two orphan class II cytokine receptors, both of which are expressed in skin, were identified as IL-20 receptor subunits. Both IL-20 receptor subunits are
5 required for ligand binding, distinguishing their role from that of subunits in the four other known class II cytokine receptors. IL-22R and IL-20RB are also coexpressed in a number of human tissues besides skin, including ovary, adrenal gland, testis, salivary gland, muscle, lung, kidney, heart and to a lesser degree the small intestine suggesting additional target tissues for IL-20 action. We conclude that the IL-20 heterodimeric
10 receptor is structurally similar to other class II cytokine receptors and is expressed in skin where we have demonstrated activity of the IL-20 ligand.

Two lines of evidence indicate that a role IL-20 and its receptor are involved in psoriasis. This multigenic skin disease is characterized by increased keratinocyte proliferation, altered keratinocyte differentiation, and infiltration of
15 immune cells into the skin. The first line of evidence for a role of IL-20 in psoriasis is that the observed hyperkeratosis and thickened epidermis in the transgenic mice that resemble human psoriatic abnormalities. Decreased numbers of tonofilaments, thought to be related to defective keratinization, are a striking feature of human psoriasis. Intramitochondrial inclusions have been found in both chemically induced and naturally
20 occurring hyperplastic skin conditions in mice. The cause of the inclusions and their effects on mitochondrial function, if any, are unknown. We conclude that IL-20 transgenic mice exhibit many of the characteristics observed in human psoriasis.

Use of Antagonist to IL-20 to Treat Psoriasis

25 As indicated in the discussion above and the examples below, IL-20 is involved in the pathology of psoriasis. Thus, the soluble receptors of the present invention can be administered to an individual to down-regulate IL-20 and thus treat psoriasis.

Psoriasis is one of the most common dermatologic diseases, affecting up
30 to 1 to 2 percent of the world's population. It is a chronic inflammatory skin disorder characterized by erythematous, sharply demarcated papules and rounded plaques,

covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic. Traumatized areas often develop lesions of psoriasis. Additionally, other external factors may exacerbate psoriasis including infections, stress, and medications, *e.g.* lithium, beta blockers, and anti-malarials.

5 The most common variety of psoriasis is called plaque type. Patients with plaque-type psoriasis will have stable, slowly growing plaques, which remain basically unchanged for long periods of time. The most common areas for plaque psoriasis to occur are the elbows knees, gluteal cleft, and the scalp. Involvement tends to be symmetrical. Inverse psoriasis affects the intertriginous regions including the
10 axilla, groin, submammary region, and navel, and it also tends to affect the scalp, palms, and soles. The individual lesions are sharply demarcated plaques but may be moist due to their location. Plaque-type psoriasis generally develops slowly and runs an indolent course. It rarely spontaneously remits.

Eruptive psoriasis (guttate psoriasis) is most common in children and
15 young adults. It develops acutely in individuals without psoriasis or in those with chronic plaque psoriasis. Patients present with many small erythematous, scaling papules, frequently after upper respiratory tract infection with beta-hemolytic streptococci. Patients with psoriasis may also develop pustular lesions. These may be localized to the palms and soles or may be generalized and associated with fever,
20 malaise, diarrhea, and arthralgias..

About half of all patients with psoriasis have fingernail involvement, appearing as punctate pitting, nail thickening or subungual hyperkeratosis. About 5 to 10 percent of patients with psoriasis have associated joint complaints, and these are most often found in patients with fingernail involvement. Although some have the
25 coincident occurrence of classic Although some have the coincident occurrence of classic rheumatoid arthritis, many have joint disease that falls into one of five type associated with psoriasis: (1) disease limited to a single or a few small joints (70 percent of cases); (2) a seronegative rheumatoid arthritis-like disease; (3) involvement of the distal interphalangeal joints; (4) severe destructive arthritis with the development
30 of "arthritis mutilans"; and (5) disease limited to the spine.

Psoriasis can be treated by administering antagonists to IL-20. The preferred antagonists are either a soluble receptor to IL-20 or antibodies, antibody fragments or single chain antibodies that bind to either the IL-20 receptor or to IL-20. The antagonists to IL-20 can be administered alone or in combination with other
5 established therapies such as lubricants, keratolytics, topical corticosteroids, topical vitamin D derivatives, anthralin, systemic antimetabolites such as methotrexate, psoralen-ultraviolet-light therapy (PUVA), etretinate, isotretinoin, cyclosporine, and the topical vitamin D3 derivative calcipotriol. The antagonists, in particularly the soluble receptor or the antibodies that bind to IL-20 or the IL-20 receptor can be administered
10 to individual subcutaneously, intravenously, or transdermally using a cream or transdermal patch that contains the antagonist of IL-20. If administered subcutaneously, the antagonist can be injected into one or more psoriatic plaques. If administered transdermally, the antagonists can be administered directly on the plaques using a cream containing the antagonist to IL-20.

15

Use of Antagonists to IL-20 to Treat Inflammatory Conditions of the Lung.

A soluble receptor of IL-20 of the present invention can be administered to a person who has asthma, bronchitis or cystic fibrosis or other inflammatory lung disease to treat the disease. The antagonists can be administered by any suitable method
20 including intravenous, subcutaneous, bronchial lavage, and the use of inhalant containing an antagonist to IL-20.

Administration of the IL-20 Soluble Receptor

The quantities of the IL-20 soluble necessary for effective therapy will depend upon many different factors, including means of administration, target site,
25 physiological state of the patient, and other medications administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in vivo* administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Methods for administration
30 include oral, intravenous, peritoneal, intramuscular, transdermal or administration into the lung or trachea in spray form by means of a nebulizer or atomizer. Pharmaceutically

acceptable carriers will include water, saline, buffers to name just a few. Dosage ranges would ordinarily be expected from 1µg to 1000µg per kilogram of body weight per day. A dosage for an average adult of the IL-20 soluble receptor would be about 25 mg given twice weekly as a subcutaneous injection. Injections could be given at the site of psoriatic lesions for the treatment of psoriasis. For subcutaneous or intravenous administration of the antagonist to IL-20, the antibody or soluble receptor can be in phosphate buffered saline. Also in skin diseases such as psoriasis, the antagonist to IL-20 can be administered via an ointment or transdermal patch. The doses by may be higher or lower as can be determined by a medical doctor with ordinary skill in the art. For a complete discussion of drug formulations and dosage ranges *see Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Co., Easton, Penn., 1996), and *Goodman and Gilman's: The Pharmacological Bases of Therapeutics*, 9th Ed. (Pergamon Press 1996).

The invention is further illustrated by the following non-limiting examples:

Example 1

Up-regulation of IL-8 by IL-20

Methods:

Normal Human Epidermal neonatal keratinocytes (NHEK) (from Clonetics) at passage 2 were plated and grown to confluency in 12 well tissue culture plates. KGM (Keratinocyte growth media) was purchased from Clonetics. When cells reached confluency, they were washed with KGM media minus growth factors = KBM (keratinocyte basal media). Cells were serum starved in KBM for 72 hours prior to the addition of test compounds. Thrombin at 1 I.U./mL and trypsin at 25nM were used as positive controls. One mL of media/well was added. KBM only was used as the negative control.

IL-20 was made up in KBM media and added at varying concentrations, from 2.5µg/ml down to 618ng/mL in a first experiment and from 2.5µg/mL down to 3ng/mL in a second experiment.

Cells were incubated at 37° C, 5% CO₂ for 48 hours. Supernatants were removed and frozen at -80° C for several days prior to assaying for IL-8 and GM-CSF

levels. Human IL-8 Immunoassay kit # D8050 (RandD Systems, Inc.) and human GM-CSF Immunoassay kit # HSGMO (RandD Systems, Inc.) were used to determine cytokine production following manufacturer's instructions.

5 Results

The results indicated that the expression of IL-8 and GM-CSF were induced by IL-20.

Example 2

10 Cloning of IL-20RB

Cloning of IL-20RB coding region

Two PCR primers were designed based on the sequence from International Patent Application No. PCT/US99/03735 (publication no. WO 99/46379) filed on March 8, 1999. SEQ ID NO: 38 contains the ATG (Met1) codon with an EcoRI restriction site, SEQ ID NO: 37 contains the stop codon (TAG) with an XhoI restriction site. The PCR amplification was carried out using a human keratinocyte (HaCaT) cDNA library DNA as a template and SEQ ID NO: 37 and SEQ ID NO: 38 as primers. The PCR reaction was performed as follows: incubation at 94°C for 1 min followed by 20 30 cycles of 94°C for 30 sec and 68°C for 2 min, after additional 68°C for 4 min, the reaction was stored at 4°C. The PCR products were run on 1% Agarose gel, and a 1 kb DNA band was observed. The PCR products were cut from the gel and the DNA was purified using a QIAquick Gel Extraction Kit (Qiagen). The purified DNA was digested with EcoRI and XhoI, and cloned into a pZP vector that was called pZP7N. A pZP 25 plasmid is a mammalian expression vector containing an expression cassette having the mouse metallothionein-1 promoter, human tPA leader peptide, multiple restriction sites for insertion of coding sequences, a Glu-Glu tag, and a human growth hormone terminator. The plasmid also has an E. coli origin of replication, a mammalian selectable marker expression unit having an SV40 promoter, an enhancer and an origin 30 of replication, as well as a DHFR gene, and the SV40 terminator. Several IL-20RB-pZP7N clones were sequenced. They all contain three non-conservative mutations

compared with the sequence of IL-20RB in PCT/US99/03735: (sequence IL-20RB-pZP7N), 146 Pro (CCC) -- Thr (ACC), 148 His (CAT) -- Asp (GAT), and 171 Thr (ACG) -- Arg (AGG).

To verify the three substitutions in IL-20RB-pZP7N clone, PCR
5 amplification was carried out using three difference cDNA sources -- fetal skin
marathon cDNA, HaCaT cDNA library DNA, and prostate smooth muscle cDNA
library DNA -- as templates. The PCR products were gel purified and sequenced. The
sequence of each of the three PCR products was consistent with that of the IL-20RB-
pZP7N clone. IL-20RB is SEQ ID NO: 22 and 23, and the mature extracellular domain
10 is SEQ ID NO: 21.

Example 3

Binding of IL-20 to IL-20RB/ IL-22R Heterodimer

15 A cell-based binding assay was used to verify IL-20 binds to IL-22R- IL-
20RB heterodimer.

Expression vectors containing known and orphan Class II cytokine
receptors (including IL-22R and IL-20RB) were transiently transfected into Baf3 cells.

Plated cells out at 5000cells/well, treated cells with IL-20 (zcyto10),
20 MDA-7, and Soluble Proteins.

-Inc. at 37 degrees for 3 days (72hrs.)

-Added 20ul/well of Alamar Blue, inc. at 37 degrees overnight (24 hrs.)

-Read on the f-Max (Molecular Devises) in the Robotics room on 544 excitation/ 590
emission setting.

25

Results:

-Positive proliferative response with treatments of IL-20 (zcyto10) and MDA-7 from
0.1ng/ml to 100ng/ml on Baf3/DIRS1/cytoR11 cell line.

-A neutralization of the positive proliferative response of IL-20 and MDA-7 (same
30 conc.'s) when IL-20 and MDA-7 were treated in combination with the IL-22R Soluble
Receptor (heterodimeric Sol. R.) at a 60 fold molar excess.

-A neutralization of the positive proliferative response of MDA-7 (from 0.1 to 10ng/ml) when MDA-7 was treated in combination with IL-20RB Soluble Protein (thrombin cleaved version) at a 60 fold molar excess.

5

Example 4

Up-regulation of Inflammatory Cytokines by IL-20

Cell Treatment

The human keratinocyte cell line, HaCaT was grown at 37°C to several days post-confluence in T-75 tissue culture flasks. At this point, normal growth media (DMEM + 10% FBS) was removed and replaced with serum-free media. Cells were then incubated for two days at 37°C. DMEM was then removed and four flasks of cells per treatment were treated with one of each of the following conditions for four hours at 37°C: recombinant human (rh) IL-1 alpha at 5 ng/mL, rh IL-1 alpha at 20 ng/mL, rh IL-1 alpha at 5 ng/mL + IL-20 at 1µg/mL, IL-20 at 1µg/mL, or rh IL-10 at 10 ng/mL.

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RNA Isolation

Following cytokine treatment, media was removed and cells were lysed using a guanidium thiocyanate solution. Total RNA was isolated from the cell lysate by an overnight spin on a cesium chloride gradient. The following day, the RNA pellet was resuspended in a TE/SDS solution and ethanol precipitated. RNA was then quantitated using a spectrophotometer, followed by a DNase treatment as per Section V.B. of Clontech's AtlasTM cDNA Expression Arrays User Manual (version PT3140-1/PR9X390, published 11/5/99). Quality of RNA samples was verified by purity calculations based on spec readings, and by visualization on agarose gel. Genomic contamination of the RNA samples was ruled out by PCR analysis of the beta-actin gene.

25

Clontech's protocols for polyA+ enrichment, probe synthesis and hybridization to AtlasTM arrays were followed (see above, plus AtlasTM Pure Total RNA Labeling System User Manual, PT3231-1/PR96157, published 6/22/99). Briefly, polyA+ RNA was isolated from 50 mg of total RNA using streptavidin coated magnetic beads (by Clontech, Paolo Alto, CA) and a magnetic particle separator. PolyA+ RNA

30

was then labeled with $\alpha^{32}\text{P}$ -dATP via RT-PCR. Clontech CDS primers specific to the 268 genes on the AtlasTM human cytokine/receptor array (Cat. #7744-1) were used in the reaction. Labeled probe was isolated using column chromatography and counted in scintillation fluid.

5

Array membrane Hybridization

AtlasTM arrays were pre-hybridized with Clontech ExpressHyb plus 100 mg/mL heat denatured salmon sperm DNA for at least thirty minutes at 68°C with continuous agitation. Membranes were then hybridized with 1.9×10^6 CPM/mL (a total of 1.14×10^7 CPM) overnight at 68°C with continuous agitation. The following day, membranes were washed for thirty minutes x 4 in 2X SSC, 1% SDS at 68°C, plus for thirty minutes x 1 in 0.1X SSC, 0.5% SDS at 68°C, followed by one final room temperature wash for five minutes in 2X SSC. Array membranes were then placed in Kodak plastic pouches sealed and exposed to a phosphor imager screen overnight at room temperature. The next day, phosphor screens were scanned on a phosphor imager and analyzed using Clontech's AtlasImageTM 1.0 software.

10

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Results

Genes Up-regulated by IL-20

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1. Tumor necrosis factor (TNF) was up-regulated 1.9-2.4 fold by IL-20.
2. Placental growth factors 1 & 2 (PLGF) were up-regulated 1.9-2.0 fold by IL-20.
3. Coagulating factor II receptor was up-regulated 2.0-2.5 fold by IL-20.
4. Calcitonin receptor was up-regulated 2.2-2.3 fold by IL-20.
5. TNF-inducible hyaluronate-binding protein TSG-6 was up-regulated 2.1-2.2 fold by IL-20.
6. Vascular endothelial growth factor (VEGF) receptor-1 precursor, tyrosine-protein kinase receptor (FLT-1) (SFLT) was up-regulated 2.1-2.7 fold by IL-20.
7. MRP-8 (calcium binding protein in macrophages MIF-related) was up-regulated 2.9-4.1 fold by IL-20.
8. MRP-14 (calcium binding protein in macrophages MIF-related) was up-regulated 3.0-3.8 fold by IL-20.

9. Relaxin H2 was up-regulated 3.14 fold by IL-20.
10. Transforming growth factor beta (TGF β) receptor III 300 kDa was up-regulated 2.4-3.6 fold by IL-20.

5 Genes Showing Synergy with IL-20 + IL-1 Treatment

1. Bone morphogenic protein 2a was up-regulated 1.8 fold with IL-20 treatment alone, 2.5 fold with IL-1 treatment alone, and 8.2 fold with both IL-20 and IL-1 treatment together.
2. MRP-8 was up-regulated 2.9 fold with IL-20 treatment alone, 10.7 fold with IL-1 treatment alone and 18.0 fold with both IL-20 and IL-1 treatment together.
3. Erythroid differentiation protein (EDF) was up-regulated 1.9 fold with IL-20 treatment alone, 9.7 fold with IL-1 treatment alone and 19.0 fold with both IL-20 and IL-1 treatment together.
4. MRP-14 (calcium binding protein in macrophages, MIF related) was up-regulated 3.0 fold with IL-20 treatment alone, 12.2 fold with IL-1 treatment alone and 20.3 fold with both IL-20 and IL-1 treatment together.
5. Heparin-binding EGF-like growth factor was up-regulated 2.0 fold with IL-20 treatment alone, 14 fold with IL-1 treatment alone and 25.0 fold with both IL-20 and IL-1 treatment together.
6. Beta-thromboglobulin-like protein was up-regulated 1.5 fold with IL-20 treatment alone, 15 fold with IL-1 treatment alone and 27 fold with both IL-20 and IL-1 treatment together.
7. Brain-derived neurotrophic factor (BDNF) was up-regulated 1.7 fold with IL-20 treatment alone, 25 fold with IL-1 treatment alone and 48 fold with both IL-20 and IL-1 treatment together.
8. Monocyte chemotactic and activating factor MCAF was up-regulated 1.3 fold with IL-20 treatment alone, 32 fold with IL-1 treatment alone and 56 fold with both IL-20 and IL-1 treatment together.

Example 5

IL-20 Transgenic Phenotype

Both human and mouse IL-20 were overexpressed in transgenic mice using a variety of promoters. The liver-specific mouse albumin promoter, directing
5 expression of human IL-20, was used initially in an attempt to achieve circulating levels of protein. Subsequent studies were conducted using the keratin 14 (K14) promoter, which primarily targets expression to the epidermis and other stratified squamous epithelia; the mouse metallothionein-1 promoter, which gives a broad expression pattern; and the E μ LCK promoter, which drives expression in cells of the lymphoid
10 lineage. Similar results were obtained in all four cases, possibly because these promoters all give rise to circulating levels of IL-20.

In all cases, transgenic pups expressing the IL-20 transgene were smaller than non-transgenic littermates, had a shiny appearance with tight, wrinkled skin and died within the first few days after birth. Pups had milk in their stomachs indicating
15 that they were able to suckle. These mice had swollen extremities, tail, nostril and mouth regions and had difficulty moving. In addition, the mice were frail, lacked visible adipose tissue and had delayed ear and toe development. Low expression levels in liver (less than 100 mRNA molecules/cell) were sufficient for both the neonatal lethality and skin abnormalities. Transgenic mice without a visible phenotype either
20 did not express the transgene, did not express it at detectable levels, or were mosaic.

Histologic analysis of the skin of the IL-20 transgenic mice showed a thickened epidermis, hyperkeratosis and a compact stratum corneum compared to non-transgenic littermates. Serocellular crusts (scabs) were observed occasionally. Electron
microscopic (EM) analysis of skin from transgenic mice showed intramitochondrial
25 lipoid inclusions, mottled keratohyaline granules, and relatively few tonofilaments similar to that observed in human psoriatic skin and in mouse skin disease models. In addition, many of the transgenic mice had apoptotic thymic lymphocytes. No other abnormalities were detected by histopathological analysis. These histological and EM results support and extend the observed gross skin alterations.

Example 6

Experimental Procedures:

Luciferase Assay

Luciferase reporter assays were performed using BHK cells stably
5 transfected with IL-22R and IL-20RB and utilizing the STAT-driven luciferase reporter
cassette. Cells were switched to serum-free medium overnight prior to treatment with
serial dilutions of IL-19, IL-20, and MDA-7 in the presence or absence of IL-20RA/IL-
20RB soluble receptor. Cells were lysed and read on the Berthold MicroLumat Plus for
luciferase reporter activity.

BaF3 Proliferation Assay

Proliferation assays used Alamar Blue, which was added to the cells 24 h prior to being read on a *f*max plate reader (Molecular Devices, Sunnyvale, CA) using the Softmax Pro program.

RT-PCR Analysis on Human Tissues

RT-PCR was performed on a human Rapid-Scan gene expression panel (Origene Technologies, Inc.) using primers 5'-ccccagacacggtctacagcat-3' and 5'-gggtcaggccgaagaactcatat-3' to amplify a 440 bp fragment of human *IL22R*. PCR conditions are 94°C for 2 min., followed by 35 cycles of 94°C for 15 sec., 72°C for 90 sec, then a final extension step of 72°C for 2 min.

Results:

Since IL-22R is a shared alpha subunit, we evaluated an Origene panel for the expression of *IL-22R* mRNA. The highest *IL-22R* expression was detected in the pancreas, with skin and lung also exhibiting strong expression.

To test the possibility that the IL-20 subfamily might activate other Class II receptor combinations, BaF3 cells were stably transfected with Class II receptor subunits alone or in combinations and treated with the ligands. The assay shows that both IL-20 and MDA-7 stimulate an additional receptor complex consisting of consisting of IL-22R/IL-20RB (Table 1). We next wanted to determine which soluble receptors could block ligand activity. As mentioned above, IL-20RA/IL-20RB heterodimeric soluble receptor blocked proliferation stimulated by IL-20, IL-19, and MDA-7. In addition, IL-20RB soluble receptor alone blocked the activity of IL-19 and MDA-7, but not IL-20.

Since IL-22R is a shared alpha subunit, we evaluated an Origene panel for the expression of *IL-22R* mRNA (Table 2). The highest expression was detected in the pancreas, with skin and lung also exhibiting strong expression. Thus, overall *IL-20Rα*, *IL-20Rβ*, and *IL-22R* all have robust expression in skin and lung.

Since *IL-20R α* , *IL-20R β* , and *IL-22R* are all expressed in the lung, we used *in situ* hybridization to evaluate whether the same cell types expressed all three receptors. Figure 3 shows that both epithelial cells as well as immune infiltrates exhibit positive staining in lung sections tested for mRNA expression by *in situ* hybridization.

SEQUENCE LISTING

<110> Chandrasekher, Yasmin A.
 Novak, Julia E.
 Foster, Donald C.
 Wenfeng, Xu
 Jaspers Stephen R.

<120> Soluble Heterodimeric Cytokine Receptor

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

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 Leu Leu Gln His Val Lys Phe Gln Ser Ser Asn Phe Glu Asn Ile Leu
 25 30 35

 acg tgg gac agc ggg cca gag ggc acc cca gac acg gtc tac agc atc 198
 Thr Trp Asp Ser Gly Pro Glu Gly Thr Pro Asp Thr Val Tyr Ser Ile
 40 45 50 55

 gag tat aag acg tac gga gag agg gac tgg gtg gca aag aag ggc tgt 246
 Glu Tyr Lys Thr Tyr Gly Glu Arg Asp Trp Val Ala Lys Lys Gly Cys
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 Gln Arg Ile Thr Arg Lys Ser Cys Asn Leu Thr Val Glu Thr Gly Asn
 75 80 85

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 Leu Thr Glu Leu Tyr Tyr Ala Arg Val Thr Ala Val Ser Ala Gly Gly
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 Arg Ser Ala Thr Lys Met Thr Asp Arg Phe Ser Ser Leu Gln His Thr
 105 110 115

 acc ctc aag cca cct gat gtg acc tgt atc tcc aaa gtg aga tcg att 438
 Thr Leu Lys Pro Pro Asp Val Thr Cys Ile Ser Lys Val Arg Ser Ile
 120 125 130 135

 cag atg att gtt cat cct acc ccc acg cca atc cgt gca ggc gat ggc 486

Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro	Ile	Arg	Ala	Gly	Asp	Gly	
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His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	His	Asp	Leu	Phe	Tyr	His	Leu	
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gag	ctc	cag	gtc	aac	cgc	acc	tac	caa	atg	cac	ctt	gga	ggg	aag	cag	582
Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	Met	His	Leu	Gly	Gly	Lys	Gln	
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Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr	Pro	Asp	Thr	Glu	Phe	Leu	Gly	
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acc	atc	atg	att	tgc	gtt	ccc	acc	tgg	gcc	aag	gag	agt	gcc	ccc	tac	678
Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp	Ala	Lys	Glu	Ser	Ala	Pro	Tyr	
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atg	tgc	cga	gtg	aag	aca	ctg	cca	gac	cgg	aca	tgg	acc	tac	tcc	ttc	726
Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp	Arg	Thr	Trp	Thr	Tyr	Ser	Phe	
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tcc	gga	gcc	ttc	ctg	ttc	tcc	atg	ggc	ttc	ctc	gtc	gca	gta	ctc	tgc	774
Ser	Gly	Ala	Phe	Leu	Phe	Ser	Met	Gly	Phe	Leu	Val	Ala	Val	Leu	Cys	
			235					240					245			
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Tyr	Leu	Ser	Tyr	Arg	Tyr	Val	Thr	Lys	Pro	Pro	Ala	Pro	Pro	Asn	Ser	
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ctg	aac	gtc	cag	cga	gtc	ctg	act	ttc	cag	ccg	ctg	cgc	ttc	atc	cag	870
Leu	Asn	Val	Gln	Arg	Val	Leu	Thr	Phe	Gln	Pro	Leu	Arg	Phe	Ile	Gln	
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gag	cac	gtc	ctg	atc	cct	gtc	ttt	gac	ctc	agc	ggc	ccc	agc	agt	ctg	918
Glu	His	Val	Leu	Ile	Pro	Val	Phe	Asp	Leu	Ser	Gly	Pro	Ser	Ser	Leu	
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gcc	cag	cct	gtc	cag	tac	tcc	cag	atc	agg	gtg	tct	gga	ccc	agg	gag	966
Ala	Gln	Pro	Val	Gln	Tyr	Ser	Gln	Ile	Arg	Val	Ser	Gly	Pro	Arg	Glu	
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ccc	gca	gga	gct	cca	cag	cgg	cat	agc	ctg	tcc	gag	atc	acc	tac	tta	1014
Pro	Ala	Gly	Ala	Pro	Gln	Arg	His	Ser	Leu	Ser	Glu	Ile	Thr	Tyr	Leu	
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ggg	cag	cca	gac	atc	tcc	atc	ctc	cag	ccc	tcc	aac	gtg	cca	cct	ccc	1062
Gly	Gln	Pro	Asp	Ile	Ser	Ile	Leu	Gln	Pro	Ser	Asn	Val	Pro	Pro	Pro	
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cag	atc	ctc	tcc	cca	ctg	tcc	tat	gcc	cca	aac	gct	gcc	cct	gag	gtc	1110
Gln	Ile	Leu	Ser	Pro	Leu	Ser	Tyr	Ala	Pro	Asn	Ala	Ala	Pro	Glu	Val	
	345					350					355					
ggg	ccc	cca	tcc	tat	gca	cct	cag	gtg	acc	ccc	gaa	gct	caa	ttc	cca	1158
Gly	Pro	Pro	Ser	Tyr	Ala	Pro	Gln	Val	Thr	Pro	Glu	Ala	Gln	Phe	Pro	
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ttc	tac	gcc	cca	cag	gcc	atc	tct	aag	gtc	cag	cct	tcc	tcc	tat	gcc	1206
Phe	Tyr	Ala	Pro	Gln	Ala	Ile	Ser	Lys	Val	Gln	Pro	Ser	Ser	Tyr	Ala	
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cct Pro	caa Gln	gcc Ala	act Thr 395	ccg Pro	gac Asp	agc Ser	tgg Trp	cct Pro 400	ccc Pro	tcc Ser	tat Tyr	ggg Gly	gta Val 405	tgc Cys	atg Met	1254	
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ctt Leu	gtg Val	tgt Cys	ccc Pro	aag Lys 540	gat Asp	gaa Glu	gcc Ala	aag Lys	agc Ser 545	cca Pro	gcc Ala	cct Pro	gag Glu 550	acc Thr	tca Ser	1686	
gac Asp	ctg Leu	gag Glu	cag Gln 555	ccc Pro	aca Thr	gaa Glu	ctg Leu	gat Asp	tct Ser	ctt Leu	ttc Phe	aga Arg	ggc Gly 565	ctg Leu	gcc Ala	1734	
ctg Leu	act Thr	gtg Val	cag Gln	tgg Trp	gag Glu	tcc Ser	tgaggggaat gggaaaggct tggtgcttcc									1785	
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Ser	Asn	Phe	Glu	Asn	Ile	Leu	Thr	Trp	Asp	Ser	Gly	Pro	Glu	Gly	Thr	
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Pro	Asp	Thr	Val	Tyr	Ser	Ile	Glu	Tyr	Lys	Thr	Tyr	Gly	Glu	Arg	Asp	
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Trp	Val	Ala	Lys	Lys	Gly	Cys	Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn	
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Leu	Thr	Val	Glu	Thr	Gly	Asn	Leu	Thr	Glu	Leu	Tyr	Tyr	Ala	Arg	Val	
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Thr	Ala	Val	Ser	Ala	Gly	Gly	Arg	Ser	Ala	Thr	Lys	Met	Thr	Asp	Arg	
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Phe	Ser	Ser	Leu	Gln	His	Thr	Thr	Leu	Lys	Pro	Pro	Asp	Val	Thr	Cys	
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Pro	Ile	Arg	Ala	Gly	Asp	Gly	His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	
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His	Asp	Leu	Phe	Tyr	His	Leu	Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	
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Met	His	Leu	Gly	Gly	Lys	Gln	Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr	
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Arg	Thr	Trp	Thr	Tyr	Ser	Phe	Ser	Gly	Ala	Phe	Leu	Phe	Ser	Met	Gly	
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Phe	Leu	Val	Ala	Val	Leu	Cys	Tyr	Leu	Ser	Tyr	Arg	Tyr	Val	Thr	Lys	
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			260					265						270		
Gln	Pro	Leu	Arg	Phe	Ile	Gln	Glu	His	Val	Leu	Ile	Pro	Val	Phe	Asp	
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	290					295					300					
Arg	Val	Ser	Gly	Pro	Arg	Glu	Pro	Ala	Gly	Ala	Pro	Gln	Arg	His	Ser	
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Leu	Ser	Glu	Ile	Thr	Tyr	Leu	Gly	Gln	Pro	Asp	Ile	Ser	Ile	Leu	Gln	
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Pro	Ser	Asn	Val	Pro	Pro	Pro	Gln	Ile	Leu	Ser	Pro	Leu	Ser	Tyr	Ala	
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Pro	Asn	Ala	Ala	Pro	Glu	Val	Gly	Pro	Pro	Ser	Tyr	Ala	Pro	Gln	Val	
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Thr	Pro	Glu	Ala	Gln	Phe	Pro	Phe	Tyr	Ala	Pro	Gln	Ala	Ile	Ser	Lys	
	370					375					380					
Val	Gln	Pro	Ser	Ser	Tyr	Ala	Pro	Gln	Ala	Thr	Pro	Asp	Ser	Trp	Pro	
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Gly	Thr	Leu	Ser	Ser	Pro	Lys	His	Leu	Arg	Pro	Lys	Gly	Gln	Leu	Gln
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Lys	Glu	Pro	Pro	Ala	Gly	Ser	Cys	Met	Leu	Gly	Gly	Leu	Ser	Leu	Gln
		435					440					445			
Glu	Val	Thr	Ser	Leu	Ala	Met	Glu	Glu	Ser	Gln	Glu	Ala	Lys	Ser	Leu
	450					455					460				
His	Gln	Pro	Leu	Gly	Ile	Cys	Thr	Asp	Arg	Thr	Ser	Asp	Pro	Asn	Val
465				470						475					480
Leu	His	Ser	Gly	Glu	Glu	Gly	Thr	Pro	Gln	Tyr	Leu	Lys	Gly	Gln	Leu
			485						490					495	
Pro	Leu	Leu	Ser	Ser	Val	Gln	Ile	Glu	Gly	His	Pro	Met	Ser	Leu	Pro
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Leu	Gln	Pro	Pro	Ser	Gly	Pro	Cys	Ser	Pro	Ser	Asp	Gln	Gly	Pro	Ser
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Pro	Trp	Gly	Leu	Leu	Glu	Ser	Leu	Val	Cys	Pro	Lys	Asp	Glu	Ala	Lys
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Ser	Pro	Ala	Pro	Glu	Thr	Ser	Asp	Leu	Glu	Gln	Pro	Thr	Glu	Leu	Asp
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Ser	Asn	Phe	Glu	Asn	Ile	Leu	Thr	Trp	Asp	Ser	Gly	Pro	Glu	Gly	Thr
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Pro	Asp	Thr	Val	Tyr	Ser	Ile	Glu	Tyr	Lys	Thr	Tyr	Gly	Glu	Arg	Asp
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Trp	Val	Ala	Lys	Lys	Gly	Cys	Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn
65				70						75					80
Leu	Thr	Val	Glu	Thr	Gly	Asn	Leu	Thr	Glu	Leu	Tyr	Tyr	Ala	Arg	Val
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Thr	Ala	Val	Ser	Ala	Gly	Gly	Arg	Ser	Ala	Thr	Lys	Met	Thr	Asp	Arg
			100					105					110		
Phe	Ser	Ser	Leu	Gln	His	Thr	Thr	Leu	Lys	Pro	Pro	Asp	Val	Thr	Cys
		115					120					125			
Ile	Ser	Lys	Val	Arg	Ser	Ile	Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr
	130					135					140				
Pro	Ile	Arg	Ala	Gly	Asp	Gly	His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe
145				150						155					160
His	Asp	Leu	Phe	Tyr	His	Leu	Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln
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Met	His	Leu	Gly	Gly	Lys	Gln	Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr
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Pro	Asp	Thr	Glu	Phe	Leu	Gly	Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp
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Ala	Lys	Glu	Ser	Ala	Pro	Tyr	Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp
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10

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 35 40 45
 Val Ala Lys Lys Gly Cys Gln Arg Ile Thr Arg Lys Ser Cys Asn Leu
 50 55 60
 Thr Val Glu Thr Gly Asn Leu Thr Glu Leu Tyr Tyr Ala Arg Val Thr
 65 70 75 80
 Ala Val Ser Ala Gly Gly Arg Ser Ala Thr Lys Met Thr Asp Arg Phe
 85 90 95
 Ser Ser Leu Gln His Thr Thr Leu Lys Pro Pro Asp Val Thr Cys Ile
 100 105 110
 Ser Lys Val Arg Ser Ile Gln Met Ile Val His Pro Thr Pro Thr Pro
 115 120 125
 Ile Arg Ala Gly Asp Gly His Arg Leu Thr Leu Glu Asp Ile Phe His
 130 135 140
 Asp Leu Phe Tyr His Leu Glu Leu Gln Val Asn Arg Thr Tyr Gln Met
 145 150 155 160
 His Leu Gly Gly Lys Gln Arg Glu Tyr Glu Phe Phe Gly Leu Thr Pro
 165 170 175
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 Thr Trp Thr
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 Trp Thr Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu
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 Leu Thr Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val
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 ctc tca acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg 194
 Leu Ser Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala
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12

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 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80
 His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
 85 90 95
 Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
 100 105 110
 Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
 115 120 125
 His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
 130 135 140
 Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
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 Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
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 Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
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 Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe Val Trp Lys
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 Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val Val Leu Pro
 260 265 270
 Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Lys Leu Ile Ser Cys Arg
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 35 40 45
 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60

13

Gly	Pro	Glu	Cys	Asp	Val	Thr	Asp	Asp	Ile	Thr	Ala	Thr	Val	Pro	Tyr
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Ile	Leu	Lys	His	Pro	Phe	Asn	Arg	Asn	Ser	Thr	Ile	Leu	Thr	Arg	Pro
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Gly	Met	Glu	Ile	Thr	Lys	Asp	Gly	Phe	His	Leu	Val	Ile	Glu	Leu	Glu
		115					120					125			
Asp	Leu	Gly	Pro	Gln	Phe	Glu	Phe	Leu	Val	Ala	Tyr	Trp	Arg	Arg	Glu
	130					135					140				
Pro	Gly	Ala	Glu	Glu	His	Val	Lys	Met	Val	Arg	Ser	Gly	Gly	Ile	Pro
145					150					155					160
Val	His	Leu	Glu	Thr	Met	Glu	Pro	Gly	Ala	Ala	Tyr	Cys	Val	Lys	Ala
				165					170					175	
Gln	Thr	Phe	Val	Lys	Ala	Ile	Gly	Arg	Tyr	Ser	Ala	Phe	Ser	Gln	Thr
			180					185					190		
Glu	Cys	Val	Glu	Val	Gln	Gly	Glu	Ala	Ile	Pro					
		195					200								

<210> 17
 <211> 201
 <212> PRT
 <213> Homo sapiens

<400> 17

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

<210> 18
 <211> 201
 <212> PRT
 <213> Homo sapiens

<400> 18

Asp	Glu	Val	Ala	Ile	Leu	Pro	Ala	Pro	Gln	Asn	Leu	Ser	Val	Leu	Ser
1				5					10					15	
Thr	Asn	Met	Lys	His	Leu	Leu	Met	Trp	Ser	Pro	Val	Ile	Ala	Pro	Gly
			20					25					30		

14

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

<210> 19
 <211> 196
 <212> PRT
 <213> Homo sapiens

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

<210> 20
 <211> 203
 <212> PRT
 <213> Homo sapiens

<400> 20

15

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

<210> 21

<211> 196

<212> PRT

<213> Homo sapiens

<400> 21

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

<210> 22

<211> 1382

16

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (132)...(1034)

<400> 22

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agatggctga	gatggacaga	atgctttatt	ttggaaagaa	acaatgttct	aggtcaaact		120
gagtctacca	a atg cag act ttc aca atg gtt cta gaa gaa atc tgg aca						170
	Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr						
	1	5		10			
agt ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca							218
Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr							
	15	20		25			
gat gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca							266
Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser							
	30	35		40			45
acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga							314
Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly							
	50		55				60
gaa aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg							362
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu							
	65		70				75
tac acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa							410
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu							
	80		85				90
ggt cct gag tgt gat gtc act gat gac atc acg gcc act gtg cca tac							458
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr							
	95		100				105
aac ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc							506
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser							
	110		115				125
atc ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc cga cct							554
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro							
	130		135				140
ggg atg gag atc ccc aaa cat ggc ttc cac ctg gtt att gag ctg gag							602
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu							
	145		150				155
gac ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg acg agg gag							650
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu							
	160		165				170
cct ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca							698
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro							
	175		180				185
gtg cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc							746
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala							
	190		195				205

17

cag aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca	794
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr	
210 215 220	
gaa tgt gtg gag gtg caa gga gag gcc att ccc ctg gta ctg gcc ctg	842
Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu	
225 230 235	
ttt gcc ttt gtt ggc ttc atg ctg atc ctt gtg gtc gtg cca ctg ttc	890
Phe Ala Phe Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe	
240 245 250	
gtc tgg aaa atg ggc cgg ctg ctc cag tac tcc tgt tgc ccc gtg gtg	938
Val Trp Lys Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val	
255 260 265	
gtc ctc cca gac acc ttg aaa ata acc aat tca ccc cag gtt aat cag	986
Val Leu Pro Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Val Asn Gln	
270 275 280 285	
ctg cag aag gga gga ggt gga tgc ctg tgc cac ggc tgt gat gtc tcc	1034
Leu Gln Lys Gly Gly Gly Gly Cys Leu Cys His Gly Cys Asp Val Ser	
290 295 300	
tgaggaactc ctcagggcct ggatctcata tcaggtttgc ggaagggccc aggtgaagcc	1094
gagaacctgg tctgcatgac atggaaacca tgaggggaca agttgtgttt ctgttttccg	1154
ccacggacaa gggatgagag aagtaggaag agcctgttgt ctacaagtct agaagcaacc	1214
atcagaggca ggggtggtttg tctaacagaa caactgactg aggctatggg ggttgtgacc	1274
tctagacttt gggcttccac ttgcttggct gagcaaccct gggaaaagtg acttcatccc	1334
ttcgggtccca agtttttctca tctgtaatgg gggatcccta caaaactg	1382

<210> 23

<211> 301

<212> PRT

<213> Homo sapiens

<400> 23

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

18

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

<210> 24

<211> 1764

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (34) ... (1752)

<400> 24

tagaggccaa	gggagggctc	tgtgccagcc	ccg	atg	agg	acg	ctg	ctg	acc	atc		54
				Met	Arg	Thr	Leu	Leu	Thr	Ile		
				1				5				

ttg	act	gtg	gga	tcc	ctg	gct	gct	cac	gcc	cct	gag	gac	ccc	tcg	gat	102
Leu	Thr	Val	Gly	Ser	Leu	Ala	Ala	His	Ala	Pro	Glu	Asp	Pro	Ser	Asp	
		10				15					20					

ctg	ctc	cag	cac	gtg	aaa	ttc	cag	tcc	agc	aac	ttt	gaa	aac	atc	ctg	150
Leu	Leu	Gln	His	Val	Lys	Phe	Gln	Ser	Ser	Asn	Phe	Glu	Asn	Ile	Leu	
	25				30					35						

acg	tgg	gac	agc	ggg	cca	gag	ggc	acc	cca	gac	acg	gtc	tac	agc	atc	198
Thr	Trp	Asp	Ser	Gly	Pro	Glu	Gly	Thr	Pro	Asp	Thr	Val	Tyr	Ser	Ile	
	40			45				50						55		

gag	tat	aag	acg	tac	gga	gag	agg	gac	tgg	gtg	gca	aag	aag	ggc	tgt	246
Glu	Tyr	Lys	Thr	Tyr	Gly	Glu	Arg	Asp	Trp	Val	Ala	Lys	Lys	Gly	Cys	
			60					65						70		

cag	cgg	atc	acc	cgg	aag	tcc	tgc	aac	ctg	acg	gtg	gag	acg	ggc	aac	294
Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn	Leu	Thr	Val	Glu	Thr	Gly	Asn	
		75				80						85				

ctc	acg	gag	ctc	tac	tat	gcc	agg	gtc	acc	gct	gtc	agt	gcg	gga	ggc	342
Leu	Thr	Glu	Leu	Tyr	Tyr	Ala	Arg	Val	Thr	Ala	Val	Ser	Ala	Gly	Gly	
		90				95						100				

cgg	tca	gcc	acc	aag	atg	act	gac	agg	ttc	agc	tct	ctg	cag	cac	act	390
Arg	Ser	Ala	Thr	Lys	Met	Thr	Asp	Arg	Phe	Ser	Ser	Leu	Gln	His	Thr	
	105					110					115					

acc	ctc	aag	cca	cct	gat	gtg	acc	tgt	atc	tcc	aaa	gtg	aga	tcg	att	438
Thr	Leu	Lys	Pro	Pro	Asp	Val	Thr	Cys	Ile	Ser	Lys	Val	Arg	Ser	Ile	
	120				125					130					135	

cag	atg	att	gtt	cat	cct	acc	ccc	acg	cca	atc	cgt	gca	ggc	gat	ggc	486
Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro	Ile	Arg	Ala	Gly	Asp	Gly	

19

140				145				150								
cac	cgg	cta	acc	ctg	gaa	gac	atc	ttc	cat	gac	ctg	ttc	tac	cac	tta	534
His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	His	Asp	Leu	Phe	Tyr	His	Leu	
			155					160					165			
gag	ctc	cag	gtc	aac	cgc	acc	tac	caa	atg	cac	ctt	gga	ggg	aag	cag	582
Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	Met	His	Leu	Gly	Gly	Lys	Gln	
		170					175					180				
aga	gaa	tat	gag	ttc	ttc	ggc	ctg	acc	cct	gac	aca	gag	ttc	ctt	ggc	630
Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr	Pro	Asp	Thr	Glu	Phe	Leu	Gly	
	185					190					195					
acc	atc	atg	att	tgc	gtt	ccc	acc	tgg	gcc	aag	gag	agt	gcc	ccc	tac	678
Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp	Ala	Lys	Glu	Ser	Ala	Pro	Tyr	
200				205						210					215	
atg	tgc	cga	gtg	aag	aca	ctg	cca	gac	cgg	aca	tgg	acc	ggt	gga	ggc	726
Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp	Arg	Thr	Trp	Thr	Gly	Gly	Gly	
				220					225					230		
ggt	tca	ggc	gga	ggt	ggc	tct	ggc	ggt	ggc	gga	tcg	gcc	tcc	acc	aag	774
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Ser	Thr	Lys	
			235					240					245			
ggc	cca	tcg	gtc	ttc	ccc	ctg	gca	ccc	tcc	tcc	aag	agc	acc	tct	ggg	822
Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	
		250					255					260				
ggc	aca	gcg	gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tac	ttc	ccc	gaa	ccg	870
Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	
	265					270					275					
gtg	acg	gtg	tcg	tgg	aac	tca	ggc	gcc	ctg	acc	agc	ggc	gtg	cac	acc	918
Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	
280					285					290					295	
ttc	ccg	gct	gtc	cta	cag	tcc	tca	gga	ctc	tac	tcc	ctc	agc	agc	gtg	966
Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	
				300					305					310		
gtg	acc	gtg	ccc	tcc	agc	agc	ttg	ggc	acc	cag	acc	tac	atc	tgc	aac	1014
Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	
			315					320					325			
gtg	aat	cac	aag	ccc	agc	aac	acc	aag	gtg	gac	aag	aaa	gtt	gag	ccc	1062
Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	
		330					335					340				
aaa	tct	tgt	gac	aaa	act	cac	aca	tgc	cca	ccg	tgc	cca	gca	cct	gaa	1110
Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	
	345					350					355					
gcc	gag	ggg	gca	ccg	tca	gtc	ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	1158
Ala	Glu	Gly	Ala	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	
360					365					370					375	
acc	ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	aca	tgc	gtg	gtg	gtg	gac	1206
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	
				380					385					390		

20

gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc	1254
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly	
395 400 405	
gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac	1302
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn	
410 415 420	
agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg	1350
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp	
425 430 435	
ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca	1398
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro	
440 445 450 455	
tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa	1446
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu	
460 465 470	
cca cag gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac	1494
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn	
475 480 485	
cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc	1542
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile	
490 495 500	
gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc	1590
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr	
505 510 515	
acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag	1638
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys	
520 525 530 535	
ctc acc gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc	1686
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys	
540 545 550	
tcc gtg atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc	1734
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu	
555 560 565	
tcc ctg tct ccg ggt aaa taatctagat ct	1764
Ser Leu Ser Pro Gly Lys	
570	

<210> 25

<211> 573

<212> PRT

<213> Homo sapiens

<400> 25

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

50	55	60
Trp Val Ala Lys Lys Gly Cys Gln Arg Ile Thr Arg Lys Ser Cys Asn		
65	70	75
Leu Thr Val Glu Thr Gly Asn Leu Thr Glu Leu Tyr Tyr Ala Arg Val		
	85	90
Thr Ala Val Ser Ala Gly Gly Arg Ser Ala Thr Lys Met Thr Asp Arg		
	100	105
Phe Ser Ser Leu Gln His Thr Thr Leu Lys Pro Pro Asp Val Thr Cys		
	115	120
Ile Ser Lys Val Arg Ser Ile Gln Met Ile Val His Pro Thr Pro Thr		
	130	135
Pro Ile Arg Ala Gly Asp Gly His Arg Leu Thr Leu Glu Asp Ile Phe		
145	150	155
His Asp Leu Phe Tyr His Leu Glu Leu Gln Val Asn Arg Thr Tyr Gln		
	165	170
Met His Leu Gly Gly Lys Gln Arg Glu Tyr Glu Phe Phe Gly Leu Thr		
	180	185
Pro Asp Thr Glu Phe Leu Gly Thr Ile Met Ile Cys Val Pro Thr Trp		
	195	200
Ala Lys Glu Ser Ala Pro Tyr Met Cys Arg Val Lys Thr Leu Pro Asp		
	210	215
Arg Thr Trp Thr Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly		
225	230	235
Gly Gly Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro		
	245	250
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val		
	260	265
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala		
	275	280
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly		
	290	295
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly		
305	310	315
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys		
	325	330
Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys		
	340	345
Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu		
	355	360
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu		
	370	375
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys		
385	390	395
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys		
	405	410
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu		
	420	425
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys		
	435	440
Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys		
	450	455
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser		
465	470	475
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys		
	485	490
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln		
	500	505
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly		
	515	520
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln		
	530	535
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn		
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545          550          555          560
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
          565          570

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<210> 26
<211> 556
<212> PRT
<213> Homo sapiens
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Asn	Phe	Glu	Asn 20	Ile	Leu	Thr	Trp	Asp 25	Ser	Gly	Pro	Glu	Gly 30	Thr	Pro	
Asp	Thr	Val 35	Tyr	Ser	Ile	Glu	Tyr 40	Lys	Thr	Tyr	Gly	Glu 45	Arg	Asp	Trp	
Val 50	Ala	Lys	Lys	Gly	Cys	Gln 55	Arg	Ile	Thr	Arg	Lys 60	Ser	Cys	Asn	Leu	
Thr 65	Val	Glu	Thr	Gly	Asn 70	Leu	Thr	Glu	Leu	Tyr 75	Tyr	Ala	Arg	Val	Thr 80	
Ala	Val	Ser	Ala	Gly 85	Gly	Arg	Ser	Ala	Thr 90	Lys	Met	Thr	Asp	Arg 95	Phe	
Ser	Ser	Leu	Gln 100	His	Thr	Thr	Leu	Lys 105	Pro	Pro	Asp	Val	Thr 110	Cys	Ile	
Ser	Lys	Val 115	Arg	Ser	Ile	Gln	Met 120	Ile	Val	His	Pro	Thr 125	Pro	Thr	Pro	
Ile 130	Arg	Ala	Gly	Asp	Gly	His 135	Arg	Leu	Thr	Leu	Glu 140	Asp	Ile	Phe	His	
Asp 145	Leu	Phe	Tyr	His 150	Leu	Glu	Leu	Gln	Val	Asn 155	Arg	Thr	Tyr	Gln	Met 160	
His	Leu	Gly	Gly 165	Lys	Gln	Arg	Glu	Tyr 170	Glu	Phe	Phe	Gly	Leu	Thr 175	Pro	
Asp	Thr	Glu	Phe 180	Leu	Gly	Thr	Ile	Met 185	Ile	Cys	Val	Pro	Thr 190	Trp	Ala	
Lys	Glu	Ser 195	Ala	Pro	Tyr	Met	Cys 200	Arg	Val	Lys	Thr	Leu 205	Pro	Asp	Arg	
Thr	Trp 210	Thr	Gly	Gly	Gly	Gly 215	Ser	Gly	Gly	Gly	Gly 220	Ser	Gly	Gly	Gly	
Gly 225	Ser	Ala	Ser	Thr	Lys 230	Gly	Pro	Ser	Val	Phe 235	Pro	Leu	Ala	Pro	Ser 240	
Ser	Lys	Ser	Thr 245	Ser	Gly	Gly	Thr	Ala	Ala 250	Leu	Gly	Cys	Leu	Val 255	Lys	
Asp	Tyr	Phe	Pro 260	Glu	Pro	Val	Thr	Val 265	Ser	Trp	Asn	Ser	Gly 270	Ala	Leu	
Thr	Ser	Gly 275	Val	His	Thr	Phe	Pro 280	Ala	Val	Leu	Gln	Ser	Ser 285	Gly	Leu	
Tyr	Ser 290	Leu	Ser	Ser	Val	Val 295	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	
Gln 305	Thr	Tyr	Ile	Cys 310	Asn	Val	Asn	His	Lys	Pro 315	Ser	Asn	Thr	Lys	Val 320	
Asp	Lys	Lys	Val 325	Glu	Pro	Lys	Ser	Cys 330	Asp	Lys	Thr	His	Thr	Cys 335	Pro	
Pro	Cys	Pro	Ala 340	Pro	Glu	Ala	Glu	Gly 345	Ala	Pro	Ser	Val	Phe	Leu	Phe	
Pro	Pro	Lys 355	Pro	Lys	Asp	Thr	Leu 360	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	
Thr	Cys 370	Val	Val	Val	Asp	Val 375	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	
Asn 385	Trp	Tyr	Val	Asp	Gly 390	Val	Glu	Val	His	Asn 395	Ala	Lys	Thr	Lys	Pro	
Arg	Glu	Glu	Gln 405	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	

Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
			420					425					430		
Ser	Asn	Lys	Ala	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala
		435					440					445			
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg
	450				455						460				
Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly
465					470					475					480
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro
				485					490					495	
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser
			500					505					510		
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln
		515					520					525			
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His
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Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys				
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<210> 27
<211> 1081
<212> DNA
<213> Homo sapiens
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	Met	Gln	Thr	Phe	Thr	Met	Val	Leu	Glu	Glu	Ile	Trp	Thr	Ser		
	1				5						10					
ctt	ttc	atg	tgg	ttt	ttc	tac	gca	ttg	att	cca	tgt	ttg	ctc	aca	gat	98
Leu	Phe	Met	Trp	Phe	Phe	Tyr	Ala	Leu	Ile	Pro	Cys	Leu	Leu	Thr	Asp	
15					20					25					30	
gaa	gtg	gcc	att	ctg	cct	gcc	cct	cag	aac	ctc	tct	gta	ctc	tca	acc	146
Glu	Val	Ala	Ile	Leu	Pro	Ala	Pro	Gln	Asn	Leu	Ser	Val	Leu	Ser	Thr	
				35					40					45		
aac	atg	aag	cat	ctc	ttg	atg	tgg	agc	cca	gtg	atc	gcg	cct	gga	gaa	194
Asn	Met	Lys	His	Leu	Leu	Met	Trp	Ser	Pro	Val	Ile	Ala	Pro	Gly	Glu	
			50					55					60			
aca	gtg	tac	tat	tct	gtc	gaa	tac	cag	ggg	gag	tac	gag	agc	ctg	tac	242
Thr	Val	Tyr	Tyr	Ser	Val	Glu	Tyr	Gln	Gly	Glu	Tyr	Glu	Ser	Leu	Tyr	
		65					70					75				
acg	agc	cac	atc	tgg	atc	ccc	agc	agc	tgg	tgc	tca	ctc	act	gaa	ggc	290
Thr	Ser	His	Ile	Trp	Ile	Pro	Ser	Ser	Trp	Cys	Ser	Leu	Thr	Glu	Gly	
	80					85					90					
cct	gag	tgt	gat	gtc	act	gat	gac	atc	acg	gcc	act	gtg	cca	tac	aac	338
Pro	Glu	Cys	Asp	Val	Thr	Asp	Asp	Ile	Thr	Ala	Thr	Val	Pro	Tyr	Asn	
95					100					105					110	
ctt	cgt	gtc	agg	gcc	aca	ttg	ggc	tca	cag	acc	tca	gcc	tgg	agc	atc	386
Leu	Arg	Val	Arg	Ala	Thr	Leu	Gly	Ser	Gln	Thr	Ser	Ala	Trp	Ser	Ile	
				115					120					125		
ctg	aag	cat	ccc	ttt	aat	aga	aac	tca	acc	atc	ctt	acc	cga	cct	ggg	434

24

Leu	Lys	His	Pro	Phe	Asn	Arg	Asn	Ser	Thr	Ile	Leu	Thr	Arg	Pro	Gly	
			130					135					140			
atg	gag	atc	ccc	aaa	cat	ggc	ttc	cac	ctg	gtt	att	gag	ctg	gag	gac	482
Met	Glu	Ile	Pro	Lys	His	Gly	Phe	His	Leu	Val	Ile	Glu	Leu	Glu	Asp	
		145				150					155					
ctg	ggg	ccc	cag	ttt	gag	ttc	ctt	gtg	gcc	tac	tgg	acg	agg	gag	cct	530
Leu	Gly	Pro	Gln	Phe	Glu	Phe	Leu	Val	Ala	Tyr	Trp	Thr	Arg	Glu	Pro	
	160					165					170					
ggt	gcc	gag	gaa	cat	gtc	aaa	atg	gtg	agg	agt	ggg	ggt	att	cca	gtg	578
Gly	Ala	Glu	Glu	His	Val	Lys	Met	Val	Arg	Ser	Gly	Gly	Ile	Pro	Val	
175					180				185						190	
cac	cta	gaa	acc	atg	gag	cca	ggg	gct	gca	tac	tgt	gtg	aag	gcc	cag	626
His	Leu	Glu	Thr	Met	Glu	Pro	Gly	Ala	Ala	Tyr	Cys	Val	Lys	Ala	Gln	
				195				200						205		
aca	ttc	gtg	aag	gcc	att	ggg	agg	tac	agc	gcc	ttc	agc	cag	aca	gaa	674
Thr	Phe	Val	Lys	Ala	Ile	Gly	Arg	Tyr	Ser	Ala	Phe	Ser	Gln	Thr	Glu	
			210				215						220			
tgt	gtg	gag	gtg	caa	gga	gag	gcc	gga	ggt	ggt	ggc	agt	gga	ggc	ggc	722
Cys	Val	Glu	Val	Gln	Gly	Glu	Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	
		225					230					235				
ggt	agc	gga	ggc	ggt	ggc	agt	cga	act	gtg	gct	gca	cca	tct	gtc	ttc	770
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	
	240					245					250					
atc	ttc	ccg	cca	tct	gat	gag	cag	ttg	aaa	tct	gga	act	gcc	tct	gtt	818
Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	
255					260				265						270	
gtg	tgc	ctg	ctg	aat	aac	ttc	tat	ccc	aga	gag	gcc	aaa	gta	cag	tgg	866
Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	
				275				280						285		
aag	gtg	gat	aac	gcc	ctc	caa	tcg	ggt	aac	tcc	cag	gag	agt	gtc	aca	914
Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	
			290				295					300				
gag	cag	gac	agc	aag	gac	agc	acc	tac	agc	ctc	agc	agc	acc	ctg	acg	962
Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	
		305					310					315				
ctg	agc	aaa	gca	gac	tac	gag	aaa	cac	aaa	gtc	tac	gcc	tgc	gaa	gtc	1010
Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	
	320					325					330					
acc	cat	cag	ggc	ctg	agc	tcg	ccc	gtc	aca	aag	agc	ttc	aac	agg	gga	1058
Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	
335					340				345						350	
gag	tgt	taa	tctagaggcg	cgcc												1081
Glu	Cys	*														

<210> 28

<211> 352

25

<212> PRT

<213> Homo sapiens

<400> 28

Met	Gln	Thr	Phe	Thr	Met	Val	Leu	Glu	Glu	Ile	Trp	Thr	Ser	Leu	Phe
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Met	Trp	Phe	Phe	Tyr	Ala	Leu	Ile	Pro	Cys	Leu	Leu	Thr	Asp	Glu	Val
			20					25					30		
Ala	Ile	Leu	Pro	Ala	Pro	Gln	Asn	Leu	Ser	Val	Leu	Ser	Thr	Asn	Met
		35				40						45			
Lys	His	Leu	Leu	Met	Trp	Ser	Pro	Val	Ile	Ala	Pro	Gly	Glu	Thr	Val
	50					55					60				
Tyr	Tyr	Ser	Val	Glu	Tyr	Gln	Gly	Glu	Tyr	Glu	Ser	Leu	Tyr	Thr	Ser
65					70					75					80
His	Ile	Trp	Ile	Pro	Ser	Ser	Trp	Cys	Ser	Leu	Thr	Glu	Gly	Pro	Glu
			85					90						95	
Cys	Asp	Val	Thr	Asp	Asp	Ile	Thr	Ala	Thr	Val	Pro	Tyr	Asn	Leu	Arg
			100					105					110		
Val	Arg	Ala	Thr	Leu	Gly	Ser	Gln	Thr	Ser	Ala	Trp	Ser	Ile	Leu	Lys
		115					120					125			
His	Pro	Phe	Asn	Arg	Asn	Ser	Thr	Ile	Leu	Thr	Arg	Pro	Gly	Met	Glu
	130					135					140				
Ile	Pro	Lys	His	Gly	Phe	His	Leu	Val	Ile	Glu	Leu	Glu	Asp	Leu	Gly
145				150						155					160
Pro	Gln	Phe	Glu	Phe	Leu	Val	Ala	Tyr	Trp	Thr	Arg	Glu	Pro	Gly	Ala
			165						170					175	
Glu	Glu	His	Val	Lys	Met	Val	Arg	Ser	Gly	Gly	Ile	Pro	Val	His	Leu
			180					185					190		
Glu	Thr	Met	Glu	Pro	Gly	Ala	Ala	Tyr	Cys	Val	Lys	Ala	Gln	Thr	Phe
		195					200					205			
Val	Lys	Ala	Ile	Gly	Arg	Tyr	Ser	Ala	Phe	Ser	Gln	Thr	Glu	Cys	Val
	210					215					220				
Glu	Val	Gln	Gly	Glu	Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
225					230					235					240
Gly	Gly	Gly	Gly	Ser	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe
			245					250					255		
Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys
			260					265					270		
Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val
		275					280					285			
Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln
	290					295					300				
Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser
305					310					315					320
Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His
			325						330					335	
Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys
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<210> 29

<211> 323

<212> PRT

<213> Homo sapiens

<400> 29

Asp	Glu	Val	Ala	Ile	Leu	Pro	Ala	Pro	Gln	Asn	Leu	Ser	Val	Leu	Ser
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Thr	Asn	Met	Lys	His	Leu	Leu	Met	Trp	Ser	Pro	Val	Ile	Ala	Pro	Gly
			20					25					30		
Glu	Thr	Val	Tyr	Tyr	Ser	Val	Glu	Tyr	Gln	Gly	Glu	Tyr	Glu	Ser	Leu
		35					40					45			
Tyr	Thr	Ser	His	Ile	Trp	Ile	Pro	Ser	Ser	Trp	Cys	Ser	Leu	Thr	Glu

50	55	60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr		
65	70	75
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser		80
	85	90
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro		95
	100	105
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu		110
	115	120
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu		125
	130	135
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro		140
	145	150
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala		155
	165	170
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr		175
	180	185
Glu Cys Val Glu Val Gln Gly Glu Ala Gly Gly Gly Ser Gly Gly		190
	195	200
Gly Gly Ser Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val		205
	210	215
Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser		220
	225	230
Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln		235
	245	250
Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val		255
	260	265
Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu		270
	275	280
Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu		285
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Leu Thr Val Gly Ser Leu Ala Ala His Ala Pro Glu Asp Pro Ser Asp	
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Leu Leu Gln His Val Lys Phe Gln Ser Ser Asn Phe Glu Asn Ile Leu	
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Thr Trp Asp Ser Gly Pro Glu Gly Thr Pro Asp Thr Val Tyr Ser Ile	
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Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn	Leu	Thr	Val	Glu	Thr	Gly	Asn	
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Leu	Thr	Glu	Leu	Tyr	Tyr	Ala	Arg	Val	Thr	Ala	Val	Ser	Ala	Gly	Gly	
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Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro	Ile	Arg	Ala	Gly	Asp	Gly	
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His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	His	Asp	Leu	Phe	Tyr	His	Leu	
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Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	Met	His	Leu	Gly	Gly	Lys	Gln	
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acc	atc	atg	att	tgc	gtt	ccc	acc	tgg	gcc	aag	gag	agt	gcc	ccc	tac	678
Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp	Ala	Lys	Glu	Ser	Ala	Pro	Tyr	
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Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp	Arg	Thr	Trp	Thr	Ala	Ser	Thr	
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Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	
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Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	
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acc	ttc	ccg	gct	gtc	cta	cag	tcc	tca	gga	ctc	tac	tcc	ctc	agc	agc	918
Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	
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Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	

28

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Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	
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Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	
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Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
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Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
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gac	gtg	agc	cac	gaa	gac	cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	1206
Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	
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ggc	gtg	gag	gtg	cat	aat	gcc	aag	aca	aag	ccg	cgg	gag	gag	cag	tac	1254
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	
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Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
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Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	
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cca	gcc	ccc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	cag	ccc	cga	1398
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
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Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	
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Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
			475				480						485			
atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	tac	aag	1542
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
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Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
	505					510					515					
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Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	
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tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	aac	cac	tac	acg	cag	aag	agc	1686
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	
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1714

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 35 40 45
 Pro Asp Thr Val Tyr Ser Ile Glu Tyr Lys Thr Tyr Gly Glu Arg Asp
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 Trp Val Ala Lys Lys Gly Cys Gln Arg Ile Thr Arg Lys Ser Cys Asn
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 Leu Thr Val Glu Thr Gly Asn Leu Thr Glu Leu Tyr Tyr Ala Arg Val
 85 90 95
 Thr Ala Val Ser Ala Gly Gly Arg Ser Ala Thr Lys Met Thr Asp Arg
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 Phe Ser Ser Leu Gln His Thr Thr Leu Lys Pro Pro Asp Val Thr Cys
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 Ile Ser Lys Val Arg Ser Ile Gln Met Ile Val His Pro Thr Pro Thr
 130 135 140
 Pro Ile Arg Ala Gly Asp Gly His Arg Leu Thr Leu Glu Asp Ile Phe
 145 150 155 160
 His Asp Leu Phe Tyr His Leu Glu Leu Gln Val Asn Arg Thr Tyr Gln
 165 170 175
 Met His Leu Gly Gly Lys Gln Arg Glu Tyr Glu Phe Phe Gly Leu Thr
 180 185 190
 Pro Asp Thr Glu Phe Leu Gly Thr Ile Met Ile Cys Val Pro Thr Trp
 195 200 205
 Ala Lys Glu Ser Ala Pro Tyr Met Cys Arg Val Lys Thr Leu Pro Asp
 210 215 220
 Arg Thr Trp Thr Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 225 230 235 240
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 245 250 255
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 260 265 270
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 275 280 285
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 290 295 300
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 305 310 315 320
 Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 325 330 335
 Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 340 345 350
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 355 360 365
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
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Asp	Thr	Val	Tyr	Ser	Ile	Glu	Tyr	Lys	Thr	Tyr	Gly	Glu	Arg	Asp	Trp	
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Val	Ala	Lys	Lys	Gly	Cys	Gln	Arg	Ile	Thr	Arg	Lys	Ser	Cys	Asn	Leu	
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Thr	Val	Glu	Thr	Gly	Asn	Leu	Thr	Glu	Leu	Tyr	Tyr	Ala	Arg	Val	Thr	
65					70						75				80	
Ala	Val	Ser	Ala	Gly	Gly	Arg	Ser	Ala	Thr	Lys	Met	Thr	Asp	Arg	Phe	
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Ser	Ser	Leu	Gln	His	Thr	Thr	Leu	Lys	Pro	Pro	Asp	Val	Thr	Cys	Ile	
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Ser	Lys	Val	Arg	Ser	Ile	Gln	Met	Ile	Val	His	Pro	Thr	Pro	Thr	Pro	
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Ile	Arg	Ala	Gly	Asp	Gly	His	Arg	Leu	Thr	Leu	Glu	Asp	Ile	Phe	His	
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Asp	Leu	Phe	Tyr	His	Leu	Glu	Leu	Gln	Val	Asn	Arg	Thr	Tyr	Gln	Met	
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His	Leu	Gly	Gly	Lys	Gln	Arg	Glu	Tyr	Glu	Phe	Phe	Gly	Leu	Thr	Pro	
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Asp	Thr	Glu	Phe	Leu	Gly	Thr	Ile	Met	Ile	Cys	Val	Pro	Thr	Trp	Ala	
			180					185					190			
Lys	Glu	Ser	Ala	Pro	Tyr	Met	Cys	Arg	Val	Lys	Thr	Leu	Pro	Asp	Arg	
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Thr	Trp	Thr	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	
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Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	
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Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	
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Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	
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Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	
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31

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 290 295 300
 Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
 305 310 315 320
 Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 325 330 335
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 340 345 350
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 355 360 365
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 370 375 380
 Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 385 390 395 400
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 405 410 415
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 420 425 430
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 435 440 445
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 450 455 460
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 465 470 475 480
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 485 490 495
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
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 Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
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 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga gaa aca gtg 192
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg tac acg agc 240
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80

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His	Ile	Trp	Ile	Pro	Ser	Ser	Trp	Cys	Ser	Leu	Thr	Glu	Gly	Pro	Glu	
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Cys	Asp	Val	Thr	Asp	Asp	Ile	Thr	Ala	Thr	Val	Pro	Tyr	Asn	Leu	Arg	
			100					105					110			
gtc	agg	gcc	aca	ttg	ggc	tca	cag	acc	tca	gcc	tgg	agc	atc	ctg	aag	384
Val	Arg	Ala	Thr	Leu	Gly	Ser	Gln	Thr	Ser	Ala	Trp	Ser	Ile	Leu	Lys	
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His	Pro	Phe	Asn	Arg	Asn	Ser	Thr	Ile	Leu	Thr	Arg	Pro	Gly	Met	Glu	
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Ile	Thr	Lys	Asp	Gly	Phe	His	Leu	Val	Ile	Glu	Leu	Glu	Asp	Leu	Gly	
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ccc	cag	ttt	gag	ttc	ctt	gtg	gcc	tac	tgg	agg	agg	gag	cct	ggt	gcc	528
Pro	Gln	Phe	Glu	Phe	Leu	Val	Ala	Tyr	Trp	Arg	Arg	Glu	Pro	Gly	Ala	
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gag	gaa	cat	gtc	aaa	atg	gtg	agg	agt	ggg	ggt	att	cca	gtg	cac	cta	576
Glu	Glu	His	Val	Lys	Met	Val	Arg	Ser	Gly	Gly	Ile	Pro	Val	His	Leu	
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Glu	Thr	Met	Glu	Pro	Gly	Ala	Ala	Tyr	Cys	Val	Lys	Ala	Gln	Thr	Phe	
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Val	Lys	Ala	Ile	Gly	Arg	Tyr	Ser	Ala	Phe	Ser	Gln	Thr	Glu	Cys	Val	
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gag	gtg	caa	gga	gag	gcc	act	gtg	gct	gca	cca	tct	gtc	ttc	atc	ttc	720
Glu	Val	Gln	Gly	Glu	Ala	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	
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Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	
				245					250					255		
ctg	ctg	aat	aac	ttc	tat	ccc	aga	gag	gcc	aaa	gta	cag	tgg	aag	gtg	816
Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	
			260					265					270			
gat	aac	gcc	ctc	caa	tcg	ggt	aac	tcc	cag	gag	agt	gtc	aca	gag	cag	864
Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	
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gac	agc	aag	gac	agc	acc	tac	agc	ctc	agc	agc	acc	ctg	acg	ctg	agc	912
Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	
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aaa	gca	gac	tac	gag	aaa	cac	aaa	gtc	tac	gcc	tgc	gaa	gtc	acc	cat	960
Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	
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34

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 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60
 Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
 65 70 75 80
 Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
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 Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
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 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val
 195 200 205
 Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
 210 215 220
 Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
 225 230 235 240
 Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
 245 250 255
 Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
 260 265 270
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 290 295 300
 Gly Glu Cys
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<400> 40
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WHAT IS CLAIMED IS:

1. An isolated soluble receptor comprised of an IL-22R subunit and a IL-20RB subunit, wherein the IL-22R subunit is comprised of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 13, 25, 26 31 and 32, and the IL-20B subunit is comprised of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15-21,23, 28, 29, 34 and 35.
2. The soluble receptor of claim 1 wherein the IL-22R subunit and the IL-20B subunit are linked together by a polypeptide linker.
3. The soluble receptor of claim 2 wherein the polypeptide linker has about 100 to 240 amino acid residues.
4. The soluble receptor of claim 3 wherein the polypeptide linker has about 170 amino acid residues.
5. The soluble receptor of claim 1 wherein the IL-22R subunit and the IL-20B subunit each have a polypeptide linker fused to the subunit, and each of the polypeptide linkers has at least one cysteine residue, wherein at least one disulfide bond forms with a cysteine from the polypeptide linker of the IL-22R subunit and with a cysteine from the polypeptide linker of the IL-20B subunit.
6. The soluble receptor of claim 5 wherein the IL-22R subunit is fused to all or a portion of the constant region of a heavy chain of an immunoglobulin (Ig) molecule, and the IL-20B subunit is fused to all or a portion of the constant region of a light chain of an immunoglobulin molecule, wherein the light chain and the heavy chain are disulfide bonded together.

7. The soluble receptor of claim 6 wherein the constant region of the heavy chain is comprised of a CH1 domain, a CH2 domain and a hinge sequence that connects the CH1 domain with the CH2 domain.
8. The soluble receptor of claim 6 wherein the IL-22R subunit fused to the constant region of the heavy chain is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 25, 26, 31 and 32, and the IL-20B subunit fused to the constant region of the light chain of the Ig molecule is comprised of an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 29, 34 and 35.
9. The soluble receptor of claim 5 wherein the IL-20B subunit is fused to all or a portion of the constant region of a heavy chain of an Ig molecule, and the IL-22R subunit is fused to all or a portion of the constant region of a light chain of an immunoglobulin molecule, wherein the light chain and the heavy chain are disulfide bonded together.
10. A for producing a soluble receptor comprised of extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised a DNA sequence that encodes the extracellular portion of IL-22R and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a DNA sequence that encodes the extracellular portion of IL-20RB and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow production of a fusion protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the polypeptide from the host cell.
11. A method for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of DNA that encodes the extracellular portion of IL-20RB and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell

a second DNA construct comprised of a DNA sequence that encodes the extracellular portion of IL-22R and a DNA sequence that encodes an immunoglobulin heavy chain constant region (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the production of a dimerized heterodimeric fusion protein comprised of the extracellular domain of IL-22R and IL-20RB; and (d) isolating the dimerized polypeptide from the host cell.

12. A method for producing a soluble receptor comprised of the extracellular domains of IL-22R and IL-20RB comprising (a) introducing into a host cell a DNA construct containing a DNA construct that encodes the extracellular portion of IL-20RB and a DNA construct of the extracellular portion of IL-22R, (b) growing the host cell in an appropriate medium under physiological conditions to allow the production of the extracellular domain of IL-22R and the extracellular domain of IL-20RB; and (d) isolating the polypeptides from the host cell.

13. A host cells transformed or transfected with a DNA construct that encodes the extracellular domain of IL-22RB and a DNA construct that encodes the extracellular domain of IL-20RB.

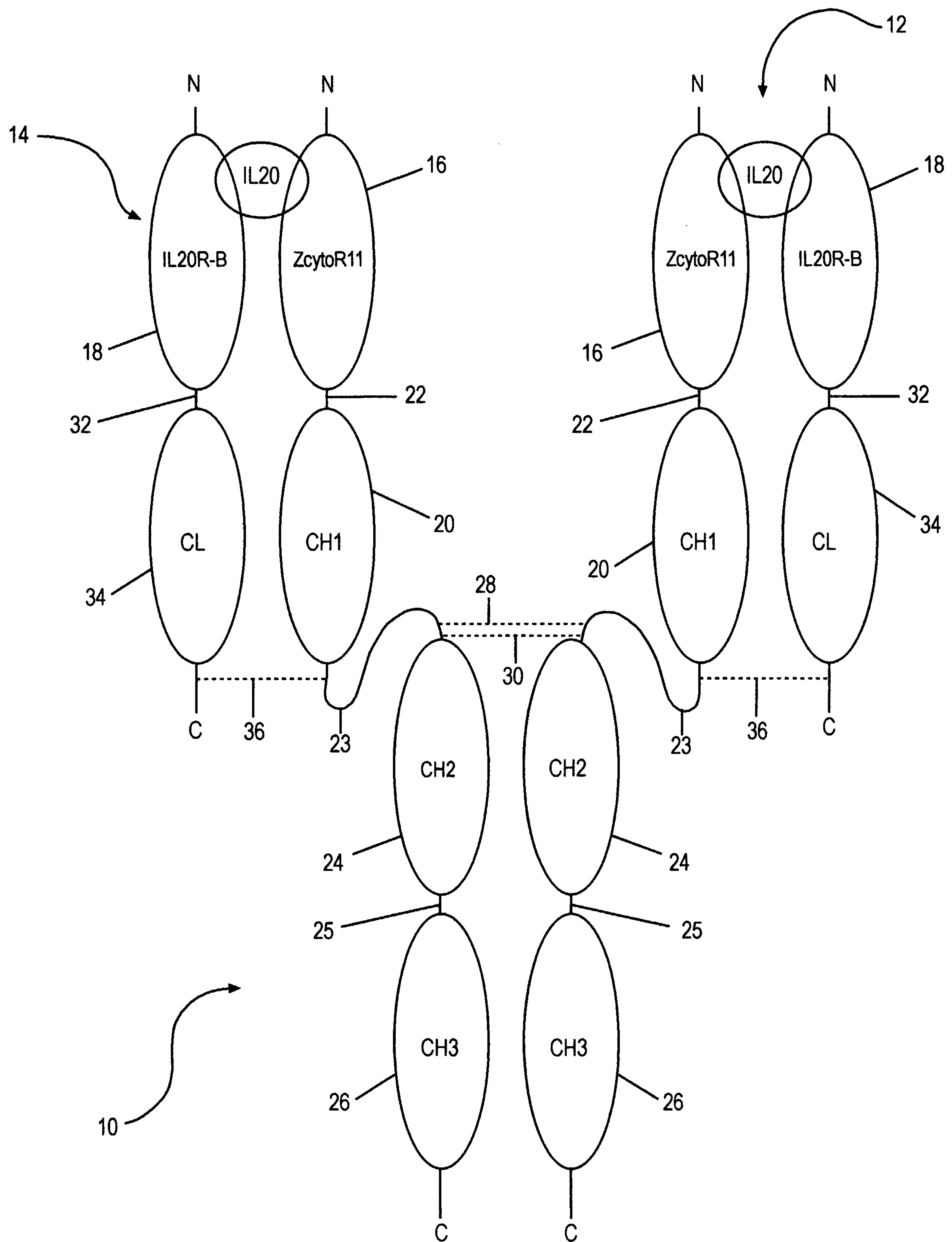


FIG.1

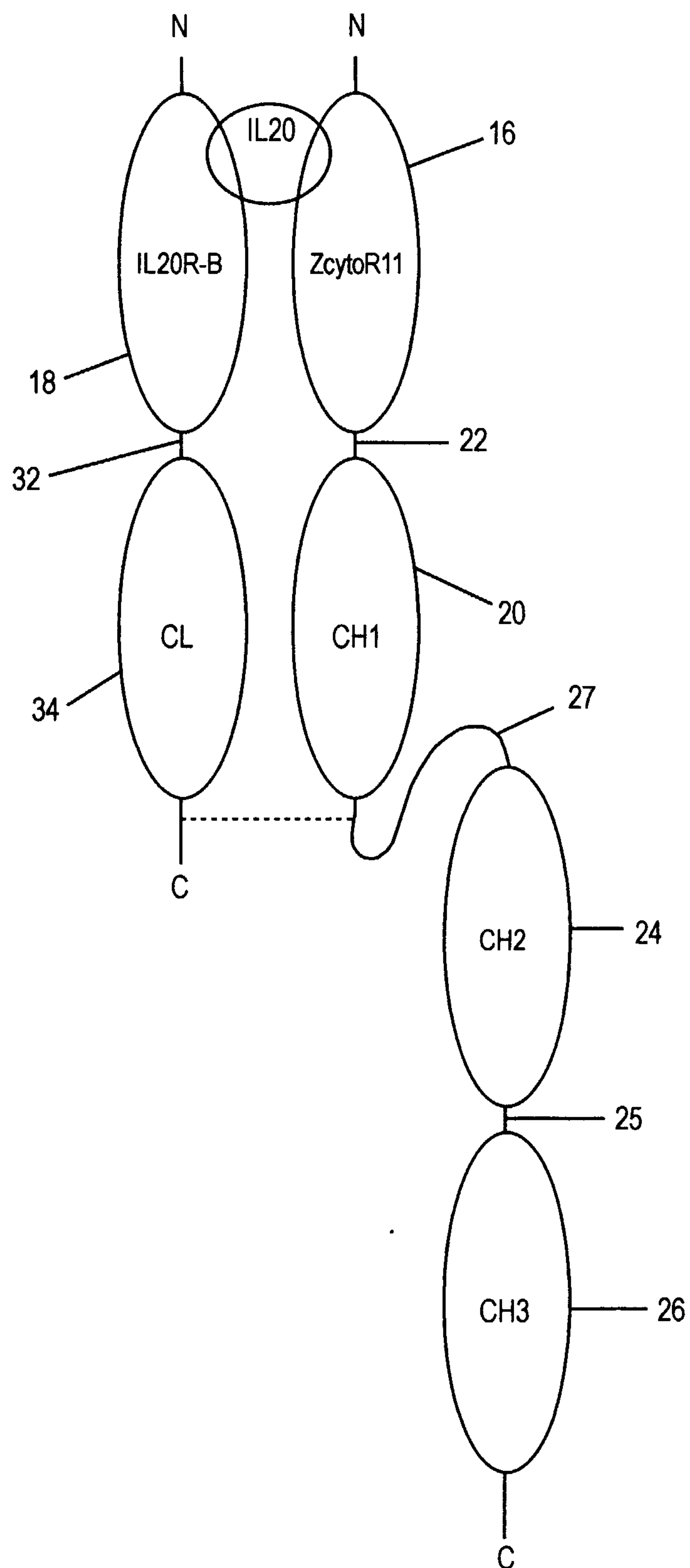


FIG.2

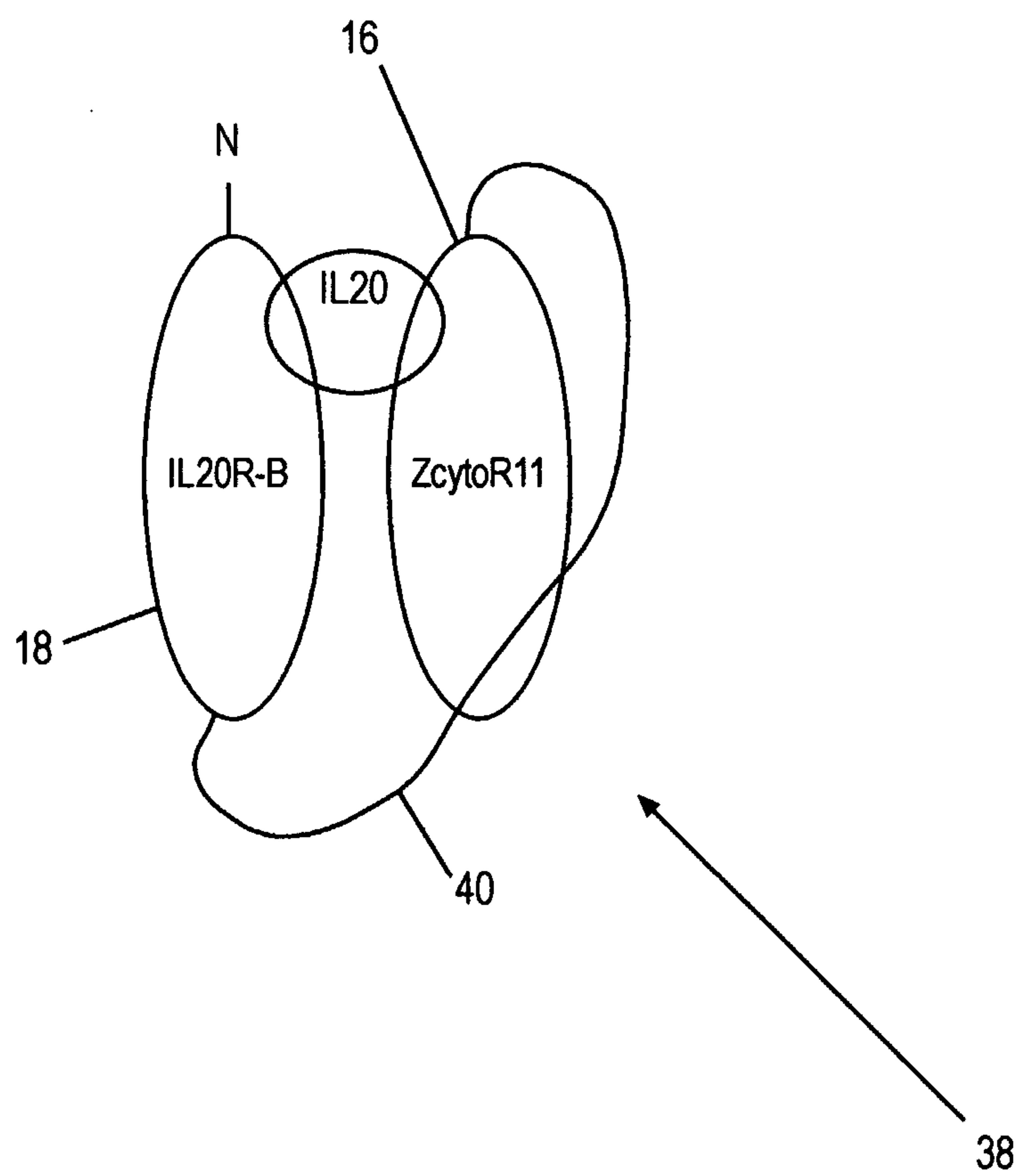


FIG.3

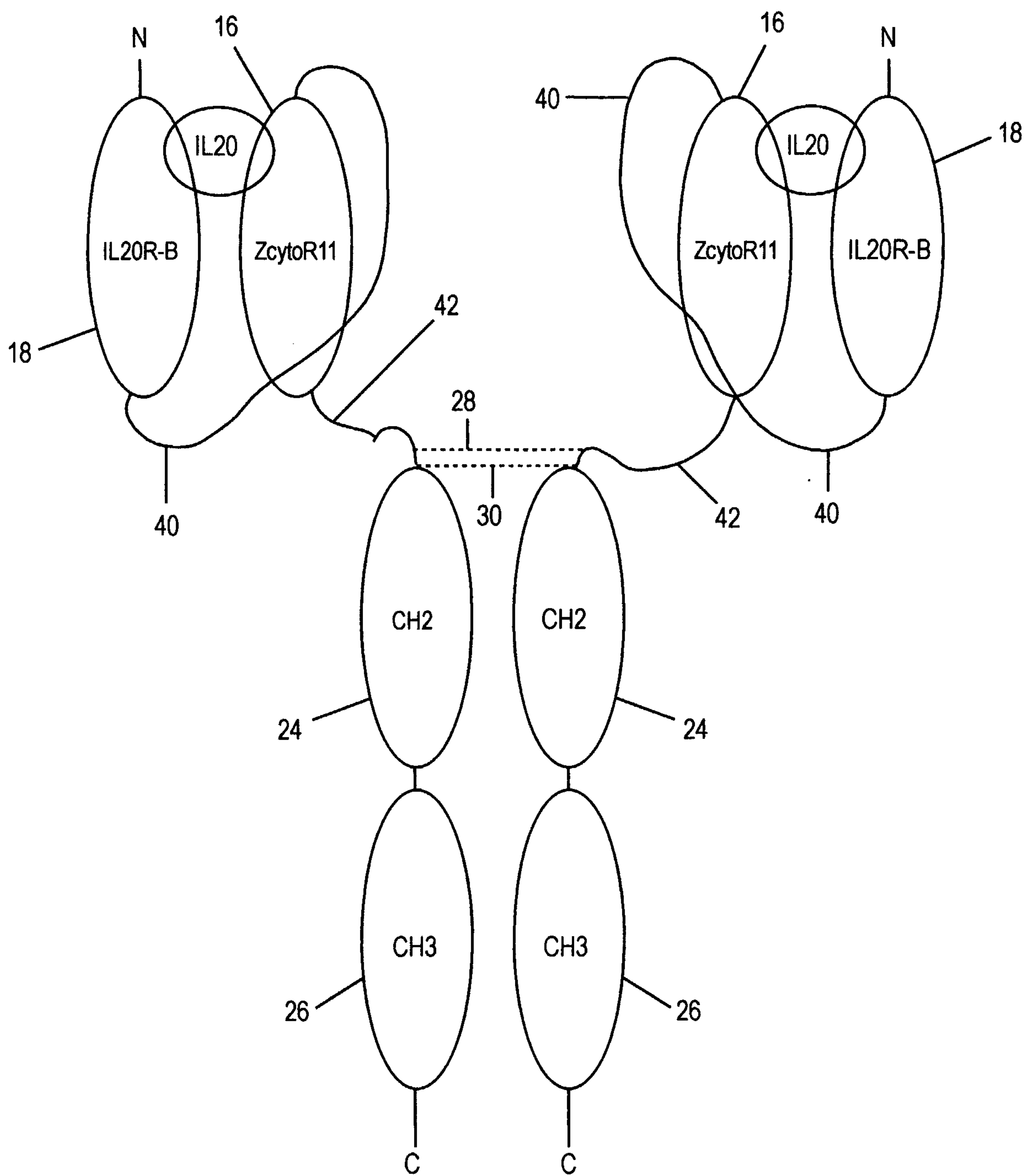


FIG.4

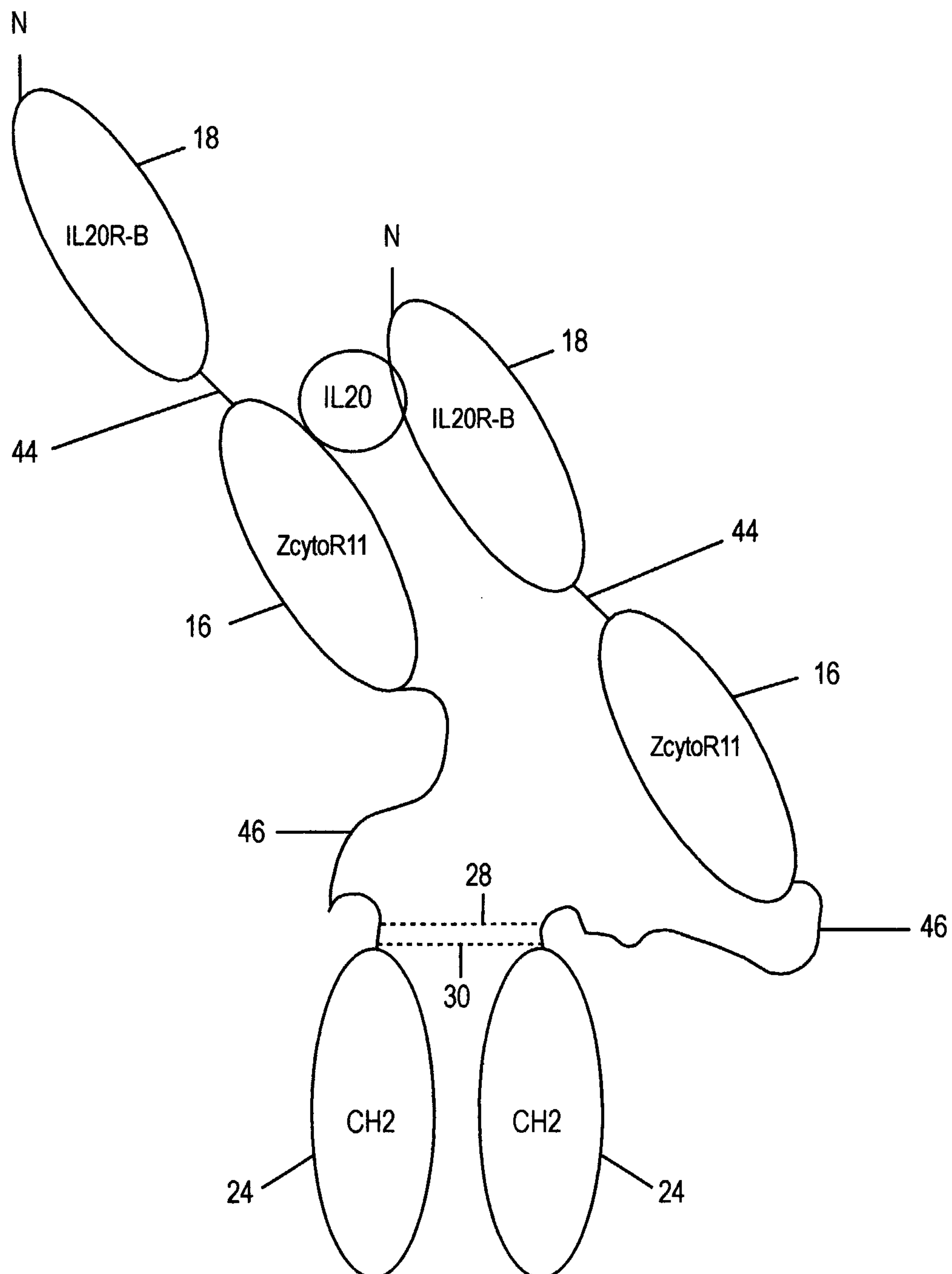


FIG.5

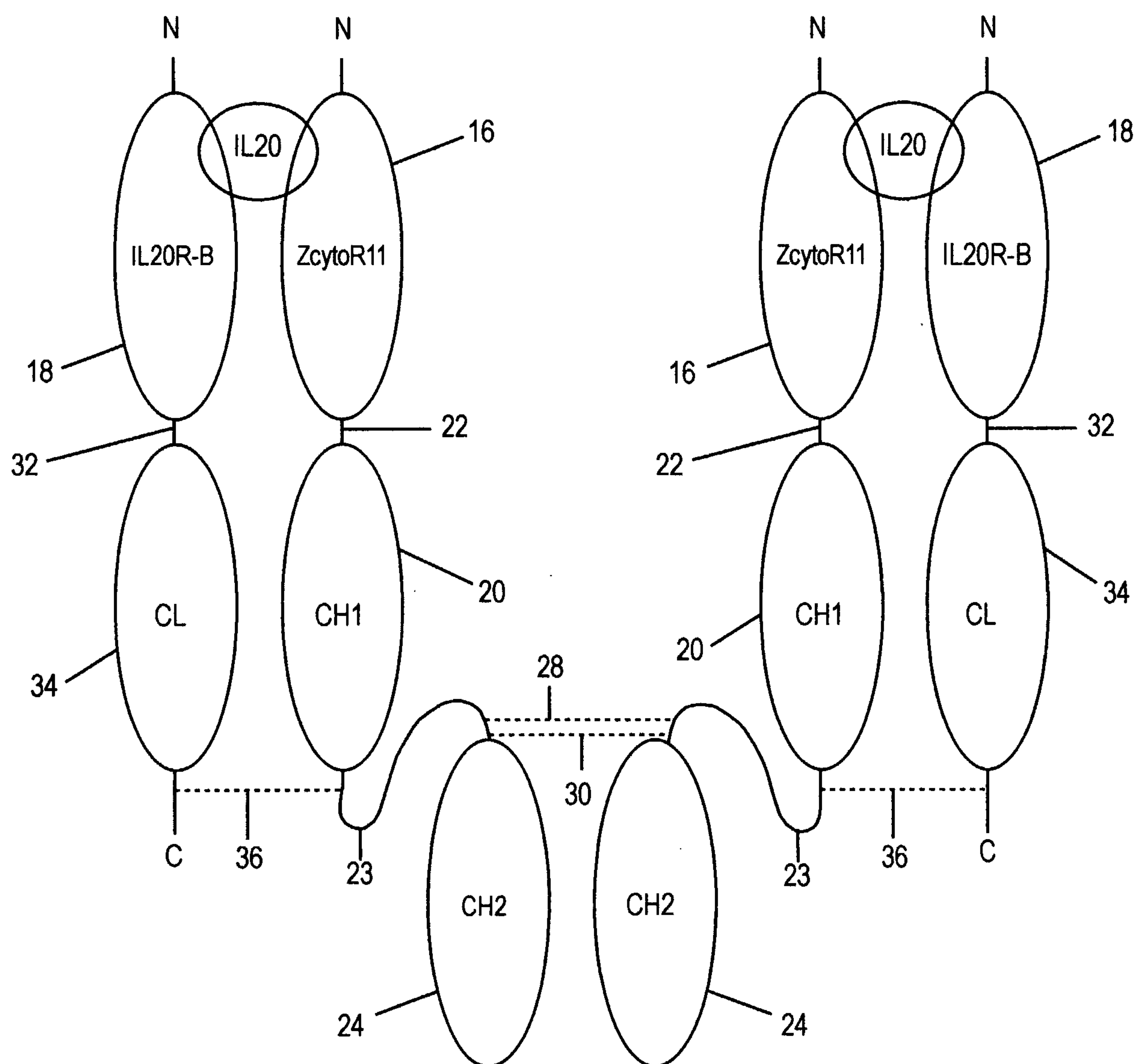


FIG.6

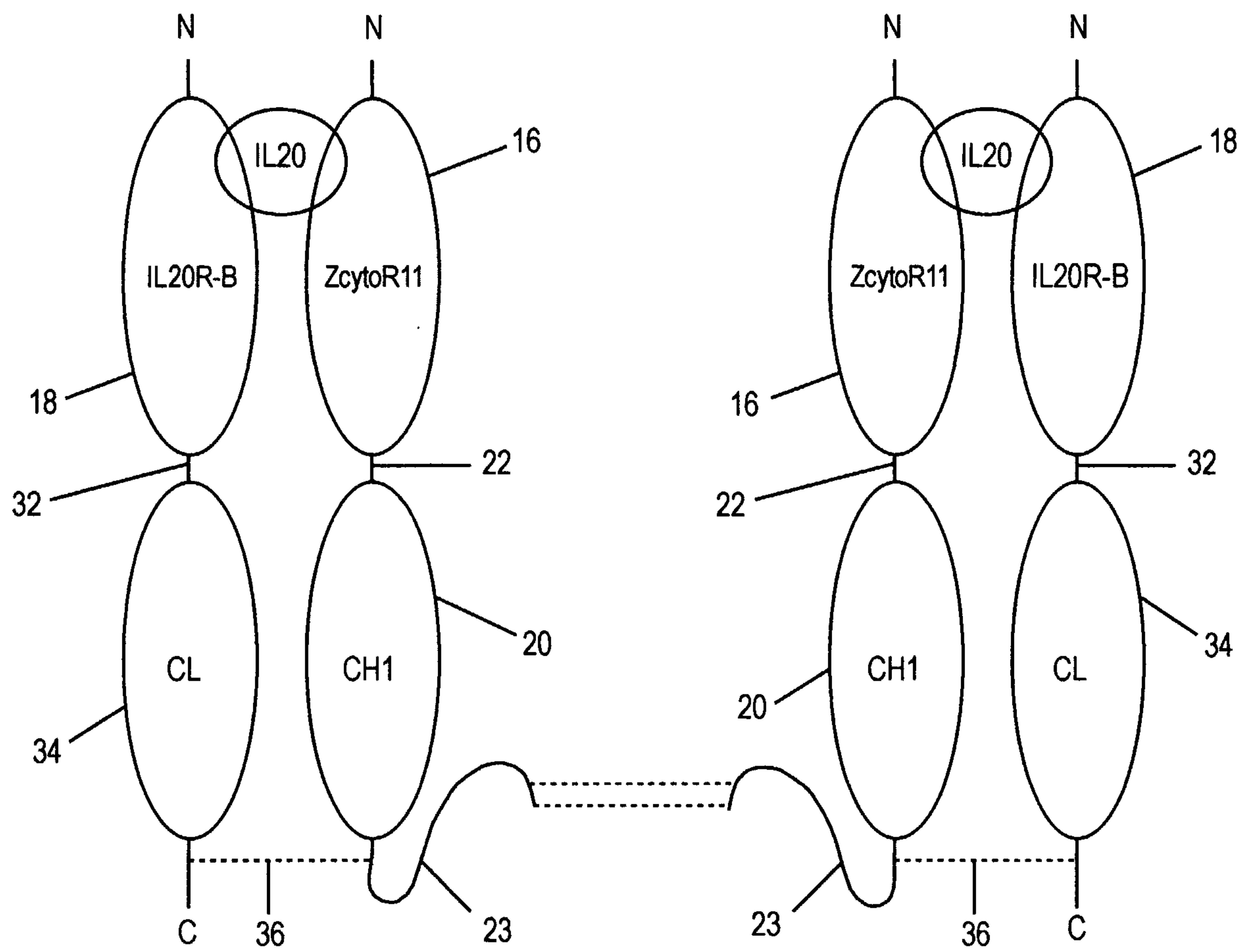


FIG.7

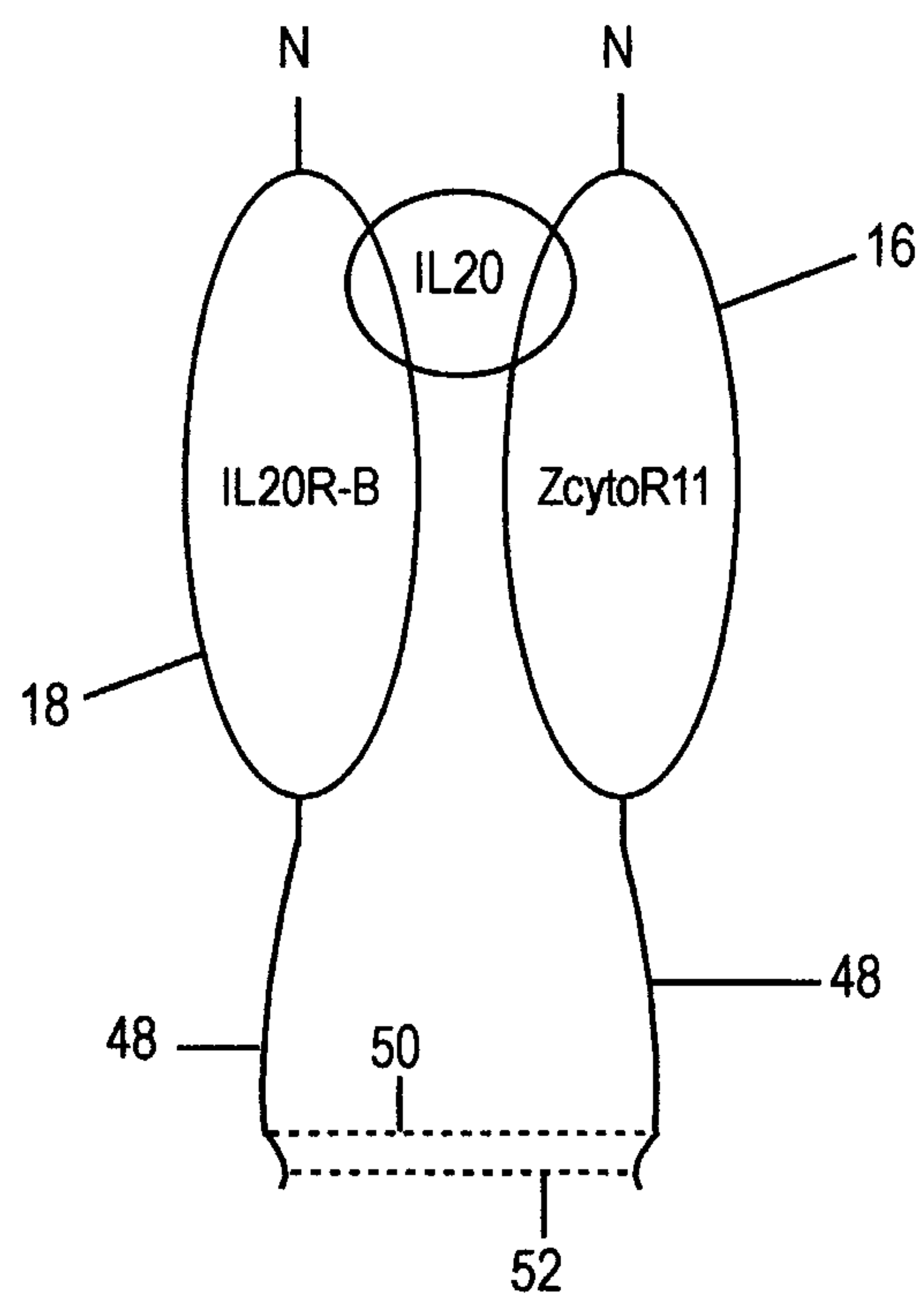


FIG.8