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(54) Title: METHODS OF TREATING SKIN DISORDERS USING AN IL-31RA ANTAGONIST

(57) Abstract: The present invention relates to methods of treating patients suffering from Contact dermatitis, Drug induced delayed type cutaneous allergic reactions, Toxic epidermal necrolysis, Cutaneous T cell Lymphoma, Bullous pemphigoid, Alopecia areata, Vitiligo, Acne Rosacea, Prurigo nodularis, Scleroderma, Herpes simplex virus, or combination by administering an IL-31RA antagonist.



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## METHODS OF TREATING SKIN DISORDERS USING AN IL-31RA ANTAGONIST

### BACKGROUND OF THE INVENTION

[1] The skin plays an important role in the immune system and consists of layers. The epidermis is a surface layer. Underneath the epidermis is the dermis, a layer of connective tissue. Underneath the dermis, is the hypodermis, a layer of large amounts of adipose tissue. Circulating T lymphocytes migrate to the skin under normal and inflammatory conditions. The cutaneous lymphocyte antigen (CLA) is considered a homing receptor for T cells with tropism for the skin. Santamaria-Babi, L., *Eur. J. Dermatol.* 14:13-18, 2004. CLA is a carbohydrate structure which is expressed on memory T cells as an epitope of the single cell-surface protein named P-selectin glycoprotein ligand-1 (PSGL-1) and facilitates binding of T cells to E-selectin, an inducible adhesion molecule expressed on vascular endothelium. See Fuhlbrigge RC, et al., *Nature* 1997; 389:978-81.

[2] Several diseases of the skin are known to express high levels of CLA<sup>+</sup> T cells, including atopic dermatitis, contact dermatitis, drug-induced allergic reactions, skin-tropic viruses and viral associated pruritis, vitiligo, cutaneous T cell lymphoma, alopecia aerata, acne rosacea, acne vulgaris, prurigo nodularis, and bullous pemphigoid. There is a need to treat such skin T cell mediated diseases.

[3] The demonstrated *in vivo* activities of the cytokine family illustrate the enormous clinical potential of, and need for, other cytokines, cytokine agonists, and cytokine antagonists. The present invention addresses these needs by providing a method of treating such diseases with IL-31RA antagonists, e.g., IL-31RA soluble receptor or neutralizing IL-31RA monoclonal antibody or fragment, a receptor for the newly identified IL-31 cytokine. IL-31, when over-expressed in mice, results in dermatitis-like symptoms. Both skin-homing T cells and epidermal keratinocytes have been implicated in the pathology of skin diseases in humans.

[4] The present invention provides such polypeptides for these and other uses that should be apparent to those skilled in the art from the teachings herein.

### SUMMARY

In one embodiment, the present invention provides a method of treating a patient suffering from a skin disorder, the method comprising administering a therapeutically effective amount of an anti-IL-31RA monoclonal antibody or antigen-binding fragment thereof to the patient, wherein the anti-IL-31RA monoclonal antibody or antigen-binding fragment specifically binds amino acid residues 20-519 of SEQ ID NO:6 or a portion thereof and wherein the anti-IL-31RA monoclonal antibody or antigen-binding fragment prevents,

inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Toxic epidermal necrolysis, Bullous pemphigoid, Vitiligo, Acne Rosacea, Prurigo nodularis, and Scleroderma.

In another embodiment, the present invention provides a method of treating a patient suffering from a skin disorder, the method comprising administering a therapeutically effective amount of a soluble IL-31RA receptor to the patient, wherein the soluble IL-31RA receptor comprises amino acid residues 20-519 of SEQ ID NO:6, wherein the soluble IL-31RA receptor specifically binds a polypeptide comprising amino acid residues 27-164 of SEQ ID NO:2, and wherein the soluble IL-31RA receptor prevents, inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Toxic epidermal necrolysis, Bullous pemphigoid, Vitiligo, Acne Rosacea, Prurigo nodularis, and Scleroderma.

#### *DETAILED DESCRIPTION OF THE INVENTION*

##### *Definitions*

[5] Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[6] Unless otherwise specified, "a," "an," "the," and "at least one" are used interchangeably and mean one or more than one.

[7] The term "affinity tag" is used herein to denote a polypeptide segment that can be attached to a second polypeptide to provide for purification or detection of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., *EMBO J.* 4:1075, 1985; Nilsson et al., *Methods Enzymol.* 198:3, 1991), glutathione S transferase (Smith and Johnson, *Gene* 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., *Proc. Natl. Acad. Sci. USA* 82:7952-4, 1985), substance P, Flag<sup>TM</sup> peptide (Hopp et al., *Biotechnology* 6:1204-10, 1988), streptavidin binding peptide, or other antigenic epitope or binding domain. See, in general, Ford et al., *Protein Expression and Purification* 2: 95-107, 1991. DNAs encoding affinity tags are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ).

[8] The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

[9] The terms "amino-terminal" and "carboxyl-terminal" are used herein to 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 polypeptide.

[10] 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 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  $<10^9 \text{ M}^{-1}$ .

[11] The term "complements of a polynucleotide molecule" denotes a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

[12] 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. For example, representative contigs to the polynucleotide sequence 5'-ATGGCTTAGCTT-3' (SEQ ID NO:18) are 5'-TAGCTTgagtct-3' (SEQ ID NO:19) and 3'-gtcgacTACCGA-5' (SEQ ID NO:20).

[13] 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).

[14] 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.

[15] 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).

[16] 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.

[17] 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.

[18] The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

[19] "Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example,  $\alpha$ -globin,  $\beta$ -globin, and myoglobin are paralogs of each other.

[20] 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 ("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 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.

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

[22] 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.

[23] 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; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

[24] 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-peptide structure comprising 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).

[25] 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.

[26] A "soluble receptor" is a receptor polypeptide that is not bound to a cell membrane. Soluble receptors are most commonly ligand-binding receptor polypeptides that lack transmembrane and cytoplasmic domains. Soluble receptors can comprise additional amino acid residues, such as affinity tags that provide for purification of the polypeptide or provide sites for attachment of the polypeptide to a substrate, or immunoglobulin constant region sequences. Many cell-surface receptors have naturally occurring, soluble counterparts that are produced by proteolysis. Soluble receptor polypeptides are said to be substantially free of transmembrane and intracellular polypeptide segments when they lack sufficient portions of these segments to provide membrane anchoring or signal transduction, respectively.

[27] 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.

[28] 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  $\pm 10\%$ .

[29] All references cited herein are incorporated by reference in their entirety.

[30] The present invention provides novel methods of using IL-31RA antagonists in detection, diagnosis, and treatment of diseases, in particular, diseases that have a high correlation of

cutaneous lymphocyte antigen (CLA). The present invention is based in part upon the discovery that a previously identified cytokine, IL-31 is expressed by skin-homing T cells, but not gut-homing T cells.

[31] IL-31 is a recently discovered protein having the structure of a four-helical-bundle cytokine. This cytokine was previously identified as IL-31 and is fully described in U.S. Patent Application No. 10/352,554, filed January 21, 2003. See published U.S. Patent Application No. 2003-0224487, and PCT application WO 03/060090, all herein incorporated by reference. See also, Dillon, et al., *Nature Immunol.* 5:752-760, 2004. IL-31 is a ligand with high specificity for the receptor IL-31RA and at least one additional subunit comprising OncostatinM receptor beta (OSMRbeta). The native polynucleotide and polypeptide sequences for human IL-31 are shown in SEQ ID NOs:1 and 2, respectively. The native polynucleotide and polypeptide sequences for mouse IL-31 are shown in SEQ ID NOs:3 and 4, respectively.

[32] As used herein the term, IL-31 also means and is interchangeably referred to as Zcytor17lig, and IL-31RA also means and is interchangeably referred to as Zcytor17, as used in U.S. patent publication number 20030224487 (herein incorporated by reference), as shown above. The heterodimeric receptor for IL-31 was also described in 20030224487 as comprising zcytor17 (HUGO name, IL-31RA) and with at least one additional subunit comprising OncostatinM receptor beta (OSMRbeta).

[33] The native polynucleotide and polypeptide sequences for the "long" form of IL-31RA are shown in SEQ ID NOs:5 and 6, respectively. The native polynucleotide and polypeptide sequences for the "short" form of IL-31RA are shown in SEQ ID NOs:7 and 8, respectively. Additionally, truncated forms of IL-31RA polypeptide appear to be naturally expressed. Both forms encode soluble IL-31RA receptors. The "long" soluble IL-31RA polynucleotide and polypeptide sequences are shown in SEQ ID NOs:9 and 10, respectively. The "short" soluble IL-31RA polynucleotide and polypeptide sequences are shown in SEQ ID NOs:11 and 12, respectively. The native polynucleotide and polypeptide sequences for mouse IL-31RA are shown in SEQ ID NOs:13 and 14, respectively. The native polynucleotide and polypeptide sequences for human OSMRbeta are shown in SEQ ID NOs:15 and 16, respectively. See PCT applications WO 02/00721 and WO 04/003140, both of which are incorporated by reference.

[34] The secretory signal sequence of IL-31 is comprised of amino acid residues 1 (Met) to 23 (Ala), and the mature polypeptide is comprised of amino acid residues 24 (Ser) to 164 (Thr) as shown in SEQ ID NO:2. Further N-terminal sequencing analysis of purified IL-31 from 293T cells showed an N-terminus at residue 27 (Leu) as shown in SEQ ID NO:2, with the mature polypeptide comprised of amino acid residues 27 (Leu) to 164 (Thr) as shown in SEQ ID NO:2.

[35] Cytokine receptor subunits are characterized by a multi-domain structure comprising an extracellular domain, a transmembrane domain that anchors the polypeptide in the cell membrane, and an intracellular domain. The extracellular domain may be a ligand-binding domain, and the intracellular domain may be an effector domain involved in signal transduction, although ligand-binding and effector functions may reside on separate subunits of a multimeric receptor. The domains and structural features of the IL-31RA polypeptides (zcytor17) are further described below.

[36] Analysis of the IL-31RA polypeptide encoded by the DNA sequence of SEQ ID NO:5 revealed an open reading frame encoding 732 amino acids (SEQ ID NO:6) comprising a predicted secretory signal peptide of 19 amino acid residues (residue 1 (Met) to residue 19 (Ala) of SEQ ID NO:6), and a mature polypeptide of 713 amino acids (residue 20 (Ala) to residue 732 (Val) of SEQ ID NO:6). Analysis of the IL-31RA polypeptide encoded by the DNA sequence of SEQ ID NO:7 revealed an open reading frame encoding 662 amino acids (SEQ ID NO:8) comprising a predicted secretory signal peptide of 32 amino acid residues (residue 1 (Met) to residue 32 (Ala) of SEQ ID NO:8), and a mature polypeptide of 630 amino acids (residue 33 (Ala) to residue 662 (Ile) of SEQ ID NO:8). In addition to the WSXWS motif (SEQ ID NO:17) (corresponding to residues 211 to 215 of SEQ ID NO:6; and residues 224 to 228 of SEQ ID NO:8), the receptor comprises an extracellular domain (residues 20 (Ala) to 519 (Glu) of SEQ ID NO:6; residues 33 (Ala) to 532 (Glu) of SEQ ID NO:8) which includes a cytokine-binding domain of approximately 200 amino acid residues (residues 20 (Ala) to 227 (Pro) of SEQ ID NO:6; residues 33 (Ala) to 240 (Pro) of SEQ ID NO:8); a domain linker (residues 122 (Thr) to 125 (Pro) of SEQ ID NO:6; residues 135 (Thr) to 138 (Pro) of SEQ ID NO:8); a penultimate strand region (residues 194 (Phe) to 202 (Arg) of SEQ ID NO:6; residues 207 (Phe) to 215 (Arg) of SEQ ID NO:8); a fibronectin type III domain (residues 228 (Cys) to 519 (Glu) of SEQ ID NO:6; residues 241 (Cys) to 532 (Glu) of SEQ ID NO:8); a transmembrane domain (residues 520 (Ile) to 543 (Leu) of SEQ ID NO:6; residues 533 (Ile) to 556 (Leu) of SEQ ID NO:8); complete intracellular signaling domain (residues 544 (Lys) to 732 (Val) of SEQ ID NO:6; and residues 557 (Lys) to 662 (Ile) of SEQ ID NO:8) which contains a "Box I" signaling site (residues 554 (Trp) to 560 (Pro) of SEQ ID NO:6; residues 567 (Trp) to 573 (Pro) of SEQ ID NO:8), and a "Box II" signaling site (residues 617 (Gln) to 620 (Phe) of SEQ ID NO:6; residues 630 (Gln) to 633 (Phe) of SEQ ID NO:8). Those skilled in the art will recognize that these domain boundaries are approximate, and are based on alignments with known proteins and predictions of protein folding. In addition to these domains, conserved receptor features in the encoded receptor include (as shown in SEQ ID NO:6) a conserved Cys residue at position 30 (position 43 as shown in SEQ ID NO:8), CXW motif (wherein X is any amino acid) at positions 40-42 of SEQ ID NO:6 (positions 53-55 as shown in SEQ ID NO:8), Trp residue at position 170 of SEQ ID NO:6 (position 183 as shown in SEQ ID NO:8), and a conserved Arg residue at position 202 of

SEQ ID NO:6 (position 215 as shown in SEQ ID NO:8). The corresponding polynucleotides encoding the IL-31RA polypeptide regions, domains, motifs, residues and sequences described above are as shown in SEQ ID NOs:5 and 7.

[37] Moreover, truncated forms of the IL-31RA polypeptide appear to be naturally expressed. Both forms encode soluble zcytor17 receptors. A polynucleotide encoding a "long-form" of the soluble zcytor17 receptor, truncated within the fibronectin type III domain, is shown in SEQ ID NO:9 and the corresponding polypeptide is shown in SEQ ID NO:10. This truncated form encodes residues 1 (Met) through 324 (Lys) of SEQ ID NO:6, and thus comprises an intact signal sequence, WSXWS (SEQ ID NO:17) motif, linker, cytokine binding domain, penultimate strand, and conserved, Cys, CXW motif, Trp and Arg residues as described above. A polynucleotide encoding a "short-form" of the soluble IL-31RA receptor, truncated at the end of the cytokine binding domain is shown in SEQ ID NO:11 and the corresponding polypeptide is shown in SEQ ID NO:12. This truncated form encodes a 239 residue polypeptide that is identical to residues 1 (Met) through 225 (Glu) of SEQ ID NO:6 and then diverges, and thus comprises an intact signal sequence, WSXWS (SEQ ID NO:17) motif, linker, cytokine binding domain, penultimate strand, and conserved, Cys, CXW motif, Trp and Arg residues as described above.

[38] Both skin-homing T cells and epidermal keratinocytes have been implicated in the pathology of skin diseases in humans. As shown herein, IL-31 mRNA and protein expression is restricted to the skin-homing CLA<sup>+</sup> T cell population in both atopic dermatitis (AD) patients and normal individuals, while analysis of the receptor for IL-31, IL-31RA, by immunohistochemistry (IHC) suggests slightly higher levels of IL-31RA expression on skin keratinocytes in skin biopsies from acute and chronic AD sufferers compared to normal individuals.

[39] When over-expressed in mice, IL-31 results in pruritus and the development of skin dermatitis resembling human atopic dermatitis (AD). Immunohistochemistry (IHC) studies shown herein show that IL-31RA protein was expressed by skin keratinocytes and infiltrating macrophages in skin biopsies from AD patients. Comparisons between AD patients and normal individuals suggested that IL-31RA was expressed at higher levels on epidermal keratinocytes in the AD samples. Skin cell infiltrates, which were present at greater numbers in skin of AD patients compared to normal individuals, expressed IL-31 mRNA. Histomorphometric analysis of these cells suggested a lymphocytic lineage with the majority of cells staining positive for cutaneous lymphocyte antigen (CLA) and CD3, demonstrating that skin-homing T cells in skin express IL-31 mRNA. Upon analysis of peripheral blood T cells for IL-31, IL-31 mRNA and protein expression is largely restricted to CD45RO<sup>+</sup> CLA<sup>+</sup> skin-homing T cells in AD and normal volunteers. Moreover, circulating CLA<sup>+</sup> T cells from AD patients are capable of producing higher levels of IL-31 compared to CLA<sup>+</sup> T cells from normal individuals, though there is large variability between patient samples.

These results provide strong evidence that IL-31 expression is associated with atopic dermatitis and may contribute to the development of AD skin inflammation and pruritus.

[40] As shown herein, IL-31 is produced both locally in the skin and by skin infiltrating cells. Local production of cytokines in tissues by T cells is thought to be a key mechanism for disease pathogenesis in AD and increased numbers of T cells both in circulation and in skin is thought to correlate with disease.

[41] Although both AD patients and normal controls have circulating CLA<sup>+</sup> T cells that express IL-31 upon activation, CLA<sup>+</sup> T cells from AD patients are reported to exist in a more activated state compared to cells from normal individuals. See Akdis M, *J Immunol.*, 159:4611-4619, 1997. Consequently, the threshold of stimulation required for the production of IL-31 by CLA<sup>+</sup> T cells may differ between dermatitis patients and control subjects. As shown herein, circulating CLA<sup>+</sup>T cells from AD patients after 24 hours of stimulation with sub-optimal concentrations of anti-CD3 in the absence of anti-CD28 have the capacity to produce higher levels of IL-31 compared to cells from normal individuals. Due to the variability in IL-31 levels produced by CLA<sup>+</sup> T cells from individual AD patients, there was no significant difference in the average IL-31 production from circulating CLA<sup>+</sup> T cells of AD and normal individuals. Nevertheless, since more CLA<sup>+</sup> T cells are localized in skin of AD patients, as compared to normal individuals, there is an increased potential for IL-31 activity in the AD skin micro-environment.

[42] Example 1 demonstrates that circulating CLA<sup>+</sup> T cells from some AD patients produce higher levels of IL-31 compared to cells from normal individuals. The detection of IL-31 in patients of such a subpopulation using the bioassay provided herein, or with any assay that detects IL-31 produced by circulating T cells in the blood, may be useful to determine if an IL-31 antagonist will be useful as treatment for diseases wherein the presence of IL-31 causes inflammation.

[43] A cell line that is dependent on the OSMRbeta and IL-31RA linked pathway for survival and growth in the absence of other growth factors can be used to measure the activity of IL-31. Such growth factor-dependent cell lines include BaF3, FDC-P1, and MO7e. For information on the BaF3 cell line, see Palacios and Steinmetz, (*Cell*, 41:727-734, 1985) and Mathey-Prevot et al., (*Mol. Cell. Biol.*, 6:4133-4135, 1986). For information on the FDC-P1 cell line, see Hapel et al. (*Blood*, 64:786-790, 1984). For information on the MO7e cell line, see Kiss et al., (*Leukemia*, 7:235-240, 1993).

[44] The amino acid sequence for the OSMRbeta, and IL-31RA receptors indicated that the encoded receptors belonged to the Class I cytokine receptor subfamily that includes, but is not limited to, the receptors for IL-2, IL-4, IL-7, Lif, IL-12, IL-15, EPO, TPO, GM-CSF and G-CSF (for a review see, Cosman, "The Hematopoietin Receptor Superfamily." in *Cytokine* 5(2): 95-106, 1993). The IL-31RA receptor is fully described in PCT Patent Application No. US01/20484 (WIPO

publication No. WO 02/00721). Analysis of the tissue distribution of the mRNA of the IL-31RA receptor revealed expression in activated CD4+ and CD8+ T-cell subsets, CD14+ monocytes, and weaker expression in CD19+ B-cells. Moreover, the mRNA was present in both resting or activated monocytic cell lines THP-1 (ATCC No. TIB-202), U937 (ATCC No. CRL-1593.2) and HL60 (ATCC No. CCL-240).

[45] Antigenic epitope-bearing peptides and polypeptides preferably contain at least four to ten amino acids, at least ten to fourteen amino acids, or about fourteen to about thirty amino acids of the extracellular domains of SEQ ID NO:6 or SEQ ID NO:8. Such epitope-bearing peptides and polypeptides can be produced by fragmenting the extracellular domain of IL-31RA polypeptide, or by chemical peptide synthesis, as described herein. Moreover, epitopes can be selected by phage display of random peptide libraries (see, for example, Lane and Stephen, Curr. Opin. Immunol. 5:268 (1993); and Cortese *et al.*, Curr. Opin. Biotechnol. 7:616 (1996)). Standard methods for identifying epitopes and producing antibodies from small peptides that comprise an epitope are described, for example, by Mole, "Epitope Mapping," in Methods in Molecular Biology, Vol. 10, Manson (ed.), pages 105-116 (The Humana Press, Inc. 1992); Price, "Production and Characterization of Synthetic Peptide-Derived Antibodies," in Monoclonal Antibodies: Production, Engineering, and Clinical Application, Ritter and Ladyman (eds.), pages 60-84 (Cambridge University Press 1995), and Coligan *et al.* (eds.), Current Protocols in Immunology, pages 9.3.1 - 9.3.5 and pages 9.4.1 - 9.4.11 (John Wiley & Sons 1997).

[46] The IL-31RA polypeptides of the present invention, including full-length polypeptides, functional fragments, and fusion polypeptides, can be produced, purified and refolded by methods well-known in the art and as described in PCT applications WO 02/00721 and WO 04/003140. 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.

[47] The present invention provides methods for using IL-31RA antagonists, including anti-IL-31RA antibodies and fragments, soluble IL-31RA receptors, and soluble IL-31RA/OSMRbeta receptors for reducing, inhibiting, or preventing inflammation in cell microenvironments where one or more cells in the microenvironment is/are T cells that are positive for the cutaneous lymphocyte antigen.

[48] Antibodies from an immune response generated by inoculation of an animal with IL-31RA antigens, e.g., extracellular domain of SEQ ID NO:6 or a portion thereof, such as ligand

binding domain) can be isolated and purified are known in the art and are described herein. Methods for preparing and isolating polyclonal and monoclonal antibodies are well known in the art. See, for example, *Current Protocols in Immunology*, Cooligan, et al. (eds.), National Institutes of Health, John Wiley and Sons, Inc., 1995; Sambrook et al., *Molecular Cloning: A Laboratory Manual, Second Edition*, Cold Spring Harbor, NY, 1989; and Hurrell, J. G. R., Ed., *Monoclonal Hybridoma Antibodies: Techniques and Applications*, CRC Press, Inc., Boca Raton, FL, 1982.

[49] As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from inoculating a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats with a IL-31RA polypeptide or a fragment thereof. The immunogenicity of an IL-31RA polypeptide may be increased through the use of an adjuvant, such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of IL-31RA or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "haptene-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

[50] As used herein, the term "antibodies" includes polyclonal antibodies, affinity-purified polyclonal antibodies, monoclonal antibodies, and antigen-binding fragments, such as Fab fragment, Fab' fragment, F(ab')<sub>2</sub> fragment, single chain Fv (scFv) 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 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 humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. Moreover, human antibodies can be produced in transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication No. WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

[51] Antibodies are considered to be specifically binding if: 1) they exhibit a threshold level of binding activity, and 2) they do not significantly cross-react with related polypeptide molecules. A threshold level of binding is determined if anti-IL-31RA antibodies herein bind to an

IL-31RA polypeptide, peptide or epitope with an affinity at least 10-fold greater than the binding affinity to control (non-IL-31RA) polypeptide. It is preferred that the antibodies exhibit a binding affinity ( $K_a$ ) of  $10^6$  M<sup>-1</sup> or greater, preferably  $10^7$  M<sup>-1</sup> or greater, more preferably  $10^8$  M<sup>-1</sup> or greater, and most preferably  $10^9$  M<sup>-1</sup> or greater. The binding affinity of an antibody can be readily determined by one of ordinary skill in the art, for example, by Scatchard analysis (Scatchard, G., *Ann. NY Acad. Sci.* 51: 660-672, 1949).

[52] The present invention provides a method of treating a patient suffering from a skin disorder, the method comprises administering a therapeutically effective amount of an anti-IL-31RA antibody or fragment to the patient, wherein the anti-IL-31RA antibody or fragment binds with amino acid residues 20-519 of SEQ ID NO:6 or portion thereof, or amino acid residues 33-532 of SEQ ID NO:8 or portion thereof, and wherein the anti-IL-31RA antibody or fragment prevents, inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Atopic Dermatitis, Contact dermatitis, Drug induced delayed type cutaneous allergic reactions, Toxic epidermal necrolysis, Cutaneous T cell Lymphoma, Bullous pemphigoid, Alopecia areata, Vitiligo, Acne Rosacea, Prurigo nodularis, Scleroderma, and Herpes simplex virus. The anti-IL-31RA antibody may optionally be a polyclonal antibody or a neutralizing monoclonal antibody (the present invention also provides for a hybridoma for producing the neutralizing IL-31RA monoclonal antibody). The anti-IL-31RA antibody fragment may optionally be a Fab fragment, a Fab' fragment, a F(ab')<sub>2</sub> fragment, single chain Fv (scFV), dual specific antibody, domain antibody, or bispecific antibody. The anti-IL-31RA antibody or fragment may bind with amino acid residues 20-277 of SEQ ID NO:6 or 33-240 of SEQ ID NO:8. The anti-IL-31RA antibody or fragment may bind with about 4-10 amino acid residues of amino acid residues 20-519 of SEQ ID NO:6 or amino acid residues 33-532 of SEQ ID NO:8. The anti-IL-31RA antibody or fragment may bind with about 10-14 amino acid residues of amino acid residues 20-519 of SEQ ID NO:6 or amino acid residues 33-532 of SEQ ID NO:8. The anti-IL-31RA antibody or fragment may bind with about 14-30 amino acid residues of amino acid residues 20-519 of SEQ ID NO:6 or amino acid residues 33-532 of SEQ ID NO:8. The anti-IL-31 antibody or fragment may be further conjugated to a polyethylene glycol or to human serum albumin.

[53] The present invention also provides for a method of treating a patient suffering from a skin disorder, the method comprises administering a therapeutically effective amount of a soluble IL-31RA receptor to the patient, wherein the soluble IL-31RA receptor binds with an IL-31 polypeptide consisting of amino acid residues 1-164 SEQ ID NO:2, and wherein the soluble IL-31RA receptor prevents, inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Atopic Dermatitis, Contact dermatitis, Drug induced delayed type cutaneous allergic

reactions, Toxic epidermal necrolysis, Cutaneous T cell Lymphoma, Bullous pemphigoid, Alopecia areata, Vitiligo, Acne Rosacea, Prurigo nodularis, Scleroderma, and Herpes simplex virus. The soluble IL-31RA receptor may comprise amino acid residues 20-519 of SEQ ID NO:6 or 33-240 of SEQ ID NO:8, amino acid residues 1-324 of SEQ ID NO:10, or amino acid residues 1-239 of SEQ ID NO:12. The soluble IL-31RA receptor may be further conjugated to the Fc region of the various immunoglobulins (IgG, IgA, IgD, IgM or IgE). Optionally, the soluble IL-31RA receptor may be an IL-31RA homodimer or an IL-31RA/OSMRbeta heterodimer. The soluble IL-31RA receptor may bind with an IL-31 polypeptide comprising, consisting essentially of, consisting of amino acid residues 24-164 of SEQ ID NO:2 or 27-164 of SEQ ID NO:2. The soluble IL-31RA receptor may be further conjugated to a polyethylene glycol or to human serum albumin.

[54] The present invention also provides isolated IL-31RA encoding nucleic acid molecules that can hybridize under stringent conditions to nucleic acid molecules having the nucleotide sequence of nucleotides 58-1557 of SEQ ID NO:5 or nucleotides 97-1596 SEQ ID NO:7, or to nucleic acid molecules having a nucleotide sequence complementary to nucleotides 58-1557 of SEQ ID NO:5 or to nucleotides 97-1596 SEQ ID NO:7. In general, stringent conditions are selected to be about 5°C lower than the thermal melting point (T<sub>m</sub>) for the specific sequence at a defined ionic strength and pH. The T<sub>m</sub> is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe.

[55] A pair of nucleic acid molecules, such as DNA-DNA, RNA-RNA and DNA-RNA, can hybridize if the nucleotide sequences have some degree of complementarity. Hybrids can tolerate mismatched base pairs in the double helix, but the stability of the hybrid is influenced by the degree of mismatch. The T<sub>m</sub> of the mismatched hybrid decreases by 1°C for every 1-1.5% base pair mismatch. Varying the stringency of the hybridization conditions allows control over the degree of mismatch that will be present in the hybrid. The degree of stringency increases as the hybridization temperature increases and the ionic strength of the hybridization buffer decreases.

[56] It is well within the abilities of one skilled in the art to adapt these conditions for use with a particular polynucleotide hybrid. The T<sub>m</sub> for a specific target sequence is the temperature (under defined conditions) at which 50% of the target sequence will hybridize to a perfectly matched probe sequence. Those conditions which influence the T<sub>m</sub> include, the size and base pair content of the polynucleotide probe, the ionic strength of the hybridization solution, and the presence of destabilizing agents in the hybridization solution. Numerous equations for calculating T<sub>m</sub> are known in the art, and are specific for DNA, RNA and DNA-RNA hybrids and polynucleotide probe sequences of varying length (see, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Edition (Cold Spring Harbor Press 1989); Ausubel et al., (eds.), *Current Protocols in Molecular Biology* (John Wiley and Sons, Inc. 1987); Berger and Kimmel (eds.), *Guide to*

*Molecular Cloning Techniques*, (Academic Press, Inc. 1987); and Wetmur, *Crit. Rev. Biochem. Mol. Biol.* 26:227 (1990)). Sequence analysis software such as OLIGO 6.0 (LSR; Long Lake, MN) and Primer Premier 4.0 (Premier Biosoft International; Palo Alto, CA), as well as sites on the Internet, are available tools for analyzing a given sequence and calculating  $T_m$  based on user defined criteria. Such programs can also analyze a given sequence under defined conditions and identify suitable probe sequences. Typically, hybridization of longer polynucleotide sequences, >50 base pairs, is performed at temperatures of about 20-25°C below the calculated  $T_m$ . For smaller probes, <50 base pairs, hybridization is typically carried out at the  $T_m$  or 5-10°C below the calculated  $T_m$ . This allows for the maximum rate of hybridization for DNA-DNA and DNA-RNA hybrids.

[57] Following hybridization, the nucleic acid molecules can be washed to remove non-hybridized nucleic acid molecules under stringent conditions, or under highly stringent conditions. Typical stringent washing conditions include washing in a solution of 0.5x - 2x SSC with 0.1% sodium dodecyl sulfate (SDS) at 55 - 65°C. That is, nucleic acid molecules encoding a variant IL-31RA polypeptide hybridize with a nucleic acid molecule having the nucleotide sequence of nucleotides 58-1557 of SEQ ID NO:5 (or its complement) or nucleotides 97-1596 SEQ ID NO:7 (or its complement) under stringent washing conditions, in which the wash stringency is equivalent to 0.5x - 2x SSC with 0.1% SDS at 55 - 65°C, including 0.5x SSC with 0.1% SDS at 55°C, or 2x SSC with 0.1% SDS at 65°C. One of skill in the art can readily devise equivalent conditions, for example, by substituting SSPE for SSC in the wash solution.

[58] Typical highly stringent washing conditions include washing in a solution of 0.1x - 0.2x SSC with 0.1% sodium dodecyl sulfate (SDS) at 50 - 65°C. In other words, nucleic acid molecules encoding a variant IL-31RA polypeptide hybridize with a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1 (or its complement) under highly stringent washing conditions, in which the wash stringency is equivalent to 0.1x - 0.2x SSC with 0.1% SDS at 50 - 65°C, including 0.1x SSC with 0.1% SDS at 50°C, or 0.2x SSC with 0.1% SDS at 65°C.

[59] The present invention also provides isolated IL-31RA polypeptides that have a substantially similar sequence identity to the polypeptides having amino acid residues 20-519 of SEQ ID NO:6 and/or amino acid residues 33-532 of SEQ ID NO:8, or their orthologs. The term "substantially similar sequence identity" is used herein to denote polypeptides comprising at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or greater than 99.5% sequence identity to the sequences shown in amino acid residues 20-519 of SEQ ID NO:6 and/or amino acid residues 33-532 of SEQ ID NO:8, or their orthologs. The present invention further includes nucleic acid molecules that encode such polypeptides. Methods for determining percent identity are described PCT publications WO 02/00721 (incorporated by reference) and 04/003140 (incorporated by reference).

[60] The present invention provides a method of treating a patient suffering from a skin disorder, the method comprises administering a therapeutically effective amount of an anti-IL-31RA antibody or fragment to the patient, wherein the anti-IL-31RA antibody or fragment binds with an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or great than 99.5% sequence identity with amino acid residues 20-519 of SEQ ID NO:6 or portion thereof, or amino acid residues 33-532 of SEQ ID NO:8 or portion thereof, and wherein the anti-IL-31RA antibody or fragment prevents, inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Atopic Dermatitis, Contact dermatitis, Drug induced delayed type cutaneous allergic reactions, Toxic epidermal necrolysis, Cutaneous T cell Lymphoma, Bullous pemphigoid, Alopecia areata, Vitiligo, Acne Rosacea, Prurigo nodularis, Scleroderma, and Herpes simplex virus. The anti-IL-31RA antibody may optionally be a polyclonal antibody or a neutralizing monoclonal antibody (the present invention also provides for a hybridoma for producing the neutralizing IL-31RA monoclonal antibody). The anti-IL-31RA antibody fragment may optionally be a Fab fragment, a Fab' fragment, a F(ab')<sub>2</sub> fragment, single chain Fv (scFV), dual specific antibody, domain antibody, or bispecific antibody. The anti-IL-31RA antibody or fragment may bind with amino acid residues 20-277 of SEQ ID NO:6 or 33-240 of SEQ ID NO:8. The anti-IL-31RA antibody or fragment may bind with about 4-10 amino acid residues of amino acid residues 20-519 of SEQ ID NO:6 or amino acid residues 33-532 of SEQ ID NO:8. The anti-IL-31RA antibody or fragment may bind with about 10-14 amino acid residues of amino acid residues 20-519 of SEQ ID NO:6 or amino acid residues 33-532 of SEQ ID NO:8. The anti-IL-31RA antibody or fragment may bind with about 14-30 amino acid residues of amino acid residues 20-519 of SEQ ID NO:6 or amino acid residues 33-532 of SEQ ID NO:8. The anti-IL-31 antibody or fragment may be further conjugated to a polyethylene glycol or to human serum albumin.

[61] The present invention also provides for a method of treating a patient suffering from a skin disorder, the method comprises administering a therapeutically effective amount of a soluble IL-31RA receptor to the patient, wherein the soluble IL-31RA receptor has at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or great than 99.5% sequence identity with amino acid residues 20-519 of SEQ ID NO:6 or portion thereof, or amino acid residues 33-532 of SEQ ID NO:8, and wherein the soluble IL-31RA receptor binds with an IL-31 polypeptide consisting of amino acid residues 1-164 SEQ ID NO:2, and wherein the soluble IL-31RA receptor prevents, inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Atopic Dermatitis, Contact dermatitis, Drug induced

delayed type cutaneous allergic reactions, Toxic epidermal necrolysis, Cutaneous T cell Lymphoma, Bullous pemphigoid, Alopecia areata, Vitiligo, Acne Rosacea, Prurigo nodularis, Scleroderma, and Herpes simplex virus. The soluble IL-31RA receptor may comprise amino acid residues 20-519 of SEQ ID NO:6 or 33-240 of SEQ ID NO:8, amino acid residues 1-324 of SEQ ID NO:10, or amino acid residues 1-239 of SEQ ID NO:12. The soluble IL-31RA receptor may be further conjugated to the Fc region of the various immunoglobulins (IgG, IgA, IgD, IgM or IgE). Optionally, the soluble IL-31RA receptor may be an IL-31RA homodimer or an IL-31RA/OSMRbeta heterodimer. The soluble IL-31RA receptor may bind with an IL-31 polypeptide comprising, consisting essentially of, consisting of amino acid residues 24-164 of SEQ ID NO:2 or 27-164 of SEQ ID NO:2. The soluble IL-31RA receptor may be further conjugated to a polyethylene glycol or to human serum albumin.

[62] A variety of assays known to those skilled in the art can be utilized to detect antibodies which bind to IL-31RA proteins or polypeptides. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring 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. In addition, antibodies can be screened for binding to wild-type versus mutant IL-31RA protein or polypeptide.

[63] Antibodies to IL-31RA may be used for tagging cells that express IL-31RA; for isolating IL-31RA by affinity purification; for diagnostic assays for determining circulating levels of IL-31RA polypeptides; for detecting or quantitating soluble IL-31RA as a marker of underlying pathology or disease; in analytical methods employing FACS; for screening expression libraries; for generating anti-idiotypic antibodies; and as neutralizing antibodies or as antagonists to block IL-31 activity in vitro and in vivo. Suitable direct tags or labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles and the like; indirect tags or labels may feature use of biotin-avidin or other complement/anti-complement pairs as intermediates. Antibodies herein may also be directly or indirectly conjugated to drugs, toxins, radionuclides and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. In addition, antibodies to IL-31RA or fragments thereof may be used in vitro to detect denatured IL-31RA or fragments thereof in assays, for example, Western Blots or other assays known in the art.

[64] Suitable detectable molecules may be directly or indirectly attached to the polypeptide or antibody, and include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles and the like. Suitable cytotoxic molecules may be directly or indirectly attached to the polypeptide or antibody, and include bacterial or plant toxins (for instance, diphtheria, toxin, saporin, Pseudomonas exotoxin, ricin, abrin and the

like), as well as therapeutic radionuclides, such as iodine-131, rhenium-188 or yttrium-90 (either directly attached to the polypeptide or antibody, or indirectly attached through means of a chelating moiety, for instance). Polypeptides or antibodies may also be conjugated to cytotoxic drugs, such as adriamycin. For indirect attachment of a detectable or cytotoxic molecule, the detectable or cytotoxic molecule can be conjugated with a member of a complementary/anticomplementary pair, where the other member is bound to the polypeptide or antibody portion. For these purposes, biotin/streptavidin is an exemplary complementary/ anticomplementary pair.

[65] Polypeptide-toxin fusion proteins or antibody-toxin fusion proteins can be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Alternatively, if the polypeptide has multiple functional domains (i.e., an activation domain or a receptor binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain only fusion protein includes a complementary molecule, the anti-complementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting carrier or vehicle for cell/tissue-specific delivery of generic anti-complementary-detectable/ cytotoxic molecule conjugates.

[66] Both skin-homing T cells and epidermal keratinocytes have been implicated in the pathology of skin diseases in humans. As shown in Example 1 herein, of the T cell subsets, IL-31 mRNA and protein expression is restricted to the skin-homing CLA<sup>+</sup> T cell population in humans. As such, an antagonist to IL-31RA, including an antibody or fragment thereof or soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors) antagonist will be useful in treating, ablating, inhibiting the progression of, and/or reducing the severity of skin and epidermal diseases which have expression of CLA<sup>+</sup> T cells. Such diseases include, for example, atopic dermatitis, contact dermatitis, psoriasis, drug-induced allergic reactions, skin-tropic viruses and viral associated pruritis, vitiligo, cutaneous T cell lymphoma, alopecia aerata, acne rosacea, acne vulgaris, prurigo nodularis, and bullous pemphigoid.

#### Atopic Dermatitis

[67] Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease with a dramatically increasing incidence over the last decades. Clinically AD is characterized by highly pruritic often excoriated plaques and papules that show a chronic relapsing course. The diagnosis of AD is mostly based on major and minor clinical findings. See Hanifin J.M., *Arch Dermatol*: 135, 1551 (1999). Histopathology reveals spongiosis, hyper and focal parakeratosis in acute lesions, whereas marked epidermal hyperplasia with hyper and parakeratosis, acanthosis/hypergranulosis and

perivascular infiltration of the dermis with lymphocytes and abundant mast cells are the hallmarks of chronic lesions.

[68] T cells play a central role in the initiation of local immune responses in tissues and evidence suggests that skin-infiltrating T cells in particular, may play a key role in the initiation and maintenance of dysregulated immune responses in the skin. Approximately 90% of infiltrating T cells in cutaneous inflammatory sites express the cutaneous lymphocyte-associated Ag (CLA+) which binds E-selectin, an inducible adhesion molecule on endothelium (reviewed in Santamaria-Babi L.F., et al., *Eur J Dermatol*: 14, 13, (2004)). A significant increase in circulating CLA+ T cells among AD patients compared with control individuals has been documented (See Teraki Y., et al., *Br J Dermatol*: 143, 373 (2000)), while others have demonstrated that memory CLA+ T cells from AD patients preferentially respond to allergen extract compared to the CLA- population (See Santamaria-Babi, L.F., et al., *J Exp Med*: 181, 1935, (1995)). In humans, the pathogenesis of atopic disorders of the skin have been associated with increases in CLA+ T cells that express increased levels of Th-2-type cytokines like IL-5 and IL-13. See Akdis M., et al., *Eur J Immunol*: 30, 3533 (2000); and Hamid Q., et al., *J Allergy Clin Immunol*: 98, 225 (1996).

[69] NC/Nga Mice spontaneously develop AD-like lesions that parallel human AD in many aspects, including clinical course and signs, histopathology and immunopathology when housed in non-specified pathogen -free (non-SPF) conditions at around 6-8 weeks of age. In contrast, NC/Nga mice kept under SPF conditions do not develop skin lesions. However, onset of spontaneous skin lesions and scratching behaviour can be synchronized in NC/Nga mice housed in a SPF facility by weekly intradermal injection of crude dust mite antigen. See Matsuoka H., et al., *Allergy*: 58, 139 (2003). Therefore, the development of AD in NC/Nga is a useful model for the evaluation of novel therapeutics for the treatment of AD.

[70] In addition to the NC/Nga model of spontaneous AD, epicutaneous sensitization of mice using OVA can also be used as a model to induce antigen-dependent epidermal and dermal thickening with a mononuclear infiltrate in skin of sensitized mice. This usually coincides with elevated serum levels of total and specific IgE, however no skin barrier dysfunction or pruritus normally occurs in this model. See Spergel J.M., et al., *J Clin Invest*, 101: 1614, (1998). This protocol can be modified in order to induce skin barrier dysregulation and pruritis by sensitizing DO11.10 OVA TCR transgenic mice with OVA. Increasing the number of antigen-specific T cells that could recognize the sensitizing antigen may increase the level of inflammation in the skin to induce visible scratching behaviour and lichenification/scaling of the skin.

[71] Both the NC/Nga spontaneous AD model and the OVA epicutaneous DO11.10 model are used to investigate expression of IL-31 and IL-31RA in AD. See Example 3.

[72] An IL-31RA neutralizing antagonist could be effective in inhibiting, reducing, minimizing or preventing atopic dermatitis reactions. See Example 3 for an in vivo model for testing the effect of an IL-31 antagonist in an atopic dermatitis model.

#### Contact dermatitis

[73] Allergic contact dermatitis is defined as a T cell mediated immune reaction to an antigen that comes into contact with the skin. The CLA+ T cell population is considered to be involved in the initiation of dermatitis since allergen dependent T cell responses are largely confined to the CLA+ population of cells (See Santamaria-Babi, L.F., et al., *J Exp Med*:181, 1935, (1995)). Recent data has found that only memory (CD45RO+) CD4+ CLA+ and not CD8+ T cells proliferate and produce both type-1 (IFN- $\gamma$ ) and type-2 (IL-5) cytokines in response to nickel, a common contact hypersensitivity allergen. Furthermore, cells expressing CLA in combination with CD4, CD45RO (memory) or CD69 are increased after nickel-specific stimulation and express the chemokine receptors CXCR3, CCR4, CCR10 but not CCR6. See Moed H., et al., *Br J Dermatol*:51, 32, (2004).

[74] In animal models, it has been demonstrated that allergic contact dermatitis is T- cell dependent and that the allergic-responsive T cells migrate to the site of allergen application. See generally: Engeman T.M., et al., *J Immunol*: 164, 5207, (2000); Ferguson T.A. & Kupper T.S. *J Immunol*: 150, 1172, (1993); and Gorbachev A.V. & Fairchild R.L. *Crit Rev Immunol*: 21, 451(2001). Since CLA+ T cells produce IL-31 and IL-31 stimulation of skin keratinocytes can induce pro-inflammatory chemokines, IL-31 may be involved in the pathophysiology of contact dermatitis.

[75] An IL-31RA neutralizing antagonist, e.g., antibody or fragment thereof or soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors), could be effective in inhibiting, reducing, minimizing or preventing contact dermatitis reactions. See Example 2 for an in vivo model for testing the effect of an IL-31 antagonist in a contact dermatitis model.

#### Drug-induced delayed type cutaneous allergic reactions

[76] Drug-induced delayed type cutaneous allergic reactions are very heterogeneous and may mirror many distinct pathophysiological events. See Brockow K., et al., *Allergy*, 57, 45 (2002). Immunological mechanisms involved in these reactions have been shown as either antibody or cell mediated. In immediate drug allergy an IgE-mediated antibody reaction can be demonstrated by a positive skin prick and/or intradermal test after 20 min, whereas non-immediate reactions to drugs can occur more than one hour after last drug intake and are often T-cell mediated. Non-immediate T-cell mediated delayed type reactions can occur in patients with adverse drug reactions to penicillins for example. Proliferative T cell responses to penicillins have been shown to be restricted to the

memory (CD45RO+) CLA+ subpopulation of T cells from penicillin allergic patients whereas the CD45RO+ CLA- subset shows no proliferative response. See Blanca M., Leyva L., et al., *Blood Cells Mol Dis*:31, 75 (2003). Delayed-type hypersensitivity (DTH) reactions can be artificially reproduced in mice, allowing assessment of factors that may be involved in the initiation and perpetuation of the DTH response. An IL-31RA neutralizing antagonist, e.g., antibody or soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors), could be effective in inhibiting, reducing, minimizing or preventing delayed type hypersensitivity reactions. See Example 4 for an in vivo model of testing the effect of an IL-31 antagonist in a DTH model.

[77] Toxic epidermal necrolysis (TEN) is a very rare but extremely severe drug reaction characterized by widespread apoptosis of epidermis with extensive blisters. Studies have shown that lymphocytes infiltrating the blister are CLA+ T cells and can exhibit cytotoxicity towards epidermal keratinocytes. See Leyva L., et al., *J Allergy Clin Immunol*: 105, 157 (2000); and Nassif A., Bensussan A., et al., *J Allergy Clin Immunol*:114, 1209 (2004). A transgenic mouse system, whereby OVA is expressed under the control of the keratin-5 (K5) promoter in the epidermal and hair follicular keratinocytes of mice, has been generated to establish an animal model for TEN. OVA specific CD8+ T cells, when adoptively transferred into K5-OVA mice, undergo activation and proliferation in the skin-draining lymph nodes and target the skin of K5-OVA mice, resulting in development of skin lesions that are reminiscent of TEN. See Azukizawa H., et al., *Eur J Immunol*: 33, 1879 (2003). An IL-31RA neutralizing antagonist, e.g., antibody or soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors), could be effective in inhibiting, reducing, minimizing or preventing TEN reactions.

#### Bullous pemphigoid

[78] Bullous pemphigoid is a subepidermal disorder which manifests as subepidermal blisters with a dermal infiltrate of neutrophils and eosinophils. Diagnosis is characterized by the presence of antigen-specific antibodies against specific adhesion proteins of the epidermis and dermal-epidermal junction. See Jordon R.E., et al., *JAMA*: 200, 751 (1967). Studies analyzing the role of T cells in the pathogenesis of bullous pemphigoid by analysis of PBL and skin blister T cells have found a predominance of CLA+ T cells expressing increased levels of Th2-cytokines like IL-4 and IL-13. See Teraki Y., et al., *J Invest Dermatol*: 117, 1097 (2001). In bullous pemphigoid patients following therapy with systemic corticosteroids, the frequency of CLA+, but not CLA-, interleukin-13-producing cells is significantly decreased. Decreases in CLA+ cells following corticosteroid treatment is associated with clinical improvement. See Teraki, *ibid*. Neutralization of IL-31 by an IL-31RA antagonist, e.g., antibody or fragment thereof or soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors), may improve clinical outcome of bullous pemphigoid.

Alopecia areata

[79] Alopecia areata (AA) is regarded as a tissue-restricted autoimmune disease of hair follicles in which follicular activity is arrested because of the continued activity of lymphocytic infiltrates. AA results in patches of complete hair loss anywhere on the body, though actual loss of hair follicles does not occur, even in hairless lesions. Although clinical signs of inflammation are absent, skin biopsies from sites of active disease show perifollicular lymphocytic inflammation of primarily CD4+ cells, along with a CD8+ intrafollicular infiltrate. See Kalish R.S. & Gilhar A. *J Invest Dermatol Symp Proc*: 8, 164 (2003).

[80] Studies have shown that scalp skin infiltrating CD4+ or CD8+ lymphocytes express CLA and, in peripheral blood of individuals with AA, the percent of CLA+ CD4+ or CD8+ lymphocytes is significantly higher than that of normal controls. Furthermore, patients with severe or progressive AA show a much higher CLA-positivity compared to patients recovering from the disease and a decrease in percent CLA+ cells parallels a good clinical course. See Yano S., et al., *Acta Derm Venereol*: 82, 82 (2002). These studies therefore suggest that CLA+ lymphocytes may play an important role in AA. Xenograft models have demonstrated that activated T cells are likely to play a role in the pathogenesis of AA. Lesional scalp from AA patients grafted onto nude mice regrows hair coincident with a loss of infiltrating lymphocytes from the graft and, transfer of activated lesional T cells to SCID mice can transfer hair loss to human scalp explants on SCID mice. See Kalish R.S. & Gilhar A. *J Invest Dermatol Symp Proc*: 8, 164 (2003).

[81] A variety of immunomodulating therapies are part of the usual treatment for this disorder however none of these treatments have been consistent in their efficacy. See Tang L., et al., *J Invest Dermatol*: 120, 400 (2003); Tang L., et al., (2004); and Tang L., et al., *J Am Acad Dermatol*: 49, 1013 (2003). Neutralizing anti-IL-31RA antibody or fragment thereof or IL-31RA soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors) may be effective to limit, reduce, inhibit, or prevent the effects of the development of AA.

Acne vulgaris /Acne rosacea

[82] Acne vulgaris, a disorder of the pilosebaceous apparatus, is the most common skin problem of adolescence. Abnormalities in follicular keratinization are thought to produce the acne lesion. Acne rosacea is differentiated from acne vulgaris by the presence of red papules, pustules, cysts and extensive telangiectasias, but the absence of comedones (white heads). Increased sebum excretion from sebaceous glands is a major factor in the pathophysiology of acne vulgaris. Other sebaceous gland functions are also associated with the development of acne, including sebaceous proinflammatory lipids; different cytokines produced locally; periglandular peptides and

neuropeptides, such as corticotrophin-releasing hormone, which is produced by sebocytes; and substance P, which is expressed in the nerve endings at the vicinity of healthy-looking glands of acne patients. See Zouboulis C.C. *Clin Dermatol*: 22, 360 (2004).

[83] Although the pathophysiology of acne vulgaris and acne rosacea remains unknown, clinical observations and histopathologic studies suggest that inflammation of the pilosebaceous follicle may be central to the pathogenesis of rosacea and acne vulgaris. Early studies on analysis of T cell subsets infiltrating rosacea lesions indicated that the majority of T cells expressed CD4. See Rufli T. & Buchner S.A. *Dermatologica*: 169, 1 (1984).

[84] CD4+ T cells produce IL-31 and IHC analysis of skin for IL-31 expression suggests that IL-31 is expressed in sebaceous and sweat glands. IL-31 stimulation of epidermal keratinocytes induces expression of chemokines which likely results in cellular infiltration suggesting that IL-31 may contribute to the pro-inflammatory response in skin. IL-31 may therefore contribute to the pathophysiology of acne rosacea and acne vulgaris. Accordingly, an IL-31RA antagonist, such as an anti-IL-31RA antibody or fragment thereof, or an IL-31RA soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors) can be useful to treat, reduce the severity of, inhibit the progression of, ablate, and/or eliminate one or more symptoms associated with acne rosacea and acne vulgaris.

#### Prurigo nodularis

[85] Prurigo nodularis is an eruption of lichenified or excoriated nodules caused by intractable pruritus that is difficult to treat. While chronic rubbing results in lichenification, and scratching in linear excoriations, individuals who pick and gouge at their itchy, irritated skin tend to produce markedly thickened papules known as prurigo nodules. Although prurigo nodularis is not specific to atopic dermatitis, many patients with these nodules also have an atopic reaction, which manifests as allergic rhinitis, asthma, or food allergy. T cells represent the majority of infiltrating cells in prurigo lesions and these lesions often represent the most pruritic skin lesion in atopy patients.

[86] Topical treatment of prurigo nodularis with capsaicin, an anti-pruritic alkaloid that interferes with the perception of pruritus and pain by depletion of neuropeptides like substance P in small sensory cutaneous nerves, has proven to be an effective and safe regimen resulting in clearing of the skin lesions. See Stander S., et al., *J Am Acad Dermatol*: 44, 471 (2001). Studies of the itch response in NC/Nga mice using capsaicin treatment showed that the spontaneous development of dermatitis lesions was almost completely prevented. Furthermore, the elevation of serum IgE levels was significantly suppressed and infiltrating eosinophils and mast cell numbers in lesional skin of capsaicin treated mice were reduced. See Mihara K., et al., *Br J Dermatol*: 151, 335 (2004). The

observations from this group suggest that scratching behaviour might contribute to the development of dermatitis by enhancing various immunological responses, therefore implying that prevention of the itch sensation and/or itch-associated scratching behaviour might be an effective treatment for AD. See Mihara K., et al., *Br J Dermatol*: 151, 335 (2004).

[87] Chronic delivery of IL-31 induces pruritis and alopecia in mice followed by the development of skin lesions resembling dermatitis suggesting that IL-31 induces itching. See Dillon S.R., et al., *Nat Immunol*: 5, 752 (2004). The involvement of IL-31 was tested in induction of the itch response by two methods (i) capsaicin treatment of IL-31-treated mice and (ii) IL-31 treatment of Tac1 knockout mice, which have significantly reduced nociceptive pain responses because of lack of expression of neuropeptides in Example 5. In addition, whether neutralization of IL-31 in IL-31 treated mice could prevent pruritis and alopecia was tested in Example 5.

#### Skin-Tropic Viruses and Viral Associated pruritis

[88] Herpes Simplex Virus (HSV)-specific CD8+ T cells in the peripheral blood and HSV-specific CD8+ T cells recovered from herpes lesions express high levels of CLA where as non-skin-tropic herpes virus-specific CD8+ T cells lack CLA expression. See Koelle D.M., et al., *J Clin Invest*: 110, 537 (2002). HSV-2 reactive CD4+ T lymphocytes also express CLA, but at levels lower than those previously observed for CD8+ T lymphocytes. See Gonzalez J.C., et al., *J Infect Dis*: 191, 243 (2005). Pruritis has also been associated with herpes viral infections (See Hung K.Y., et al., *Blood Purif*: 16, 147 (1998), though other viral diseases, like HIV, have also been associated with pruritic skin lesions. Severe, intractable pruritus, often associated with erythematopapular skin lesions and hypereosinophilia, is a condition observed in some nonatopic, HIV-infected patients 36. See Singh F. & Rudikoff D, *Am J Clin Dermatol*; 4, 177 (2003); and Milazzo F., Piconi S., et al., *Allergy*: 54, 266 (1999).

[89] The association of skin-tropic viruses with pruritis and CLA+ T cells suggests that IL-31 producing T cells may be involved in the pathophysiology of viral infections.

[90] Inflammation is a protective response by an organism to fend off an invading agent. Inflammation is a cascading event that involves many cellular and humoral mediators. On one hand, suppression of inflammatory responses can leave a host immunocompromised; however, if left unchecked, inflammation can lead to serious complications including chronic inflammatory diseases (e.g., rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and the like), septic shock and multiple organ failure. Importantly, these diverse disease states share common inflammatory mediators. The collective diseases that are characterized by inflammation have a large impact on human morbidity and mortality. Therefore it is clear that anti-inflammatory molecules, such as anti-IL-31RA antibodies and fragments thereof, and IL-31RA soluble receptors as described herein, could

have crucial therapeutic potential for a vast number of human and animal diseases, from asthma and allergy to autoimmunity and septic shock. As such, use of anti-inflammatory anti-IL-31RA antibodies and fragments thereof, and IL-31RA soluble receptors as described herein can be used therapeutically as IL-31RA antagonists for treating, reducing the severity of, inhibiting the progression of, and ablating diseases such as arthritis, endotoxemia, inflammatory bowel disease, psoriasis, related disease and the like.

[91] IL-31 has been shown to induce several chemokine and cytokine genes in normal human epidermal keratinocytes (NHEKs), including genes encoding GRO $\alpha$ , (CXCL1), TARC (CC117), MIP3 $\beta$ , (CCL19), MDC (CCL22), MIP-3 (CCL23), MIP-1  $\beta$  (CCL4), and I-309. See Dillon S.R., et al., *Nat Immunol*: 5, 752 (2004). TARC and MDC bind CCR4, a chemokine receptor associated with Th2-type T cells and predominantly expressed by CLA+ T cells in peripheral blood. Both chemokines have been implicated in the recruitment of T cells into the skin of AD patients suggesting that these chemokines contribute to the inflammatory process associated with the pathogenesis of AD. See Example 10 for a model to measure the reduction in TARC and MDC levels by administering an IL-31 antagonist.

[92] Psoriasis is a chronic skin condition that affects more than seven million Americans. Psoriasis occurs when new skin cells grow abnormally, resulting in inflamed, swollen, and scaly patches of skin where the old skin has not shed quickly enough. Plaque psoriasis, the most common form, is characterized by inflamed patches of skin ("lesions") topped with silvery white scales. Psoriasis may be limited to a few plaques or involve moderate to extensive areas of skin, appearing most commonly on the scalp, knees, elbows and trunk. Although it is highly visible, psoriasis is not a contagious disease. The pathogenesis of the diseases involves chronic inflammation of the affected tissues. Anti-IL-31RA antibodies and fragment thereof and soluble receptors (IL-31RA and IL-31RA/OSMRbeta soluble receptors) could serve as a valuable therapeutic to treat, inhibit the progression of, reduce the severity of, reduce inflammation and pathological effects in psoriasis, other inflammatory skin diseases, skin and mucosal allergies, and related diseases.

[93] Psoriasis is a T-cell mediated inflammatory disorder of the skin that can cause considerable discomfort. It is a disease for which there is no cure and affects people of all ages. Psoriasis affects approximately two percent of the populations of European and North America. Although individuals with mild psoriasis can often control their disease with topical agents, more than one million patients worldwide require ultraviolet or systemic immunosuppressive therapy. Unfortunately, the inconvenience and risks of ultraviolet radiation and the toxicities of many therapies limit their long-term use. Moreover, patients usually have recurrence of psoriasis, and in some cases rebound, shortly after stopping immunosuppressive therapy.

[94] The present invention provides a method for inhibiting activation or differentiation of monocytes/macrophages. Monocytes are incompletely differentiated cells that migrate to various tissues where they mature and become macrophages. Macrophages play a central role in the immune response by presenting antigen to lymphocytes and play a supportive role as accessory cells to lymphocytes by secreting numerous cytokines. Macrophages can internalize extracellular molecules and upon activation have an increased ability to kill intracellular microorganisms and tumor cells. Activated macrophages are also involved in stimulating acute or local inflammation.

[95] The molecules of the present invention have particular use in the monocyte/macrophage arm of the immune system. Methods are known that can assess such activity. For example, interferon gamma (IFN- $\gamma$ ) is a potent activator of mononuclear phagocytes. For example, an increase in expression of IL-31RA upon activation of THP-1 cells (ATCC No. TIB-202) with interferon gamma could suggest that this receptor is involved in monocyte activation. Monocytes are incompletely differentiated cells that migrate to various tissues where they mature and become macrophages. Macrophages play a central role in the immune response by presenting antigen to lymphocytes and play a supportive role as accessory cells to lymphocytes by secreting numerous cytokines. Macrophages can internalize extracellular molecules and upon activation have an increased ability to kill intracellular microorganisms and tumor cells. Activated macrophages are also involved in stimulating acute or local inflammation. Moreover, monocyte-macrophage function has been shown to be abnormal in a variety of diseased states. For example see, Johnston, RB, *New Eng. J. Med.* 318:747-752, 1998.

[96] One of skill in the art would recognize that agonists of IL-31RA receptor, such as agonist IL-31RA antibody, are useful. For example, depressed migration of monocytes has been reported in populations with a predisposition to infection, such as newborn infants, patients receiving corticosteroid or other immunosuppressive therapy, and patients with diabetes mellitus, burns, or AIDS. Agonists for IL-31RA, such as agonist IL-31RA antibody, could result in an increase in the ability of monocytes to migrate and possibly prevent infection in these populations. There is also a profound defect of phagocytic killing by mononuclear phagocytes from patients with chronic granulomatous disease. This results in the formation of subcutaneous abscesses, as well as abscesses in the liver, lungs, spleen, and lymph nodes. An agonist of IL-31RA receptor such as agonist IL-31RA antibody, could correct or improve this phagocytic defect. In addition, defective monocyte cytotoxicity has been reported in patients with cancer and Wiskott-Aldrich syndrome (eczema, thrombocytopenia, and recurrent infections). Activation of monocytes by agonists of IL-31RA receptor, such as agonist IL-31RA antibody, could aid in treatment of these conditions. The monocyte-macrophage system is prominently involved in several lipid-storage diseases (sphingolipidoses) such as Gaucher's disease. Resistance to infection can be impaired because of a

defect in macrophage function, which could be treated by agonists to IL-31RA receptor such as agonist IL-31RA antibody.

[97] Using methods known in the art, and disclosed herein, one of skill could readily assess the activity of IL-31RA agonists and antagonists in diseases that have a high correlation of CLA+ T cells. In addition, as IL-31 is expressed in a T-cell, macrophage and monocyte-specific manner, and these diseases involve abnormalities in monocytic cells, such as cell proliferation, function, localization, and activation, the polynucleotides, polypeptides, and antibodies of the present invention can be used to as diagnostics to detect such monocytic cell abnormalities, and indicate the presence of disease. Such methods involve taking a biological sample from a patient, such as blood, saliva, or biopsy, and comparing it to a normal control sample. Histological, cytological, flow cytometric, biochemical and other methods can be used to determine the relative levels or localization of IL-31, or cells expressing IL-31, i.e., monocytes, in the patient sample compared to the normal control. A change in the level (increase or decrease) of IL-31 expression, or a change in number or localization of monocytes (e.g., increase or infiltration of monocytic cells in tissues where they are not normally present) compared to a control would be indicative of disease. Such diagnostic methods can also include measuring TARC and MDC, for example. Such methods are well known in the art and disclosed herein.

[98] IL-31RA antagonists, such as anti-IL-31RA antibodies, can be used to modulate the immune system by binding IL-31RA receptor, and thus, preventing the binding of IL-31 with endogenous IL-31 receptor. Alternatively, IL-31RA antagonists, such as soluble IL-31RA and IL-31RA/OSMRbeta receptors, can also be used to modulate the immune system by inhibiting the binding of IL-31 with the endogenous IL-31RA receptor. Accordingly, the present invention includes the use of IL-31RA antibodies and fragments thereof as well as IL-31RA soluble receptors (IL-31RAa dn IL-31RA/OSMRbeta) which can be administered to a subject which has excess IL-31. IL-31RA antagonists (e.g., anti-IL-31RA antibodies and fragments thereof and soluble IL-31RA and soluble IL-31RA/OSMRbeta receptors) can be also used to treat diseases that have a high correlation of CLA+ T cells. Suitable subjects include mammals, such as humans.

[99] IL-31 has been shown to be expressed in activated mononuclear cells, and may be involved in regulating inflammation. As such, antibodies and soluble receptors of the present invention can be assayed and used for their ability to modify inflammation, or can be used as a marker for inflammation. Methods to determine proinflammatory and anti-inflammatory qualities of IL-31 are known in the art and discussed herein. Moreover, it may be involved in up-regulating the production of acute phase reactants, such as serum amyloid A (SAA),  $\alpha$ 1-antichymotrypsin, and haptoglobin, and that expression of IL-31RA receptor may be increased upon injection of lipopolysaccharide (LPS) *in vivo* that are involved in inflammatory response (Dumoutier, L. et al.,

*Proc. Nat'l. Acad. Sci.* 97:10144-10149, 2000). Production of acute phase proteins, such as SAA, is considered a short-term survival mechanism where inflammation is beneficial; however, maintenance of acute phase proteins for longer periods contributes to chronic inflammation and can be harmful to human health. For review, see Uhlar, CM and Whitehead, AS, *Eur. J. Biochem.* 265:501-523, 1999, and Baumann H. and Gauldie, J. *Immunology Today* 15:74-80, 1994. Moreover, the acute phase protein SAA is implicated in the pathogenesis of several chronic inflammatory diseases, is implicated in atherosclerosis and rheumatoid arthritis, and is the precursor to the amyloid A protein deposited in amyloidosis (Uhlar, CM and Whitehead, *supra.*). Thus, where a ligand such as IL-31 that acts as a pro-inflammatory molecule and induces production of SAA, antagonists would be useful in treating inflammatory disease and other diseases associated with acute phase response proteins induced by the ligand. Such antagonists are provided by the present invention. For example, a method of reducing inflammation comprises administering to a mammal with inflammation a therapeutically effective amount of a composition comprising anti-IL-31RA antibody (e.g., neutralizing antibody) or fragment thereof, or a soluble receptor (e.g., IL-31RA and IL-31RA/OSMRbeta soluble receptors) that is sufficient to reduce inflammation. Moreover, a method of suppressing an inflammatory response in a mammal with inflammation can comprise: (1) determining a level of serum amyloid A protein; (2) administering a composition comprising an anti- IL-31RA antibody as described herein or soluble receptor (IL-31RA and IL-31RA/OSMRbeta soluble receptors) in an acceptable pharmaceutical carrier; (3) determining a post administration level of serum amyloid A protein; (4) comparing the level of serum amyloid A protein in step (1) to the level of serum amyloid A protein in step (3), wherein a lack of increase or a decrease in serum amyloid A protein level is indicative of suppressing an inflammatory response.

[100] Moreover, anti-IL-31RA antibodies and fragments thereof that block the binding and/or signaling of IL-31 to IL-31RA, and soluble IL-31RA receptors (IL-31RA and IL-31RA/OSMRbeta) that bind IL-31 and thus prevent the binding of IL-31 to cellular-based IL-31RA are useful to antagonize or block signaling of IL-31 and are thus useful in the treatment of, inhibit the progression of, reduce the severity of, reduce one or more symptoms associated with Contact dermatitis, Drug induced delayed type cutaneous allergic reactions, Toxic epidermal necrolysis, Cutaneous T cell Lymphoma, Bullous pemphigoid, Alopecia areata, Vitiligo, Acne Rosacea, Prurigo nodularis, Scleroderma, and Herpes simplex virus.

[101] Anti-IL-31RA antibodies, and soluble IL-31RA (IL-31RA and IL-31RA/OSMRbeta soluble receptors) comprising receptors are useful as antagonists of IL-31. Such antagonistic effects can be achieved by direct neutralization or binding of its natural ligand. In addition to antagonistic uses, the soluble receptors can bind IL-31 and act as carrier or carrier proteins, in order to transport IL-31 to different tissues, organs, and cells within the body. As such, the soluble receptors can be

fused or coupled to molecules, polypeptides or chemical moieties that direct the soluble-receptor-Ligand complex to a specific site, such as a tissue, specific immune cell, monocytes, or tumor. For example, in acute infection or some cancers, benefit may result from induction of inflammation and local acute phase response proteins. Thus, the soluble receptors described herein or antibodies (and fragments thereof) of the present invention can be used to specifically direct the action of a pro-inflammatory IL-31 ligand. See, Cosman, D. *Cytokine* 5: 95-106, 1993; and Fernandez-Botran, R. *Exp. Opin. Invest. Drugs* 9:497-513, 2000.

[102] IL-31 may also be used within diagnostic systems for the detection of circulating levels of ligand, and in the detection of acute phase inflammatory response. Within a related embodiment, antibodies or other agents that specifically bind to IL-31, e.g., soluble IL-31RA and soluble IL-31RA/OSMRbeta, can be used to detect circulating IL-31 polypeptides. Elevated or depressed levels of ligand or receptor polypeptides may be indicative of pathological conditions, including inflammation or cancer. Moreover, detection of acute phase proteins or molecules such as IL-31 can be indicative of a chronic inflammatory condition in certain disease states (e.g., rheumatoid arthritis). Detection of such conditions serves to aid in disease diagnosis as well as help a physician in choosing proper therapy.

[103]. Generally, the dosage of administered IL-31RA antibody or fragment thereof or soluble IL-31RA receptor or soluble IL-31RA/OSMRbeta receptor will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition and previous medical history. Typically, it is desirable to provide the recipient with a dosage of IL-31RA antibody or fragment thereof or soluble IL-31RA receptor or soluble IL-31RA/OSMRbeta receptor which is in the range of from about 1 pg/kg to 10 mg/kg (amount of agent/body weight of patient), although a lower or higher dosage also may be administered as circumstances dictate. One skilled in the art can readily determine such dosages, and adjustments thereto, using methods known in the art.

[104] Administration of IL-31RA antibody or fragment thereof or soluble IL-31RA receptor or soluble IL-31RA/OSMRbeta receptor to a subject can be topical, intradermal, inhalant, intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, by perfusion through a regional catheter, or by direct intralesional injection. When administering therapeutic proteins by injection, the administration may be by continuous infusion or by single or multiple boluses.

[105] Additional routes of administration include oral, mucosal-membrane, pulmonary, and transcutaneous. Oral delivery is suitable for polyester microspheres, zein microspheres, proteinoid microspheres, polycyanoacrylate microspheres, and lipid-based systems (see, for example, DiBase and Morrel, "Oral Delivery of Microencapsulated Proteins," in *Protein Delivery: Physical Systems*, Sanders and Hendren (eds.), pages 255-288 (Plenum Press 1997)). The feasibility of an intranasal

delivery is exemplified by such a mode of insulin administration (see, for example, Hinchcliffe and Illum, *Adv. Drug Deliv. Rev.* 35:199 (1999)). Dry or liquid particles comprising IL-31RA antibody or fragment thereof or soluble IL-31RA receptor or soluble IL-31RA/OSMRbeta receptor can be prepared and inhaled with the aid of dry-powder dispersers, liquid aerosol generators, or nebulizers (e.g., Pettit and Gombotz, *TIBTECH* 16:343 (1998); Patton *et al.*, *Adv. Drug Deliv. Rev.* 35:235 (1999)). This approach is illustrated by the AERX diabetes management system, which is a hand-held electronic inhaler that delivers aerosolized insulin into the lungs. Studies have shown that proteins as large as 48,000 kDa have been delivered across skin at therapeutic concentrations with the aid of low-frequency ultrasound, which illustrates the feasibility of transcutaneous administration (Mitragotri *et al.*, *Science* 269:850 (1995)). Transdermal delivery using electroporation provides another means to administer IL-31RA antibody or fragment thereof or soluble IL-31RA receptor or soluble IL-31RA/OSMRbeta receptor (Potts *et al.*, *Pharm. Biotechnol.* 10:213 (1997)).

[106] A pharmaceutical composition comprising a IL-31RA antibody or fragment thereof (antagonist and agonist) or a soluble IL-31RA receptor or a soluble IL-31RA/OSMRbeta receptor can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the therapeutic proteins are combined in a mixture with a pharmaceutically acceptable carrier. A composition is said to be a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers are well-known to those in the art. See, for example, Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 19th Edition (Mack Publishing Company 1995).

[107] For purposes of therapy, an IL-31RA antibody or fragment thereof (antagonist and agonist) or a soluble IL-31RA receptor or a soluble IL-31RA/OSMRbeta receptor and a pharmaceutically acceptable carrier are administered to a patient in a therapeutically effective amount. A combination of an IL-31RA antibody (antagonist and agonist) or a soluble IL-31RA receptor (e.g., IL-31RA homodimer and a zcytor17/OSMRbeta heterodimer) and a pharmaceutically acceptable carrier is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient. For example, an agent used to treat inflammation is physiologically significant if its presence alleviates at least a portion of the inflammatory response.

[108] A pharmaceutical composition comprising an IL-31RA antibody or fragment thereof (antagonist and agonist) or a soluble IL-31RA receptor or a soluble IL-31RA/OSMRbeta receptor can be furnished in liquid form, in an aerosol, or in solid form. Liquid forms, are illustrated by injectable solutions, aerosols, droplets, topological solutions and oral suspensions. Exemplary solid forms

include capsules, tablets, and controlled-release forms. The latter form is illustrated by miniosmotic pumps and implants (Bremer *et al.*, *Pharm. Biotechnol.* 10:239 (1997); Ranade, "Implants in Drug Delivery," in *Drug Delivery Systems*, Ranade and Hollinger (eds.), pages 95-123 (CRC Press 1995); Bremer *et al.*, "Protein Delivery with Infusion Pumps," in *Protein Delivery: Physical Systems*, Sanders and Hendren (eds.), pages 239-254 (Plenum Press 1997); Yewey *et al.*, "Delivery of Proteins from a Controlled Release Injectable Implant," in *Protein Delivery: Physical Systems*, Sanders and Hendren (eds.), pages 93-117 (Plenum Press 1997)). Other solid forms include creams, pastes, other topological applications, and the like.

[109] An IL-31RA antibody or fragment thereof (antagonist and agonist) or a soluble IL-31RA receptor or a soluble IL-31RA/OSMRbeta receptor can be encapsulated within liposomes using standard techniques of protein microencapsulation (see, for example, Anderson *et al.*, *Infect. Immun.* 31:1099 (1981), Anderson *et al.*, *Cancer Res.* 50:1853 (1990), and Cohen *et al.*, *Biochim. Biophys. Acta* 1063:95 (1991), Alving *et al.* "Preparation and Use of Liposomes in Immunological Studies," in *Liposome Technology*, 2nd Edition, Vol. III, Gregoriadis (ed.), page 317 (CRC Press 1993), Wassef *et al.*, *Meth. Enzymol.* 149:124 (1987)). As noted above, therapeutically useful liposomes may contain a variety of components. For example, liposomes may comprise lipid derivatives of poly(ethylene glycol) (Allen *et al.*, *Biochim. Biophys. Acta* 1150:9 (1993)).

[110] Other dosage forms can be devised by those skilled in the art, as shown, for example, by Ansel and Popovich, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5<sup>th</sup> Edition (Lea & Febiger 1990), Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 19<sup>th</sup> Edition (Mack Publishing Company 1995), and by Ranade and Hollinger, *Drug Delivery Systems* (CRC Press 1996).

[111] The complete disclosure of all patents, patent applications, and publications, and electronically available material (e.g., GenBank amino acid and nucleotide sequence submissions) cited herein are incorporated by reference. The foregoing detailed description and examples have been given for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described, for variations obvious to one skilled in the art will be included within the invention defined by the claims.

## EXAMPLES

### Example 1

[112] *Determination of Human Primary T Cell Types that Express IL-31 Upon Stimulation*

[113] *Selection of Study Subjects and Biopsies*

[114] Twelve patients with AD (moderate to severe disease; median age was 32 years old with skin involvement of 5-45%), 6 patients with psoriasis (median age was 56 years old with skin involvement of 10-65%) and 12 healthy individuals (median age 34 years) were included in A study after informed consent. None of the patients had received any systemic corticosteroids previously. All patients were off topical corticosteroids for one week before their skin biopsy or blood drawing. Two mm punch biopsies were taken from 1) acute erythematous AD lesions of less than three days' onset, 2) chronic, lichenified AD lesions of greater than two weeks' duration, 3) chronic psoriasis lesions, and 4) normal skin. The skin samples were immediately frozen at -70°C for immunohistochemistry or Western and immuno-dot blotting.

[115] *Isolation and activation of primary human T cell subsets:*

[116] To isolate various T cell subsets, human PBMCs from the donors were isolated using standard Ficoll gradient centrifugation. Total T cells were then isolated using the T Cell Isolation Kit II (Miltenyi Biotec) according to the manufacturer's instructions. Separation efficiency was assessed using standard flow cytometry and determined to be >95% T cells. To separate CD45RA+ "naïve" T cells from the CD45RO+ "memory" T cells, the total T cell population was incubated with anti-CD45RO microbeads (Miltenyi Biotec) for 15 minutes at +4°C and magnetically separated according to the manufacturers instructions. The naïve and memory T cell populations were determined to be >90% pure by flow cytometry.

[117] CD45RO+ memory T cells are often tissue specific and cutaneous lymphocyte antigen (CLA) is used to differentiate skin-homing T cells from gut-homing T cells expressing  $\alpha 4/\beta 7$  on their surface. To determine which of these cell types produce IL-31, CLA+ T cells were isolated from total T cells, activated and conditioned media was collected for the IL-31 bioassay. To do this, total T cells were isolated and then incubated on ice for 20 minutes in 1 mL of a 1:50 dilution of anti-CLA-FITC antibody (PharMingen). Cells were then washed, resuspended in MACS buffer and incubated with anti-FITC microbeads (Miltenyi Biotec) for 15 minutes at +4°C. The cells were then washed, resuspended and magnetically separated over an LS column according to the manufacturer's instructions. The labeled T cells were later determined to be >80% pure while the CLA-depleted T cells were >98% CLA-. Both CLA+ and CLA- T cells were collected and cultured concurrently.

[118] To activate the CD45RA+ and CD45RO+ T cell subsets, cells were cultured overnight in 24-well tissue culture plates pretreated with 2.0  $\mu\text{g/mL}$  anti-CD3 antibody (Southern Biotechnology). The cells were plated at a concentration of  $2.5 \times 10^6$  cells/mL in tissue culture media (RPMI, 5% fetal bovine serum, L-Glutamine and Sodium Pyruvate (all Gibco)) supplemented with 2.0  $\mu\text{g/mL}$  anti-CD28 (Southern Biotechnology) and placed in a +37°C incubator. After four hours, half of the wells were harvested, cells pelleted and conditioned media frozen at -20°C until time of IL-31 bioassay.

[119] The CLA+ and CLA- T cell subsets were activated similarly in 48-well tissue culture plates that were pretreated with 2.0  $\mu\text{g/mL}$  anti-CD3 antibody (Southern Biotechnology). The cells were activated for 16 hours or 24 hours in a +37°C incubator at a concentration of  $6.25 \times 10^5$  cells/mL. Samples were harvested, cells pelleted and conditioned media frozen at -20°C until time of IL-31 bioassay. For suboptimal activation, CLA+ T cells were cultured in plates pre-treated with 0.5  $\mu\text{g/mL}$  of anti-CD3 antibody.

[120] *Human IL-31 Bioassay Protocol:*

[121] BAF3 cells transfected with hIL-31RA, hOSMRbeta, and KZ134 were grown to  $5 \times 10^5$  and  $1 \times 10^6$  cells/mL. Cells were washed with assay media (RPMI 1640, 10% FBS, L-Glutamine, Sodium Pyruvate, and Pen/Strep (all Gibco)) and resuspended at  $3 \times 10^5$  cell/mL in assay medium. In a 96-well opaque plate, hIL-31 standards were titrated in duplicate from 600 pg/mL to 9.38 pg/mL in assay medium via a 100  $\mu\text{L}$ /well, 1:2 serial dilution. Quality control standards were added in duplicate to the plate at 350 pg/mL and 35 pg/mL in 100  $\mu\text{L}$ . Test samples were often diluted 1:2 or 1:4 and added in duplicate to the sample wells. 100  $\mu\text{L}$  of the washed BAF3 cells were then added to each well for a final concentration of  $3 \times 10^4$  cells/well. The plate was then incubated for 16-24 hours at +37°C in a 5% CO<sub>2</sub> incubator. The plate was then centrifuged at 1200RPM for 5 minutes, media flicked off and 25  $\mu\text{L}$ /well of lysis buffer (Promega) added to each well. After 10 minutes the plate was read on a luminometer (Berthold). The luminometer added 40  $\mu\text{L}$ /well of luciferase substrate mix (Promega) and integrated the luminescence for a period of 4 seconds. Luminescence values were exported to a spreadsheet where they were analyzed and converted into picograms of IL-31 per  $10^6$  cells per mL of volume. The data is summarized in Table 1.

[122] *Results of IL-31 Bioassay:*

[123] The results from the CD45RA+ and the CD45RO+ T cell samples revealed that IL-31 was primarily produced by activated CD45RO+ memory T cells. The CD45RA+ and CD45RO+ T cells from both donors produced no detectable IL-31 when unstimulated. However, the CD45RO+ samples from both donors #3 and #4 generated significant levels of IL-31 following a 24 hour activation with plate-bound anti-CD3 and soluble anti-CD28 (110.4 pg/ $10^6$ cells/mL and 145.6 pg/ $10^6$ cells/mL respectively). Conversely, when the CD45RA+ T cells from donors #3 and #4 were activated with anti-CD3 and anti-CD28, they produced very low amounts of IL-31 (13.1 pg/ $10^6$ cells/mL and 12.7 pg/ $10^6$ cells/mL respectively).

[124] The CLA+ and CLA- T cell samples revealed that IL-31 seems to be made almost entirely by activated CLA+ T cells. The CLA- population of T cells (which includes naïve T cells,  $\alpha 4/\beta 7$  gut-homing memory T cells, and tissue uncommitted T cells) from both donors generated no detectable levels of IL-31 regardless of time point or activation condition. The CLA+ T cells on the other hand, generated very high levels of IL-31 when stimulated with 2.0  $\mu\text{g/mL}$  plate-bound anti-

CD3 antibody. Donor #5 generated 1385.7 pg/10<sup>6</sup>cells/mL IL-31 by 16 hours and >1920 pg/10<sup>6</sup>cells/mL by 24 hours. Donor #6 generated 121.3 pg/10<sup>6</sup>cells/mL IL-31 at 16 hours and 328.9 pg/10<sup>6</sup>cells/mL IL-31 at 24 hours. These results clearly demonstrate that of the T cell subsets, IL-31 seems to be made specifically by cutaneous (CLA+) T cells under standard activation conditions.

Table 1

| Donor# | Cell Type    | Activation                  | IL-31<br>(pg/10 <sup>6</sup> cells/mL) | IL-31<br>(pg/10 <sup>6</sup> cells/mL) |
|--------|--------------|-----------------------------|----------------------------------------|----------------------------------------|
|        |              |                             | 6hr                                    | 24hr                                   |
| 3      | CD45RA+      | $\alpha$ CD3+ $\alpha$ CD28 | Below Detection                        | 13.1                                   |
| 3      | CD45RO+      | $\alpha$ CD3+ $\alpha$ CD28 | 8.6                                    | 110.4                                  |
| 4      | CD45RA+      | $\alpha$ CD3+ $\alpha$ CD28 | 6.7                                    | 12.7                                   |
| 4      | CD45RO+      | $\alpha$ CD3+ $\alpha$ CD28 | 11.9                                   | 145.6                                  |
|        |              |                             |                                        |                                        |
|        |              |                             | 16hr                                   | 24hr                                   |
| 5      | CLA+ T Cells | Unstimulated                | Below Detection                        | Below Detection                        |
| 5      | CLA+ T Cells | $\alpha$ CD3                | 1385.7                                 | >1920                                  |
| 5      | CLA- T Cells | Unstimulated                | Below Detection                        | Below Detection                        |
| 5      | CLA- T Cells | $\alpha$ CD3                | Below Detection                        | Below Detection                        |
| 6      | CLA+ T Cells | Unstimulated                | Below Detection                        | Below Detection                        |
| 6      | CLA+ T Cells | $\alpha$ CD3                | 121.3                                  | 328.9                                  |
| 6      | CLA- T Cells | Unstimulated                | Below Detection                        | Below Detection                        |
| 6      | CLA- T Cells | $\alpha$ CD3                | Below Detection                        | Below Detection                        |

Example 2**[125]** *IL-31 Involvement in Initiation and Perpetuation of Contact Hyper-Sensitivity***[126]** *Method I*

**[127]** BALB/c mice are painted on shaved mid-back with 25  $\mu$ l of 0.5% DNFB dissolved (2,4, dinitro-fluoro-benzene, Sigma, St. Louis MO) in acetone:olive oil (4:1) solution using a pipettor. A vehicle control group receives 25  $\mu$ l of acetone:olive oil only. After 5 days, mice are anaesthetized with isoflurane in an inhalation chamber and both ear pinnae of experimental and control animals are measured with an engineer's micrometer (Mitutoyo) to obtain a baseline measurement. Mice are then challenged by applying 10  $\mu$ l of 0.25% DNFB in acetone:olive oil (4:1) to both sides of each ear of all mice. Contact hyper-sensitivity is measured at 24 h and 48 h later as the difference between the right ear (challenged) and the left ear (unchallenged). All measurements are done with an engineer's micrometer. Background values are determined by the difference in ear swelling between the challenged and unchallenged ears of naive mice.

**[128]** Whole blood and serum for FACS and/or ELISA analysis are collected prior to sacrifice and ears are collected for histology.

**[129]** *Method II (Induces Th2 responses)*

**[130]** BALB/c mice are painted on shaved mid-back with 100ul of 0.5% FITC (fluorescein isothiocyanate) in a 1:1 solution of acetone/dibutyl phthalate (MSDS available using pipettor on days 1, 2 and 8. On day 13, mice are anaesthetized with isoflurane in an inhalation chamber and both ear pinnae of experimental and control animals are measured with an engineer's micrometer (Mitutoyo) to obtain a baseline measurement. Mice are challenged by applying 25ul of 0.5% FITC (in 1:1

acetone/dibutyl phthalate) to the dorsal surface of each ear. Contact hyper-sensitivity is measured at 24 h and 48 h later as the difference between the right ear (challenged) and the left ear (unchallenged). All measurements are done with an engineer's micrometer. Background values are determined by the difference in ear swelling between the challenged and unchallenged ears of naive mice. Whole blood and serum for FACS and/or ELISA analysis are collected prior to sacrifice and ears are collected for histology.

**[131]** *Method III (induces Th1 responses)*

**[132]** BALB/c mice are painted on shaved mid-back with 25ul of 2% oxazalone (in 4:1 acetone/olive oil) using pipettor. On day 7, mice are anaesthetized with isoflurane in an inhalation chamber and both ear pinnae of experimental and control animals are measured with an engineer's micrometer (Mitutoyo) to obtain a baseline measurement. Mice are challenged by applying 8ul of oxazalone to the dorsal surface of each ear. Contact hyper-sensitivity is measured at 24 h and 48 h later as the difference between the right ear (challenged) and the left ear (unchallenged). All measurements are done with an engineer's micrometer. Background values are determined by the difference in ear swelling between the challenged and unchallenged ears of naive mice. Whole blood and serum for FACS and/or ELISA analysis are collected prior to sacrifice and ears are collected for histology.

**[133]** Involvement of IL-31 in the initiation and perpetuation of contact hyper-sensitivity is tested using a neutralizing antibody against IL-31 both at the sensitization and challenge phases of the experiment.

**Example 3**

**[134]** *IL-31 Involvement in Atopic Dermatitis*

**[135]** *Methods I (Sensitization of NC/Nga mice)*

**[136]** Male NC/Nga mice were purchased from Charles River Laboratories, Japan. The mice were 4 weeks old on arrival and housed in SPF quarantine conditions for 4 weeks to acclimate. The mice were approximately 10-11 weeks old at the start of the antigen sensitization. Mice were anaesthetized with isoflurane and backs were shaved with electric clippers. Approximately 10 ug of *Dermatophagoides pteronyssinus* (Dp) (Indoor Biotechnologies, Charlottesville, Virginia, special order) extract was injected intradermally at the nape of the neck 3 times per week for 5 to 6 weeks until mice developed skin lesions. Control animals received 10ul PBS intradermal injections 3 times per week. The Dp extract was prepared according to method by Matsuoka and colleagues. Matsuoka H., et al., *Allergy*: 58, 139 (2003). Briefly, 595mg Dp lyophilized spent culture extract was dissolved in 12mL sterile PBS (Gibco). Dp was mixed in a 50mL Falcon tube on a shaking rocker for 30

minutes. The extract was spun for 10 minutes at 2000rpm and the supernatant was collected and aliquoted into 1mL cryovial tubes and stored at -20°C.

[137] *Method II (Sensitization of DO11.10 mice)*

[138] DO11.10 transgenic mice were bred from an in-house colony and were between 9.5 and 14 weeks old at start of antigen sensitization. Twenty-four hours prior to epicutaneous sensitization mice were anaesthetized with isoflurane and the entire trunk (back and abdomen) of mice were shaved with electric clippers. The mice were then tape stripped with Elastin surgical tape (Johnson and Johnson) on the back. One cm<sup>2</sup> sterile gauze patches were wetted with either 500ug ovalbumin (Calbiochem 32467) or sterile PBS (Gibco) and adhered to left backside of mice with DuoDerm Extra Thin Dressing (ConvaTec 187932). The patch and dressing were then covered in a body wrap of the Elastin surgical tape so mice could not remove or destroy the patches. Patches were worn for 7 days and removed. The mice were rested for two weeks before having another round of epicutaneous sensitization. Mice received a total of three one-week sensitizations.

[139] *Results*

[140] Immunohistochemical analysis of IL-31RA expression in lesional and non-lesional skin from dust mite sensitized NC/Nga and OVA sensitized DO11.10 animals showed that IL-31RA is expressed by epidermal keratinocytes in mice, however no significant difference in levels of expression can be found between antigen sensitized versus PBS sensitized animals.

Example 4

[141] *IL-31 Involvement Delayed Type Hypersensitivity*

[142] *Methods*

[143] To generate a DTH response, mice were sensitized to antigen on day 0 by subcutaneous immunization at the base of the tail with 100 ug ovalbumin (OVA) in complete Freund's adjuvant (CFA, 50-100 µl total volume). One week later mice were anesthetized with isoflurane in an inhalation chamber and both ear pinnae of experimental and control animals were measured with an engineer's micrometer (Mitutoyo) to obtain a baseline measurement. Mice were challenged intradermally with 10 ug OVA in PBS in a total volume of 10 µl into the left ear pinnae, just below the skin without hitting any veins. As a control, mice also received an injection of 10 µl PBS in the right ear pinnae. In some cases, a separate control group given an i.d. injection of OVA in the ear may also be treated with topical corticosteroids as a positive control to inhibit the reaction. At 24 and 48 hr after challenge, mice were anesthetized and ear thickness was measured. Results were expressed as: Specific ear swelling = (24hr measurement - 0hr measurement) for experimental ear - (24hr measurement - 0hr measurement) for negative control ear. Induration, the hallmark of DTH, is

detectable by 18 hours after injection of sensitized antigen and is maximal by 24-48 hours. The lag in the onset of palpable induration is the reason for naming the response "delayed type."

[144] *Results*

[145] IL-31 transgenic mice were tested for DTH, however, due to an increase in ear thickness in un-challenged IL-31 transgenic animals, no statistically significant difference in DTH could be determined between IL-31 Tg animals compared to wildtype controls. IL-31RA knockout animals were also tested in a DTH response and no significant difference in the DTH response could be observed between receptor knockout and wildtype animals.

Example 5

[146] *IL-31 Involvement in Induction of the Itch Response*

[147] *Methods I (IL-31 treatment of Capsaicin pre-treated mice)*

[148] Ten week old BALB/c animals (CRL) were anaesthetized and injected with a long-lasting analgesic agent, bupranorphine hydrochloride, subcutaneously at 0.1 mg/kg before injection of 0.25 ml of 4 mg/ml solution of capsaicin in 10% ethanol + 10% Tween-80 in saline subcutaneously into scruff of neck. Animals were kept anaesthetized for at least 30 min following neurotoxin treatment. Forty-eight hours later, 14-day osmotic pumps were implanted subcutaneously for continuous delivery of 20 ug/day of IL-31 for 14 days. Mice were monitored daily for 6 days for alopecia and pruritis using the following criteria: 0 = no scratching, animal appears normal, 1 = thinning of coat in small areas, scratching noted, 2 = minor hair loss (small patches), scratching, 3 = moderate hair loss, scratching, and 4 = severe hair loss, excessive scratching.

[149] Results demonstrated that while non-capsaicin-treated mice showed a mean scratch/hairloss score of 2.625 following three days of IL-31 delivery, capsaicin-treated mice showed a significantly lower score of 1. Thus mice treated with capsaicin prior to IL-31 delivery showed both a delay in incidence of scratching and hairloss and a lower score in the intensity of scratching and hairloss over the six days of the experiment. These data suggest that IL-31 does induce some neuronal component that contributes to the alopecia and pruritis induced by IL-31. Therefore, neutralization of IL-31 may decrease the incidence and intensity of itch, and therefore dermatitis, in patients suffering from skin disorders that involve itch.

[150] *Method II (IL-31 treatment of Tac1 gene deficient mice)*

[151] Mice that are homozygous null for the Tac1 gene express no detectable substance P or neurokinin A. These mice have significantly reduced nociceptive pain responses to moderate to intense stimuli and are therefore a useful tool for studying the contribution of tachykinin peptides to pain/itch processing and inflammatory disease states. Twelve week old, Tac1 knockout mice were

implanted with 14-day osmotic pumps delivering 1 $\mu$ g/day of IL-31 protein and observed daily for alopecia and pruritis using the following criteria: 0 = no scratching, animal appears normal, 1 = thinning of coat in small areas, scratching noted, 2 = minor hair loss (small patches), scratching, 3 = moderate hair loss, scratching, and 4 = severe hair loss, excessive scratching.

[152] Results of this study show that Tac1 deficient mice were less susceptible to IL-31 induced scratching/hairloss compared to wildtype control mice. While 100% (10/10) of wildtype mice had developed evidence of scratching and hairloss by day 6 of IL-31 treatment, only 33.3 % (2/6) Tac1 deficient mice were showing signs of scratching and hairloss at the same time-point. These data show that IL-31 induces a neuronal component that contributes to the scratch/hairloss phenotype in IL-31-treated mice and neutralization of IL-31 may decrease the incidence and intensity of scratching in the context of dermatitis.

[153] *Method III (Effect of administration of IL-31 neutralizing antibody on IL-31 treated mice)*

[154] Normal female BALB/c mice (CRL) approximately 8 to 12 weeks old were implanted subcutaneously with 14-day osmotic pumps (Alzet, #2002) delivering 1 $\mu$ g/day mIL-31. Groups of mice received intraperitoneal (i.p.) injections of rat anti-mouse IL-31 monoclonal antibody 10mg/kg (200 $\mu$ g/mouse) twice weekly starting 1 week prior to IL-31 delivery. Control groups of mice received i.p. injections of vehicle (PBS/0.1%BSA) with the identical dosing schedules. Mice were scored daily for alopecia and pruritis using the following criteria: 0 = no scratching, animal appears normal, 1 = thinning of coat in small areas, scratching noted, 2 = minor hair loss (small patches), scratching, 3 = moderate hair loss, scratching, and 4 = severe hair loss, excessive scratching.

[155] In all experiments, mice treated with rat anti-mIL-31 mAb had a delay in onset of symptoms of approximately 5 to 7 days and a lower overall score for alopecia and pruritis. All groups of mAb treated mice (regardless of dose frequency or concentration) developed alopecia and pruritis similar to control mice by 13 day of the study. These data suggest that neutralization of IL-31 can delay the onset of the scratch/hairloss response induced by IL-31.

#### Example 6

[156] *Immunohistochemical (IHC) Staining of IL-31 in Skin Lesions from Uninvolved Psoriatic, and Atopic Dermatitis*

[157] Uninvolved psoriatic, atopic dermatitis and normal skin were tested for the IL-31 ligand by IHC. Positive control cells consisted of BHK cells transfected with IL-31. Negative controls performed included: (1) un-transfected BHK cells, (2) staining representative tissues and cells with protein A purified Normal Rabbit serum and detecting antibody binding as usual.

Antibody reagent was E5758 (Rabbit anti-huIL-31 CEE, Aff. Purified at 1.0 mg/ml). Control cells included C02-6020: BHK cells expressing zcytor17 Lig hu-CEE/21, and a BHK wild type. Tissues tested included acute atopic dermatitis skin samples, chronic atopic dermatitis skin samples, unaffected area skin samples, and normal control skin samples and other in-house control samples.

[158] The cells and tissues described above were fixed overnight in 10% NBF and embedded in paraffin using standard techniques.

[159] Five  $\mu$ M sections were baked at 61°C for 30min for tissue adhesion. Slides were subsequently dewaxed in 3X5' in xylene and rehydrated through graded alcohols as follows: 2X2' in 100% EtOH, 2x2' in X95% EtOH, 1x2' in 70% EtOH. Slides were rinsed in dH2O, and then heat induced epitope retrieval (HIER) was performed for 20 minutes under steam followed by 20 minutes cooling to RT in 10mM Tris, 1mM EDTA, pH 9.0

[160] Slides were loaded onto a DakoCytomation Autostainer. Slides were rinsed with TBS/Tween buffer (TBST), prepared as recommend by manufacturer. Endogenous biotin was blocked with a 10 minute incubation in avidin solution, washed in TBST followed by a 10 minute incubation in biotin solution. Slides were washed in TBST. A protein block (PBSB) (0.5% Blocking Powder in PBS, Perkin Elmer NEL700001KT.) was applied for 30 minutes and rinsed off slides. The primary antibody was diluted to 500ng/ml and was applied for 60 minutes in ChemMate Antibody Dilution Buffer (part# ADB250, Ventana Medical systems).

[161] Tissues washed twice in TBST, and then incubated 45 minutes in biotinylated Goat anti-Rabbit Ab, 750ng/ml in PBSB (catalog # BA-1000, Vector Labs). Slides washed twice in TBST. Vectastain Elite ABC Reagent (catalog# PK-7100, Vector Labs) was incubated for 45 minutes. Slides washed twice in TBST. Signals were developed with DAB+ (catalog# K-3468, DakoCytomation) for 10 minutes at room temperature. Tissue slides were then counterstained in hematoxylin (catalog# H-3401 Vector Labs), dehydrated and coverslipped in VectorMount (catalog# H-5000, Vector Labs).

[162] *Results*

[163] *Cell controls:*

[164] BHK cells transfected with IL-31 was positively stained with IL-31 antibody E5758 while un-transfected cells was negative for this antibody. The same transfected and un-transfected cells were negative with anti-rabbit sera.

[165] *2) Atopic dermatitis skin analysis:*

[166] The staining pattern for IL31 in the AD skin samples is identical to that of psoriasis skins reported previously: keratinocyte and CD3 positive T-cells stained negative for IL31. A weak but rather uniform staining of the epithelial cells in the secretory portion of the sweat glands was present, but a strong signal was observed in the inner layer of epithelium in the duct portion.

Sebaceous gland was positive for IL31. There was no difference in the IL31 staining between AD and normal skin.

[167] Immunohistochemical (IHC) staining of uninvolved psoriatic, atopic dermatitis and normal skin showed strong staining of IL-31 in the holocrine secretion of the sebaceous glands. Considering the phenotype of IL 31 transgenic mice, it is interesting to note that the sebaceous glands originate as an epithelial bud from the outer root sheath of hair follicles. In addition to sebaceous glands weak but rather uniform staining of IL-31 was observed in the epithelial cells in the secretory portion of the sweat glands and a strong signal in the inner layer of epithelium was observed in the duct portion of sweat glands.

#### Example 7

##### [168] *Immunohistochemical (IHC) Staining of IL-31RA in Uninvolved Psoriatic, and Atopic Dermatitis*

[169] Uninvolved psoriatic, atopic dermatitis and normal skin were tested for the IL-31RA by IHC. Positive control cells consisted of BHK cells dual transfected with IL-31RA and OSMR. Negative controls performed included: (1) un-transfected BHK cells, (2) staining representative tissues and cells with protein A purified Normal Rabbit serum and detecting antibody binding as usual. Antibody reagent was E6292 (Rabbit anti-huIL-31RAs-CEE v.4 at 1.33 mg/ml). Control cells included C02-5117 BHK cells expressing human IL-31RA and human OSMR (Total cells in the pellet:  $3.9 \times 10^6$ , vitality was >90%) and C04-1587: BHK wild type (Total cells in the pellet:  $5 \times 10^6$ ). Other tissues examined included: 5 Acute atopic dermatitis skin samples, 10 Chronic atopic dermatitis skin samples, 10 Unaffected area skin samples, Normal control skin samples, and other in-house skin samples.

[170] The cells and tissues described above were fixed overnight in 10% NBF and embedded in paraffin using standard techniques.

[171] Five  $\mu$ M sections were baked at 61°C for 30min for tissue adhesion. Slides were subsequently dewaxed in 3X5' in xylene and rehydrated through graded alcohols as follows: 2X2' in 100% EtOH, 2x2' in X95% EtOH, 1x2' in 70% EtOH. Slides were rinsed in dH<sub>2</sub>O, and then heat induced epitope retrieval (HIER) was performed for 20 minutes under steam followed by 20 minutes cooling to RT in 10mM Tris, 1mM EDTA, pH 9.0

[172] Slides were loaded onto a DakoCytomation Autostainer. Slides were rinsed with TBS/Tween buffer (TBST), prepared as recommend by manufacturer. Endogenous biotin was blocked with a 10-minute incubation in avidin solution, washed in TBST followed by a 10-minute incubation in biotin solution. Slides were washed in TBST. A protein block (PBSB) (0.5% Blocking Powder in PBS, Perkin Elmer NEL700001KT.) was applied for 30 minutes and rinsed off slides.

Primary antibodies diluted from 665ng/ml to 1330 ng/ml for IL31RA were applied for 60 minutes in ChemMate Antibody Dilution Buffer (part# ADB250, Ventana Medical systems).

[173] Tissues were washed twice in TBST, and then incubated 45 minutes in biotinylated Goat anti-Rabbit Ab, 750ng/ml in PBSB (catalog # BA-1000, Vector Labs). Slides were washed twice in TBST. Vectastain Elite ABC Reagent (catalog# PK-7100, Vector Labs) was incubated for 45 minutes. Slides were washed twice in TBST. Signals were developed with DAB+ (catalog# K-3468, DakoCytomation) for 10 minutes at room temperature. Tissue slides were then counterstained in hematoxylin (catalog# H-3401 Vector Labs), dehydrated and coverslipped in VectorMount (catalog# H-5000, Vector Labs).

[174] Results are shown in Table 2.

[175] Table 2: Results of IHC for IL-31RA in Skin Biopsies from Acute and Uninvolved AD Compared to Normal Volunteers

| CASE ID  | IL-31RA IHC<br>SCORE* | CD3 IHC SCORE* |
|----------|-----------------------|----------------|
| AD-1     | 2-3                   | 0-1            |
| AD-2     | 2-3                   | 2              |
| AD-3     | 2-3                   | 1-2            |
| AD-4     | 3                     | 1              |
| AD-5     | 2                     | 2              |
| UAD-1    | 1-2                   | 1              |
| UAD-2    | 1                     | 0-1            |
| UAD-3    | ND                    | ND             |
| UAD-4    | ND                    | ND             |
| UAD-5    | 1-2                   | 0-1            |
| UAD-6    | 2-3                   | ND             |
| UAD-7    | 2                     | 1              |
| UAD-8    | 1                     | 1              |
| UAD-9    | 1-2                   | 1              |
| UAD-10   | 2                     | ND             |
| Normal-1 | 1                     | 0-1            |
| Normal-2 | 0-1                   | 0-1            |
| Normal-3 | 1                     | 0-1            |

[176] Abbreviations: AD: atopic dermatitis; UAD: uninvolved AD; ND: Not Done

[177] \*IHC signal was scored from 0 (no signal) to 4 (intense signal)

[178] There was a slight up regulation of IL31RA in the epidermis of AD skin samples. Possibly a small percentage of CD3 positive T-cells were positive for IL31RA in the AD skins. There were CLA positive cells in all skin samples tested. AD skins may have more CLA positive cells than that of the normal or UAD samples.

[179] IL-31RA was also expressed in the epithelial cells of eccrine sweat glands with the cuboidal epithelial cells in the secretory portion of the eccrine glands demonstrating slightly higher level of IL-31RA protein compared to the duct portion.

[180] Collectively, these data demonstrate that IL-31RA is expressed by epidermal keratinocytes from both control volunteers and AD patients. However, the levels of IL-31RA expressed on keratinocytes from AD skin biopsies were higher than the levels observed in skin biopsies from normal controls, indicating a potential for increased responsiveness to IL-31 in the context of AD.

[181] IL-31RA was also found expressed on a subset of perivascular infiltrating cells present in skin biopsies from AD patients but was not present in control skin biopsies. These IL-31RA+ cells were recognized by an antibody specific for the tissue macrophage marker CD68, indicating these cells were skin-infiltrating tissue macrophages.

#### Example 8

##### **[182]** *Isolation of Skin Infiltrating cells by Laser Capture Microscopy and Analysis of IL-31MRNA by RT-PCR*

[183] The presence of skin infiltrating T cells is a distinguishing feature in skin biopsies from AD patients compared to normal individuals. Since IL-31 is a T cell associated cytokine, the expression of IL-31 in skin-infiltrating T cells in tissue biopsies from AD patients was examined. First, the presence of increased numbers of CD3+ T cells in skin tissue biopsies from AD patients compared to normal individuals was confirmed by IHC. See Table 2. Next, laser capture microscopy was used to specifically isolate skin infiltrating cells for analysis of IL-31 mRNA by RT-PCR. IL-31 mRNA was expressed by skin infiltrating cells from acute AD patients. In normal tissues, infiltrating cells are not normally found and therefore could not be tested. However, the epidermal keratinocyte layer, which is present in both AD and normal skin, was analyzed for IL-31 mRNA expression and lower levels of IL-31 mRNA were found in normal samples compared to the epidermal keratinocyte layer of AD samples. Semi-quantitative analysis of IL-31 mRNA expression compared to an internal control gene (HPRT) showed that although IL-31 mRNA levels were not significantly different between AD and normal samples, there was a trend towards higher IL-31 expression in skin from AD patients.

#### Example 9

##### **[184]** *IL-31 is produced by memory T cells with a skin-homing phenotype*

[185] Analysis of skin biopsies confirmed that the infiltrating CD3+ T cells in the skin, which express IL-31 mRNA, express the skin-homing marker cutaneous lymphocyte antigen (CLA).

Of the total T cell population in normal human peripheral blood, IL-31 expression was found to be largely restricted to CD45RO+ memory/effector cells as opposed to the CD45RA+ naïve T cell population.

[186] In order to determine if IL-31 production was associated with CLA+ skin-homing T cells, CLA+ and CLA- T cells were isolated from peripheral blood of patients diagnosed with AD and control volunteers and compared IL-31 mRNA and protein levels following anti-CD3 plus anti-CD28 stimulation. Our results indicate that IL-31 mRNA was significantly elevated in CLA+ T cells from both AD and normal individuals at both 4 h (p0.0087 and p0.0022 CLA+ compared to CLA- for AD and normal, respectively) and 24 h (p0.0022 CLA+ compared to CLA- for both AD and normal samples) post stimulation. Analysis of IL-31 protein levels in culture supernatants confirmed that IL-31 was produced predominantly by CLA+ T cells as there was no detectible IL-31 in culture supernatants from CLA- T cells from both AD and control individuals. There were no significant differences in IL-31 levels between AD and normal patients. We also analysed the production of IL-31 by peripheral blood T cells that express other tissue-specific homing markers, such as the gut-specific homing marker  $\alpha 4\beta 7$ , from normal volunteers. Comparison of the IL-31 levels produced by CLA+ T cells and  $\alpha 4\beta 7$ + cells demonstrated CLA+ T cells preferentially produce IL-31 compared to the  $\alpha 4\beta 7$ + cells (average of 34.5 pg/ml and 14.42 pg/ml IL-31, respectively).

[187] Although both AD patients and normal controls have circulating CLA+ T cells that express IL-31 upon activation, CLA+ T cells from AD patients are reported to exist in a more activated state compared to cells from normal individuals. Consequently, the threshold of stimulation required for the production of IL-31 by CLA+ T cells may differ between dermatitis patients and control subjects. To test this hypothesis, we stimulated CLA+ T cells from AD patients and control individuals with sub-optimal concentrations of anti-CD3 in the absence of anti-CD28 and analyzed the production of IL-31 in culture supernatants at 24h after stimulation. Our results demonstrate that circulating CLA+ T cells from some AD patients produce higher levels of IL-31 compared to cells from normal individuals in this study with maximum levels reaching 1200 pg/mL, whereas maximal detected levels in normal CLA+ supernatants was only 400 pg/ml and maximal detected levels for psoriasis patients was 73 pg/ml at suboptimal concentrations of anti-CD3 stimulation. Five of eleven AD patients showed IL-31 levels below the limit of detection of our assay suggesting there might be a subset of AD patients where IL-31 is produced at low levels. This may reflect variations in the stage of disease of our study population. Nevertheless, more than half of the AD patients showed a trend towards higher IL-31 levels compared to psoriasis patients and normal individuals following suboptimal stimulation with anti-CD3. Since more CLA+ T cells are localized in skin of AD patients as compared to normal individuals, our studies suggest that there is an increased potential for IL-31

activity in the AD skin micro-environment. Thus, this study may suggest a subpopulation of AD patients, which have more activated CLA+ T cells producing IL-31.

#### Example 10

[188] *Reduction of TARC and MDC in response to anti-IL-31 antibody in AD mouse models*

[189] *Method I*

[190] Six-week old male NC/Nga mice (CRL Japan) were sensitized intradermally with 50 $\mu$ g dust mite extract (*D. pteronyssinus*, Indoor Biotechnologies) three times a week on the back and scored for AD-like lesions. After 5 weeks of sensitization the mice were euthanized and the right ears were excised and placed into a single well of a 48-well culture dish (Corning) supplemented with RPMI+2%FBS (GIBCO Invitrogen). Plates were placed in 5% CO<sub>2</sub> humidity controlled incubators. Supernatants were collected after 24 hours and frozen at -20 °C until further analysis.

[191] *Method II*

[192] Twelve-week old female NC/Nga mice (CRL Japan) were sensitized intradermally with 10 $\mu$ g SEB (Toxin Technology) in the ear and on the back three times per week. The mice were scored for AD-like lesions. After 5 weeks of sensitization the mice were euthanized and 6mm biopsy punches were taken from the injected ear of each mouse and placed into a single well of a 48-well culture dish supplemented with RPMI+2%FBS. Plates were placed in 5% CO<sub>2</sub> humidity controlled incubators. Supernatants were collected after 24 hours and frozen at -20 °C until further analysis.

[193] Groups of mice in both studies were treated with either a rat anti-mouse IL-31 monoclonal antibody at 10mg/kg or vehicle, intraperitoneally two times each week starting after 1 to 2 weeks of sensitization.

[194] TARC and MDC concentrations in the 24-hour supernatant samples were measured by conventional ELISA (R&D Systems).

[195] TARC and MDC concentrations were lower in ear supernatants from anti-IL-31 treated mice compared to control mice in both studies, however, these results were not statistically significant when analyzed by ANOVA, probably due to small sample size. When the data from both experiments is combined and analyzed there is a statistically significant difference between treated groups.

The claims defining the invention are as follows:

1. A method of treating a patient suffering from a skin disorder, the method comprising:  
administering a therapeutically effective amount of an anti-IL-31RA monoclonal antibody or antigen-binding fragment thereof to the patient, wherein the anti-IL-31RA monoclonal antibody or antigen-binding fragment specifically binds amino acid residues 20-519 of SEQ ID NO:6 or a portion thereof and wherein the anti-IL-31RA monoclonal antibody or antigen-binding fragment prevents, inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Toxic epidermal necrolysis, Bullous pemphigoid, Vitiligo, Acne Rosacea, Prurigo nodularis, and Scleroderma.
2. A method according to claim 1, wherein the anti-IL-31RA monoclonal antibody is a neutralizing monoclonal antibody.
3. A method according to claim 1 or 2, wherein the antigen-binding fragment is selected from the group consisting of:
  - (a) a Fab fragment;
  - (b) a Fab' fragment;
  - (c) is a F(ab')<sub>2</sub> fragment; and
  - (d) a single chain Fv.
4. A method according to any one of claims 1 to 3, wherein the anti-IL-31RA monoclonal antibody or antigen-binding fragment thereof specifically binds amino acid residues 20-277 of SEQ ID NO:6.
5. A method according to any one of claims 1 to 4, wherein the antigen-binding fragment is conjugated to a polyethylene glycol or human serum albumin.
6. A method of treating a patient suffering from a skin disorder, the method comprising:  
administering a therapeutically effective amount of a soluble IL-31RA receptor to the patient, wherein the soluble IL-31RA receptor comprises amino acid residues 20-519 of SEQ ID NO:6, wherein the soluble IL-31RA receptor specifically binds a polypeptide comprising amino acid residues 27-164 of SEQ ID NO:2, and wherein the soluble IL-31RA receptor prevents, inhibits the progression of, delays the onset of, reduces the severity of, and/or inhibits at least one of the conditions or symptoms of the skin disorder selected from the group consisting of Toxic epidermal necrolysis, Bullous pemphigoid, Vitiligo, Acne Rosacea, Prurigo nodularis, and Scleroderma.

7. A method according to claim 6, wherein the soluble IL-31RA receptor comprises amino acid residues 20-519 of SEQ ID NO:6.

8. A method according to claim 6 or 7, wherein the soluble IL-31RA receptor is conjugated to the Fc region of IgG, IgA, IgD, IgM or IgE.

9. Use of an anti-IL-31RA monoclonal antibody or antigen-binding fragment thereof in the manufacture of a medicament used to treat a patient suffering a skin disorder selected from the group consisting of from Toxic epidermal necrolysis, Bullous pemphigoid, Vitiligo, Acne Rosacea, Prurigo nodularis, and Scleroderma, wherein said monoclonal antibody or antigen-binding fragment thereof specifically binds amino acid residues 20-519 of SEQ ID NO:6 or a portion thereof thereby preventing, inhibiting the progression of, delaying the onset of, reducing the severity of, and/or inhibiting at least one of the conditions or symptoms of said skin disorder.

10. Use of a soluble IL-31RA receptor in the manufacture of a medicament used to treat a patient suffering a skin disorder selected from the group consisting of from Toxic epidermal necrolysis, Bullous pemphigoid, Vitiligo, Acne Rosacea, Prurigo nodularis, and Scleroderma, wherein said soluble IL-31RA receptor comprises amino acid residues 20-519 of SEQ ID NO:6 and wherein the soluble IL-31RA receptor specifically binds a polypeptide comprising amino acid residues 27-164 of SEQ ID NO:2 thereby preventing, inhibiting the progression of, delaying the onset of, reducing the severity of, and/or inhibiting at least one of the conditions or symptoms of said skin disorder.

11. A kit when used in a method according to any one of claims 1 to 5, wherein said kit comprises:

(i) an anti-IL-31RA monoclonal antibody or antigen-binding fragment thereof which specifically binds amino acid residues 20-519 of SEQ ID NO:6 or a portion thereof; and

(ii) instructions for treating a skin disorder selected from the group consisting of from Toxic epidermal necrolysis, Bullous pemphigoid, Vitiligo, Acne Rosacea, Prurigo nodularis, and Scleroderma in a patient in need thereof.

## SEQUENCE LISTING

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<120> METHODS OF TREATING SKIN DISORDERS USING  
AN IL-31RA ANTAGONIST

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| Cys Leu Gly Gly Trp Leu Ala Ser His Thr Leu Pro Val Arg Leu Leu |     |
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| cga cca agt gat gat gta cag aaa ata gtc gag gaa tta cag tcc ctc | 144 |
| Arg Pro Ser Asp Asp Val Gln Lys Ile Val Glu Glu Leu Gln Ser Leu |     |
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| Ser Lys Met Leu Leu Lys Asp Val Glu Glu Glu Lys Gly Val Leu Val |     |
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| Ser Gln Asn Tyr Thr Leu Pro Cys Leu Ser Pro Asp Ala Gln Pro Pro |     |
| 65 70 75 80                                                     |     |
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| Asn Asn Ile His Ser Pro Ala Ile Arg Ala Tyr Leu Lys Thr Ile Arg |     |
| 85 90 95                                                        |     |
| cag cta gac aac aaa tct gtt att gat gag atc ata gag cac ctc gac | 336 |
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agt tat acc cag tac aca gtt aag aga act tac gct ttt gga gaa aaa 192
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gag gtg gaa gct gaa aat gga gat ggt gta att aaa tct cat atg aca 336
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| Gly Lys Gly Phe Ser Lys Thr Val Asn Ser Ser Ile Leu Gln Tyr Gly |      |
| 465 470 475 480                                                 |      |
| ctg gag tcc ctg aaa cga aag acc tct tac att gtt cag gtc atg gcc | 1488 |
| Leu Glu Ser Leu Lys Arg Lys Thr Ser Tyr Ile Val Gln Val Met Ala |      |
| 485 490 495                                                     |      |
| agc acc agt gct ggg gga acc aac ggg acc agc ata aat ttc aag aca | 1536 |
| Ser Thr Ser Ala Gly Gly Thr Asn Gly Thr Ser Ile Asn Phe Lys Thr |      |
| 500 505 510                                                     |      |
| ttg tca ttc agt gtc ttt gag att atc ctc ata act tct ctg att ggt | 1584 |
| Leu Ser Phe Ser Val Phe Glu Ile Ile Leu Ile Thr Ser Leu Ile Gly |      |
| 515 520 525                                                     |      |
| gga ggc ctt ctt att ctc att atc ctg aca gtg gca tat ggt ctc aaa | 1632 |
| Gly Gly Leu Leu Ile Leu Ile Ile Leu Thr Val Ala Tyr Gly Leu Lys |      |
| 530 535 540                                                     |      |
| aaa ccc aac aaa ttg act cat ctg tgt tgg ccc acc gtt ccc aac cct | 1680 |
| Lys Pro Asn Lys Leu Thr His Leu Cys Trp Pro Thr Val Pro Asn Pro |      |
| 545 550 555 560                                                 |      |
| gct gaa agt agt ata gcc aca tgg cat gga gat gat ttc aag gat aag | 1728 |
| Ala Glu Ser Ser Ile Ala Thr Trp His Gly Asp Asp Phe Lys Asp Lys |      |
| 565 570 575                                                     |      |
| cta aac ctg aag gag tct gat gac tct gtg aac aca gaa gac agg atc | 1776 |
| Leu Asn Leu Lys Glu Ser Asp Asp Ser Val Asn Thr Glu Asp Arg Ile |      |
| 580 585 590                                                     |      |
| tta aaa cca tgt tcc acc ccc agt gac aag ttg gtg att gac aag ttg | 1824 |
| Leu Lys Pro Cys Ser Thr Pro Ser Asp Lys Leu Val Ile Asp Lys Leu |      |
| 595 600 605                                                     |      |
| gtg gtg aac ttt ggg aat gtt ctg caa gaa att ttc aca gat gaa gcc | 1872 |
| Val Val Asn Phe Gly Asn Val Leu Gln Glu Ile Phe Thr Asp Glu Ala |      |
| 610 615 620                                                     |      |
| aga acg ggt cag gaa aac aat tta gga ggg gaa aag aat ggg tat gtg | 1920 |
| Arg Thr Gly Gln Glu Asn Asn Leu Gly Gly Glu Lys Asn Gly Tyr Val |      |
| 625 630 635 640                                                 |      |
| acc tgc ccc ttc agg cct gat tgt ccc ctg ggg aaa agt ttt gag gag | 1968 |
| Thr Cys Pro Phe Arg Pro Asp Cys Pro Leu Gly Lys Ser Phe Glu Glu |      |
| 645 650 655                                                     |      |
| ctc cca gtt tca cct gag att ccg ccc aga aaa tcc caa tac cta cgt | 2016 |
| Leu Pro Val Ser Pro Glu Ile Pro Pro Arg Lys Ser Gln Tyr Leu Arg |      |
| 660 665 670                                                     |      |
| tcg agg atg cca gag ggg acc cgc cca gaa gcc aaa gag cag ctt ctc | 2064 |
| Ser Arg Met Pro Glu Gly Thr Arg Pro Glu Ala Lys Glu Gln Leu Leu |      |
| 675 680 685                                                     |      |
| ttt tct ggt caa agt tta gta cca gat cat ctg tgt gag gaa gga gcc | 2112 |
| Phe Ser Gly Gln Ser Leu Val Pro Asp His Leu Cys Glu Glu Gly Ala |      |
| 690 695 700                                                     |      |
| cca aat cca tat ttg aaa aat tca gtg aca gcc agg gaa ttt ctt gtg | 2160 |
| Pro Asn Pro Tyr Leu Lys Asn Ser Val Thr Ala Arg Glu Phe Leu Val |      |
| 705 710 715 720                                                 |      |
| tct gaa aaa ctt cca gag cac acc aag gga gaa gtc taa             | 2199 |

Ser Glu Lys Leu Pro Glu His Thr Lys Gly Glu Val \*  
 725 730

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 <212> PRT  
 <213> Homo sapiens

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 Tyr Tyr Arg Lys Asn Leu Thr Cys Thr Trp Ser Pro Gly Lys Glu Thr  
 35 40 45  
 Ser Tyr Thr Gln Tyr Thr Val Lys Arg Thr Tyr Ala Phe Gly Glu Lys  
 50 55 60  
 His Asp Asn Cys Thr Thr Asn Ser Ser Thr Ser Glu Asn Arg Ala Ser  
 65 70 75 80  
 Cys Ser Phe Phe Leu Pro Arg Ile Thr Ile Pro Asp Asn Tyr Thr Ile  
 85 90 95  
 Glu Val Glu Ala Glu Asn Gly Asp Gly Val Ile Lys Ser His Met Thr  
 100 105 110  
 Tyr Trp Arg Leu Glu Asn Ile Ala Lys Thr Glu Pro Pro Lys Ile Phe  
 115 120 125  
 Arg Val Lys Pro Val Leu Gly Ile Lys Arg Met Ile Gln Ile Glu Trp  
 130 135 140  
 Ile Lys Pro Glu Leu Ala Pro Val Ser Ser Asp Leu Lys Tyr Thr Leu  
 145 150 155 160  
 Arg Phe Arg Thr Val Asn Ser Thr Ser Trp Met Glu Val Asn Phe Ala  
 165 170 175  
 Lys Asn Arg Lys Asp Lys Asn Gln Thr Tyr Asn Leu Thr Gly Leu Gln  
 180 185 190  
 Pro Phe Thr Glu Tyr Val Ile Ala Leu Arg Cys Ala Val Lys Glu Ser  
 195 200 205  
 Lys Phe Trp Ser Asp Trp Ser Gln Glu Lys Met Gly Met Thr Glu Glu  
 210 215 220  
 Glu Ala Pro Cys Gly Leu Glu Leu Trp Arg Val Leu Lys Pro Ala Glu  
 225 230 235 240  
 Ala Asp Gly Arg Arg Pro Val Arg Leu Leu Trp Lys Lys Ala Arg Gly  
 245 250 255  
 Ala Pro Val Leu Glu Lys Thr Leu Gly Tyr Asn Ile Trp Tyr Tyr Pro  
 260 265 270  
 Glu Ser Asn Thr Asn Leu Thr Glu Thr Met Asn Thr Thr Asn Gln Gln  
 275 280 285  
 Leu Glu Leu His Leu Gly Gly Glu Ser Phe Trp Val Ser Met Ile Ser  
 290 295 300  
 Tyr Asn Ser Leu Gly Lys Ser Pro Val Ala Thr Leu Arg Ile Pro Ala  
 305 310 315 320  
 Ile Gln Glu Lys Ser Phe Gln Cys Ile Glu Val Met Gln Ala Cys Val  
 325 330 335  
 Ala Glu Asp Gln Leu Val Val Lys Trp Gln Ser Ser Ala Leu Asp Val  
 340 345 350  
 Asn Thr Trp Met Ile Glu Trp Phe Pro Asp Val Asp Ser Glu Pro Thr  
 355 360 365  
 Thr Leu Ser Trp Glu Ser Val Ser Gln Ala Thr Asn Trp Thr Ile Gln  
 370 375 380  
 Gln Asp Lys Leu Lys Pro Phe Trp Cys Tyr Asn Ile Ser Val Tyr Pro  
 385 390 395 400  
 Met Leu His Asp Lys Val Gly Glu Pro Tyr Ser Ile Gln Ala Tyr Ala  
 405 410 415  
 Lys Glu Gly Val Pro Ser Glu Gly Pro Glu Thr Lys Val Glu Asn Ile  
 420 425 430  
 Gly Val Lys Thr Val Thr Ile Thr Trp Lys Glu Ile Pro Lys Ser Glu  
 435 440 445

Arg Lys Gly Ile Ile Cys Asn Tyr Thr Ile Phe Tyr Gln Ala Glu Gly  
 450 455 460  
 Gly Lys Gly Phe Ser Lys Thr Val Asn Ser Ser Ile Leu Gln Tyr Gly  
 465 470 475 480  
 Leu Glu Ser Leu Lys Arg Lys Thr Ser Tyr Ile Val Gln Val Met Ala  
 485 490 495  
 Ser Thr Ser Ala Gly Gly Thr Asn Gly Thr Ser Ile Asn Phe Lys Thr  
 500 505 510  
 Leu Ser Phe Ser Val Phe Glu Ile Ile Leu Ile Thr Ser Leu Ile Gly  
 515 520 525  
 Gly Gly Leu Leu Ile Leu Ile Ile Leu Thr Val Ala Tyr Gly Leu Lys  
 530 535 540  
 Lys Pro Asn Lys Leu Thr His Leu Cys Trp Pro Thr Val Pro Asn Pro  
 545 550 555 560  
 Ala Glu Ser Ser Ile Ala Thr Trp His Gly Asp Asp Phe Lys Asp Lys  
 565 570 575  
 Leu Asn Leu Lys Glu Ser Asp Asp Ser Val Asn Thr Glu Asp Arg Ile  
 580 585 590  
 Leu Lys Pro Cys Ser Thr Pro Ser Asp Lys Leu Val Ile Asp Lys Leu  
 595 600 605  
 Val Val Asn Phe Gly Asn Val Leu Gln Glu Ile Phe Thr Asp Glu Ala  
 610 615 620  
 Arg Thr Gly Gln Glu Asn Asn Leu Gly Gly Glu Lys Asn Gly Tyr Val  
 625 630 635 640  
 Thr Cys Pro Phe Arg Pro Asp Cys Pro Leu Gly Lys Ser Phe Glu Glu  
 645 650 655  
 Leu Pro Val Ser Pro Glu Ile Pro Pro Arg Lys Ser Gln Tyr Leu Arg  
 660 665 670  
 Ser Arg Met Pro Glu Gly Thr Arg Pro Glu Ala Lys Glu Gln Leu Leu  
 675 680 685  
 Phe Ser Gly Gln Ser Leu Val Pro Asp His Leu Cys Glu Glu Gly Ala  
 690 695 700  
 Pro Asn Pro Tyr Leu Lys Asn Ser Val Thr Ala Arg Glu Phe Leu Val  
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 Ser Glu Lys Leu Pro Glu His Thr Lys Gly Glu Val  
 725 730

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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1)...(1989)

<221> misc\_feature  
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 <223> IL-31RA "short" form

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 1 5 10 15  
 acc tgg gca ctg tgg atg ctc cct tca ctc tgc aaa ttc agc ctg gca 96  
 Thr Trp Ala Leu Trp Met Leu Pro Ser Leu Cys Lys Phe Ser Leu Ala  
 20 25 30  
 gct ctg cca gct aag cct gag aac att tcc tgt gtc tac tac tat agg 144  
 Ala Leu Pro Ala Lys Pro Glu Asn Ile Ser Cys Val Tyr Tyr Tyr Arg  
 35 40 45  
 aaa aat tta acc tgc act tgg agt cca gga aag gaa acc agt tat acc 192  
 Lys Asn Leu Thr Cys Thr Trp Ser Pro Gly Lys Glu Thr Ser Tyr Thr

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| 50                                                                                                                                                    | 55 | 60 |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|-----|
| cag tac aca gtt aag aga act tac gct ttt gga gaa aaa cat gat aat<br>Gln Tyr Thr Val Lys Arg Thr Tyr Ala Phe Gly Glu Lys His Asp Asn<br>65 70 75 80     |    |    | 240 |
| tgt aca acc aat agt tct aca agt gaa aat cgt gct tcg tgc tct ttt<br>Cys Thr Thr Asn Ser Ser Thr Ser Glu Asn Arg Ala Ser Cys Ser Phe<br>85 90 95        |    |    | 288 |
| ttc ctt cca aga ata acg atc cca gat aat tat acc att gag gtg gaa<br>Phe Leu Pro Arg Ile Thr Ile Pro Asp Asn Tyr Thr Ile Glu Val Glu<br>100 105 110     |    |    | 336 |
| gct gaa aat gga gat ggt gta att aaa tct cat atg aca tac tgg aga<br>Ala Glu Asn Gly Asp Gly Val Ile Lys Ser His Met Thr Tyr Trp Arg<br>115 120 125     |    |    | 384 |
| tta gag aac ata gcg aaa act gaa cca cct aag att ttc cgt gtg aaa<br>Leu Glu Asn Ile Ala Lys Thr Glu Pro Pro Lys Ile Phe Arg Val Lys<br>130 135 140     |    |    | 432 |
| cca gtt ttg ggc atc aaa cga atg att caa att gaa tgg ata aag cct<br>Pro Val Leu Gly Ile Lys Arg Met Ile Gln Ile Glu Trp Ile Lys Pro<br>145 150 155 160 |    |    | 480 |
| gag ttg gcg cct gtt tca tct gat tta aaa tac aca ctt cga ttc agg<br>Glu Leu Ala Pro Val Ser Ser Asp Leu Lys Tyr Thr Leu Arg Phe Arg<br>165 170 175     |    |    | 528 |
| aca gtc aac agt acc agc tgg atg gaa gtc aac ttc gct aag aac cgt<br>Thr Val Asn Ser Thr Ser Trp Met Glu Val Asn Phe Ala Lys Asn Arg<br>180 185 190     |    |    | 576 |
| aag gat aaa aac caa acg tac aac ctc acg ggg ctg cag cct ttt aca<br>Lys Asp Lys Asn Gln Thr Tyr Asn Leu Thr Gly Leu Gln Pro Phe Thr<br>195 200 205     |    |    | 624 |
| gaa tat gtc ata gct ctg cga tgt gcg gtc aag gag tca aag ttc tgg<br>Glu Tyr Val Ile Ala Leu Arg Cys Ala Val Lys Glu Ser Lys Phe Trp<br>210 215 220     |    |    | 672 |
| agt gac tgg agc caa gaa aaa atg gga atg act gag gaa gaa gct cca<br>Ser Asp Trp Ser Gln Lys Met Gly Met Thr Glu Glu Glu Ala Pro<br>225 230 235 240     |    |    | 720 |
| tgt ggc ctg gaa ctg tgg aga gtc ctg aaa cca gct gag gcg gat gga<br>Cys Gly Leu Glu Leu Trp Arg Val Leu Lys Pro Ala Glu Ala Asp Gly<br>245 250 255     |    |    | 768 |
| aga agg cca gtg cgg ttg tta tgg aag aag gca aga gga gcc cca gtc<br>Arg Arg Pro Val Arg Leu Leu Trp Lys Lys Ala Arg Gly Ala Pro Val<br>260 265 270     |    |    | 816 |
| cta gag aaa aca ctt ggc tac aac ata tgg tac tat cca gaa agc aac<br>Leu Glu Lys Thr Leu Gly Tyr Asn Ile Trp Tyr Tyr Pro Glu Ser Asn<br>275 280 285     |    |    | 864 |
| act aac ctc aca gaa aca atg aac act act aac cag cag ctt gaa ctg<br>Thr Asn Leu Thr Glu Thr Met Asn Thr Thr Asn Gln Gln Leu Glu Leu<br>290 295 300     |    |    | 912 |
| cat ctg gga ggc gag agc ttt tgg gtg tct atg att tct tat aat tct<br>His Leu Gly Gly Glu Ser Phe Trp Val Ser Met Ile Ser Tyr Asn Ser<br>305 310 315 320 |    |    | 960 |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| ctt ggg aag tct cca gtg gcc acc ctg agg att cca gct att caa gaa | 1008 |
| Leu Gly Lys Ser Pro Val Ala Thr Leu Arg Ile Pro Ala Ile Gln Glu |      |
| 325 330 335                                                     |      |
| aaa tca ttt cag tgc att gag gtc atg cag gcc tgc gtt gct gag gac | 1056 |
| Lys Ser Phe Gln Cys Ile Glu Val Met Gln Ala Cys Val Ala Glu Asp |      |
| 340 345 350                                                     |      |
| cag cta gtg gtg aag tgg caa agc tct gct cta gac gtg aac act tgg | 1104 |
| Gln Leu Val Val Lys Trp Gln Ser Ser Ala Leu Asp Val Asn Thr Trp |      |
| 355 360 365                                                     |      |
| atg att gaa tgg ttt ccg gat gtg gac tca gag ccc acc acc ctt tcc | 1152 |
| Met Ile Glu Trp Phe Pro Asp Val Asp Ser Glu Pro Thr Thr Leu Ser |      |
| 370 375 380                                                     |      |
| tgg gaa tct gtg tct cag gcc acg aac tgg acg atc cag caa gat aaa | 1200 |
| Trp Glu Ser Val Ser Gln Ala Thr Asn Trp Thr Ile Gln Gln Asp Lys |      |
| 385 390 395 400                                                 |      |
| tta aaa cct ttc tgg tgc tat aac atc tct gtg tat cca atg ttg cat | 1248 |
| Leu Lys Pro Phe Trp Cys Tyr Asn Ile Ser Val Tyr Pro Met Leu His |      |
| 405 410 415                                                     |      |
| gac aaa gtt ggc gag cca tat tcc atc cag gct tat gcc aaa gaa ggc | 1296 |
| Asp Lys Val Gly Glu Pro Tyr Ser Ile Gln Ala Tyr Ala Lys Glu Gly |      |
| 420 425 430                                                     |      |
| gtt cca tca gaa ggt cct gag acc aag gtg gag aac att ggc gtg aag | 1344 |
| Val Pro Ser Glu Gly Pro Glu Thr Lys Val Glu Asn Ile Gly Val Lys |      |
| 435 440 445                                                     |      |
| acg gtc acg atc aca tgg aaa gag att ccc aag agt gag aga aag ggt | 1392 |
| Thr Val Thr Ile Thr Trp Lys Glu Ile Pro Lys Ser Glu Arg Lys Gly |      |
| 450 455 460                                                     |      |
| atc atc tgc aac tac acc atc ttt tac caa gct gaa ggt gga aaa gga | 1440 |
| Ile Ile Cys Asn Tyr Thr Ile Phe Tyr Gln Ala Glu Gly Gly Lys Gly |      |
| 465 470 475 480                                                 |      |
| ttc tcc aag aca gtc aat tcc agc atc ttg cag tac ggc ctg gag tcc | 1488 |
| Phe Ser Lys Thr Val Asn Ser Ser Ile Leu Gln Tyr Gly Leu Glu Ser |      |
| 485 490 495                                                     |      |
| ctg aaa cga aag acc tct tac att gtt cag gtc atg gcc agc acc agt | 1536 |
| Leu Lys Arg Lys Thr Ser Tyr Ile Val Gln Val Met Ala Ser Thr Ser |      |
| 500 505 510                                                     |      |
| gct ggg gga acc aac ggg acc agc ata aat ttc aag aca ttg tca ttc | 1584 |
| Ala Gly Gly Thr Asn Gly Thr Ser Ile Asn Phe Lys Thr Leu Ser Phe |      |
| 515 520 525                                                     |      |
| agt gtc ttt gag att atc ctc ata act tct ctg att ggt gga ggc ctt | 1632 |
| Ser Val Phe Glu Ile Ile Leu Ile Thr Ser Leu Ile Gly Gly Gly Leu |      |
| 530 535 540                                                     |      |
| ctt att ctc att atc ctg aca gtg gca tat ggt ctc aaa aaa ccc aac | 1680 |
| Leu Ile Leu Ile Ile Leu Thr Val Ala Tyr Gly Leu Lys Lys Pro Asn |      |
| 545 550 555 560                                                 |      |
| aaa ttg act cat ctg tgt tgg ccc acc gtt ccc aac cct gct gaa agt | 1728 |
| Lys Leu Thr His Leu Cys Trp Pro Thr Val Pro Asn Pro Ala Glu Ser |      |
| 565 570 575                                                     |      |
| agt ata gcc aca tgg cat gga gat gat ttc aag gat aag cta aac ctg | 1776 |
| Ser Ile Ala Thr Trp His Gly Asp Asp Phe Lys Asp Lys Leu Asn Leu |      |

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| 580 |     |     |     |     |     |     |     |     |     | 585 |     |     |     |     | 590 |      |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--|--|--|--|
| aag | gag | tct | gat | gac | tct | gtg | aac | aca | gaa | gac | agg | atc | tta | aaa | cca | 1824 |  |  |  |  |
| Lys | Glu | Ser | Asp | Asp | Ser | Val | Asn | Thr | Glu | Asp | Arg | Ile | Leu | Lys | Pro |      |  |  |  |  |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |      |  |  |  |  |
| tgt | tcc | acc | ccc | agt | gac | aag | ttg | gtg | att | gac | aag | ttg | gtg | gtg | aac | 1872 |  |  |  |  |
| Cys | Ser | Thr | Pro | Ser | Asp | Lys | Leu | Val | Ile | Asp | Lys | Leu | Val | Val | Asn |      |  |  |  |  |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |      |  |  |  |  |
| ttt | ggg | aat | gtt | ctg | caa | gaa | att | ttc | aca | gat | gaa | gcc | aga | acg | ggg | 1920 |  |  |  |  |
| Phe | Gly | Asn | Val | Leu | Gln | Glu | Ile | Phe | Thr | Asp | Glu | Ala | Arg | Thr | Gly |      |  |  |  |  |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |      |  |  |  |  |
| cag | gaa | aac | aat | tta | gga | ggg | gaa | aag | aat | ggg | act | aga | att | ctg | tct | 1968 |  |  |  |  |
| Gln | Glu | Asn | Asn | Leu | Gly | Gly | Glu | Lys | Asn | Gly | Thr | Arg | Ile | Leu | Ser |      |  |  |  |  |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |      |  |  |  |  |
| tcc | tgc | cca | act | tca | ata | taa |     |     |     |     |     |     |     |     |     | 1989 |  |  |  |  |
| Ser | Cys | Pro | Thr | Ser | Ile | *   |     |     |     |     |     |     |     |     |     |      |  |  |  |  |
|     |     |     | 660 |     |     |     |     |     |     |     |     |     |     |     |     |      |  |  |  |  |

&lt;210&gt; 8

&lt;211&gt; 662

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 8

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Leu | Ser | Pro | Gln | Pro | Ser | Cys | Val | Asn | Leu | Gly | Met | Met | Trp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     | 15  |     |     |
| Thr | Trp | Ala | Leu | Trp | Met | Leu | Pro | Ser | Leu | Cys | Lys | Phe | Ser | Leu | Ala |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     | 30  |     |     |     |
| Ala | Leu | Pro | Ala | Lys | Pro | Glu | Asn | Ile | Ser | Cys | Val | Tyr | Tyr | Tyr | Arg |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Lys | Asn | Leu | Thr | Cys | Thr | Trp | Ser | Pro | Gly | Lys | Glu | Thr | Ser | Tyr | Thr |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Gln | Tyr | Thr | Val | Lys | Arg | Thr | Tyr | Ala | Phe | Gly | Glu | Lys | His | Asp | Asn |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Cys | Thr | Thr | Asn | Ser | Ser | Thr | Ser | Glu | Asn | Arg | Ala | Ser | Cys | Ser | Phe |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Phe | Leu | Pro | Arg | Ile | Thr | Ile | Pro | Asp | Asn | Tyr | Thr | Ile | Glu | Val | Glu |
|     |     | 100 |     |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Ala | Glu | Asn | Gly | Asp | Gly | Val | Ile | Lys | Ser | His | Met | Thr | Tyr | Trp | Arg |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Leu | Glu | Asn | Ile | Ala | Lys | Thr | Glu | Pro | Pro | Lys | Ile | Phe | Arg | Val | Lys |
|     |     | 130 |     |     |     |     | 135 |     |     |     | 140 |     |     |     |     |
| Pro | Val | Leu | Gly | Ile | Lys | Arg | Met | Ile | Gln | Ile | Glu | Trp | Ile | Lys | Pro |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Glu | Leu | Ala | Pro | Val | Ser | Ser | Asp | Leu | Lys | Tyr | Thr | Leu | Arg | Phe | Arg |
|     |     |     | 165 |     |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Thr | Val | Asn | Ser | Thr | Ser | Trp | Met | Glu | Val | Asn | Phe | Ala | Lys | Asn | Arg |
|     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Lys | Asp | Lys | Asn | Gln | Thr | Tyr | Asn | Leu | Thr | Gly | Leu | Gln | Pro | Phe | Thr |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Glu | Tyr | Val | Ile | Ala | Leu | Arg | Cys | Ala | Val | Lys | Glu | Ser | Lys | Phe | Trp |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Ser | Asp | Trp | Ser | Gln | Glu | Lys | Met | Gly | Met | Thr | Glu | Glu | Glu | Ala | Pro |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Cys | Gly | Leu | Glu | Leu | Trp | Arg | Val | Leu | Lys | Pro | Ala | Glu | Ala | Asp | Gly |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Arg | Arg | Pro | Val | Arg | Leu | Leu | Trp | Lys | Lys | Ala | Arg | Gly | Ala | Pro | Val |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Leu | Glu | Lys | Thr | Leu | Gly | Tyr | Asn | Ile | Trp | Tyr | Tyr | Pro | Glu | Ser | Asn |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Thr | Asn | Leu | Thr | Glu | Thr | Met | Asn | Thr | Thr | Asn | Gln | Gln | Leu | Glu | Leu |

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290 295 300  
 His Leu Gly Gly Glu Ser Phe Trp Val Ser Met Ile Ser Tyr Asn Ser  
 305 310 315 320  
 Leu Gly Lys Ser Pro Val Ala Thr Leu Arg Ile Pro Ala Ile Gln Glu  
 325 330 335  
 Lys Ser Phe Gln Cys Ile Glu Val Met Gln Ala Cys Val Ala Glu Asp  
 340 345 350  
 Gln Leu Val Val Lys Trp Gln Ser Ser Ala Leu Asp Val Asn Thr Trp  
 355 360 365  
 Met Ile Glu Trp Phe Pro Asp Val Asp Ser Glu Pro Thr Thr Leu Ser  
 370 375 380  
 Trp Glu Ser Val Ser Gln Ala Thr Asn Trp Thr Ile Gln Gln Asp Lys  
 385 390 395 400  
 Leu Lys Pro Phe Trp Cys Tyr Asn Ile Ser Val Tyr Pro Met Leu His  
 405 410 415  
 Asp Lys Val Gly Glu Pro Tyr Ser Ile Gln Ala Tyr Ala Lys Glu Gly  
 420 425 430  
 Val Pro Ser Glu Gly Pro Glu Thr Lys Val Glu Asn Ile Gly Val Lys  
 435 440 445  
 Thr Val Thr Ile Thr Trp Lys Glu Ile Pro Lys Ser Glu Arg Lys Gly  
 450 455 460  
 Ile Ile Cys Asn Tyr Thr Ile Phe Tyr Gln Ala Glu Gly Gly Lys Gly  
 465 470 475 480  
 Phe Ser Lys Thr Val Asn Ser Ser Ile Leu Gln Tyr Gly Leu Glu Ser  
 485 490 495  
 Leu Lys Arg Lys Thr Ser Tyr Ile Val Gln Val Met Ala Ser Thr Ser  
 500 505 510  
 Ala Gly Gly Thr Asn Gly Thr Ser Ile Asn Phe Lys Thr Leu Ser Phe  
 515 520 525  
 Ser Val Phe Glu Ile Ile Leu Ile Thr Ser Leu Ile Gly Gly Gly Leu  
 530 535 540  
 Leu Ile Leu Ile Ile Leu Thr Val Ala Tyr Gly Leu Lys Lys Pro Asn  
 545 550 555 560  
 Lys Leu Thr His Leu Cys Trp Pro Thr Val Pro Asn Pro Ala Glu Ser  
 565 570 575  
 Ser Ile Ala Thr Trp His Gly Asp Asp Phe Lys Asp Lys Leu Asn Leu  
 580 585 590  
 Lys Glu Ser Asp Asp Ser Val Asn Thr Glu Asp Arg Ile Leu Lys Pro  
 595 600 605  
 Cys Ser Thr Pro Ser Asp Lys Leu Val Ile Asp Lys Leu Val Val Asn  
 610 615 620  
 Phe Gly Asn Val Leu Gln Glu Ile Phe Thr Asp Glu Ala Arg Thr Gly  
 625 630 635 640  
 Gln Glu Asn Asn Leu Gly Gly Glu Lys Asn Gly Thr Arg Ile Leu Ser  
 645 650 655  
 Ser Cys Pro Thr Ser Ile  
 660

&lt;210&gt; 9

&lt;211&gt; 975

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)...(975)

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(975)

&lt;223&gt; soluble IL-31RA "long" form

&lt;400&gt; 9

atg atg tgg acc tgg gca ctg tgg atg ctc ccc tca ctc tgc aaa ttc 48

Met Met Trp Thr Trp Ala Leu Trp Met Leu Pro Ser Leu Cys Lys Phe

1

5

10

15

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| agc | ctg | gca | gct | ctg | cca | gct | aag | cct | gag | aac | att | tcc | tgt | gtc | tac | 96  |
| Ser | Leu | Ala | Ala | Leu | Pro | Ala | Lys | Pro | Glu | Asn | Ile | Ser | Cys | Val | Tyr |     |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |
| tac | tat | agg | aaa | aat | tta | acc | tgc | act | tgg | agt | cca | gga | aag | gaa | acc | 144 |
| Tyr | Tyr | Arg | Lys | Asn | Leu | Thr | Cys | Thr | Trp | Ser | Pro | Gly | Lys | Glu | Thr |     |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |
| agt | tat | acc | cag | tac | aca | gtt | aag | aga | act | tac | gct | ttt | gga | gaa | aaa | 192 |
| Ser | Tyr | Thr | Gln | Tyr | Thr | Val | Lys | Arg | Thr | Tyr | Ala | Phe | Gly | Glu | Lys |     |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |
| cat | gat | aat | tgt | aca | acc | aat | agt | tct | aca | agt | gaa | aat | cgt | gct | tcg | 240 |
| His | Asp | Asn | Cys | Thr | Thr | Asn | Ser | Ser | Thr | Ser | Glu | Asn | Arg | Ala | Ser |     |
|     | 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     | 80  |     |
| tgc | tct | ttt | ttc | ctt | cca | aga | ata | acg | atc | cca | gat | aat | tat | acc | att | 288 |
| Cys | Ser | Phe | Phe | Leu | Pro | Arg | Ile | Thr | Ile | Pro | Asp | Asn | Tyr | Thr | Ile |     |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |
| gag | gtg | gaa | gct | gaa | aat | gga | gat | ggg | gta | att | aaa | tct | cat | atg | aca | 336 |
| Glu | Val | Glu | Ala | Glu | Asn | Gly | Asp | Gly | Val | Ile | Lys | Ser | His | Met | Thr |     |
|     |     | 100 |     |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |
| tac | tgg | aga | tta | gag | aac | ata | gcg | aaa | act | gaa | cca | cct | aag | att | ttc | 384 |
| Tyr | Trp | Arg | Leu | Glu | Asn | Ile | Ala | Lys | Thr | Glu | Pro | Pro | Lys | Ile | Phe |     |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |
| cgt | gtg | aaa | cca | gtt | ttg | ggc | atc | aaa | cga | atg | att | caa | att | gaa | tgg | 432 |
| Arg | Val | Lys | Pro | Val | Leu | Gly | Ile | Lys | Arg | Met | Ile | Gln | Ile | Glu | Trp |     |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |     |
| ata | aag | cct | gag | ttg | gcg | cct | gtt | tca | tct | gat | tta | aaa | tac | aca | ctt | 480 |
| Ile | Lys | Pro | Glu | Leu | Ala | Pro | Val | Ser | Ser | Asp | Leu | Lys | Tyr | Thr | Leu |     |
|     | 145 |     |     |     |     | 150 |     |     |     | 155 |     |     |     |     | 160 |     |
| cga | ttc | agg | aca | gtc | aac | agt | acc | agc | tgg | atg | gaa | gtc | aac | ttc | gct | 528 |
| Arg | Phe | Arg | Thr | Val | Asn | Ser | Thr | Ser | Trp | Met | Glu | Val | Asn | Phe | Ala |     |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |
| aag | aac | cgt | aag | gat | aaa | aac | caa | acg | tac | aac | ctc | acg | ggg | ctg | cag | 576 |
| Lys | Asn | Arg | Lys | Asp | Lys | Asn | Gln | Thr | Tyr | Asn | Leu | Thr | Gly | Leu | Gln |     |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |
| cct | ttt | aca | gaa | tat | gtc | ata | gct | ctg | cga | tgt | gcg | gtc | aag | gag | tca | 624 |
| Pro | Phe | Thr | Glu | Tyr | Val | Ile | Ala | Leu | Arg | Cys | Ala | Val | Lys | Glu | Ser |     |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |
| aag | ttc | tgg | agt | gac | tgg | agc | caa | gaa | aaa | atg | gga | atg | act | gag | gaa | 672 |
| Lys | Phe | Trp | Ser | Asp | Trp | Ser | Gln | Glu | Lys | Met | Gly | Met | Thr | Glu | Glu |     |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |     |
| gaa | gct | cca | tgt | ggc | ctg | gaa | ctg | tgg | aga | gtc | ctg | aaa | cca | gct | gag | 720 |
| Glu | Ala | Pro | Cys | Gly | Leu | Glu | Leu | Trp | Arg | Val | Leu | Lys | Pro | Ala | Glu |     |
|     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |     |
| gcg | gat | gga | aga | agg | cca | gtg | cgg | ttg | tta | tgg | aag | aag | gca | aga | gga | 768 |
| Ala | Asp | Gly | Arg | Arg | Pro | Val | Arg | Leu | Leu | Trp | Lys | Lys | Ala | Arg | Gly |     |
|     |     |     |     | 245 |     |     |     | 250 |     |     |     |     |     | 255 |     |     |
| gcc | cca | gtc | cta | gag | aaa | aca | ctt | ggc | tac | aac | ata | tgg | tac | tat | cca | 816 |
| Ala | Pro | Val | Leu | Glu | Lys | Thr | Leu | Gly | Tyr | Asn | Ile | Trp | Tyr | Tyr | Pro |     |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |
| gaa | agc | aac | act | aac | ctc | aca | gaa | aca | atg | aac | act | act | aac | cag | cag | 864 |

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<210> 10
<211> 324
<212> PRT
<213> Homo sapiens
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[illegible]

<210> 11  
 <211> 720  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)...(720)  
 <221> misc\_feature  
 <222> (1)...(720)  
 <223> soluble IL-31RA "short" form

<400> 11  
 atg atg tgg acc tgg gca ctg tgg atg ctc ccc tca ctc tgc aaa ttc 48  
 Met Met Trp Thr Trp Ala Leu Trp Met Leu Pro Ser Leu Cys Lys Phe  
 1 5 10 15  
 agc ctg gca gct ctg cca gct aag cct gag aac att tcc tgt gtc tac 96  
 Ser Leu Ala Ala Leu Pro Ala Lys Pro Glu Asn Ile Ser Cys Val Tyr  
 20 25 30  
 tac tat agg aaa aat tta acc tgc act tgg agt cca gga aag gaa acc 144  
 Tyr Tyr Arg Lys Asn Leu Thr Cys Thr Trp Ser Pro Gly Lys Glu Thr  
 35 40 45  
 agt tat acc cag tac aca gtt aag aga act tac gct ttt gga gaa aaa 192  
 Ser Tyr Thr Gln Tyr Thr Val Lys Arg Thr Tyr Ala Phe Gly Glu Lys  
 50 55 60  
 cat gat aat tgt aca acc aat agt tct aca agt gaa aat cgt gct tcg 240  
 His Asp Asn Cys Thr Thr Asn Ser Ser Thr Ser Glu Asn Arg Ala Ser  
 65 70 75 80  
 tgc tct ttt ttc ctt cca aga ata acg atc cca gat aat tat acc att 288  
 Cys Ser Phe Phe Leu Pro Arg Ile Thr Ile Pro Asp Asn Tyr Thr Ile  
 85 90 95  
 gag gtg gaa gct gaa aat gga gat ggt gta att aaa tct cat atg aca 336  
 Glu Val Glu Ala Glu Asn Gly Asp Gly Val Ile Lys Ser His Met Thr  
 100 105 110  
 tac tgg aga tta gag aac ata gcg aaa act gaa cca cct aag att ttc 384  
 Tyr Trp Arg Leu Glu Asn Ile Ala Lys Thr Glu Pro Pro Lys Ile Phe  
 115 120 125  
 cgt gtg aaa cca gtt ttg ggc atc aaa cga atg att caa att gaa tgg 432  
 Arg Val Lys Pro Val Leu Gly Ile Lys Arg Met Ile Gln Ile Glu Trp  
 130 135 140  
 ata aag cct gag ttg gcg cct gtt tca tct gat tta aaa tac aca ctt 480  
 Ile Lys Pro Glu Leu Ala Pro Val Ser Ser Asp Leu Lys Tyr Thr Leu  
 145 150 155 160  
 cga ttc agg aca gtc aac agt acc agc tgg atg gaa gtc aac ttc gct 528  
 Arg Phe Arg Thr Val Asn Ser Thr Ser Trp Met Glu Val Asn Phe Ala  
 165 170 175  
 aag aac cgt aag gat aaa aac caa acg tac aac ctc acg ggg ctg cag 576  
 Lys Asn Arg Lys Asp Lys Asn Gln Thr Tyr Asn Leu Thr Gly Leu Gln  
 180 185 190  
 cct ttt aca gaa tat gtc ata gct ctg cga tgt gcg gtc aag gag tca 624  
 Pro Phe Thr Glu Tyr Val Ile Ala Leu Arg Cys Ala Val Lys Glu Ser  
 195 200 205

aag ttc tgg agt gac tgg agc caa gaa aaa atg gga atg act gag gaa 672  
 Lys Phe Trp Ser Asp Trp Ser Gln Glu Lys Met Gly Met Thr Glu Glu  
 210 215 220

gaa ggc aag cta ctc cct gcg att ccc gtc ctg tct gct ctg gtg tag 720  
 Glu Gly Lys Leu Leu Pro Ala Ile Pro Val Leu Ser Ala Leu Val \*  
 225 230 235

<210> 12  
 <211> 239  
 <212> PRT  
 <213> Homo sapiens

<400> 12  
 Met Met Trp Thr Trp Ala Leu Trp Met Leu Pro Ser Leu Cys Lys Phe  
 1 5 10 15  
 Ser Leu Ala Ala Leu Pro Ala Lys Pro Glu Asn Ile Ser Cys Val Tyr  
 20 25 30  
 Tyr Tyr Arg Lys Asn Leu Thr Cys Thr Trp Ser Pro Gly Lys Glu Thr  
 35 40 45  
 Ser Tyr Thr Gln Tyr Thr Val Lys Arg Thr Tyr Ala Phe Gly Glu Lys  
 50 55 60  
 His Asp Asn Cys Thr Thr Asn Ser Ser Thr Ser Glu Asn Arg Ala Ser  
 65 70 75 80  
 Cys Ser Phe Phe Leu Pro Arg Ile Thr Ile Pro Asp Asn Tyr Thr Ile  
 85 90 95  
 Glu Val Glu Ala Glu Asn Gly Asp Gly Val Ile Lys Ser His Met Thr  
 100 105 110  
 Tyr Trp Arg Leu Glu Asn Ile Ala Lys Thr Glu Pro Pro Lys Ile Phe  
 115 120 125  
 Arg Val Lys Pro Val Leu Gly Ile Lys Arg Met Ile Gln Ile Glu Trp  
 130 135 140  
 Ile Lys Pro Glu Leu Ala Pro Val Ser Ser Asp Leu Lys Tyr Thr Leu  
 145 150 155 160  
 Arg Phe Arg Thr Val Asn Ser Thr Ser Trp Met Glu Val Asn Phe Ala  
 165 170 175  
 Lys Asn Arg Lys Asp Lys Asn Gln Thr Tyr Asn Leu Thr Gly Leu Gln  
 180 185 190  
 Pro Phe Thr Glu Tyr Val Ile Ala Leu Arg Cys Ala Val Lys Glu Ser  
 195 200 205  
 Lys Phe Trp Ser Asp Trp Ser Gln Glu Lys Met Gly Met Thr Glu Glu  
 210 215 220  
 Glu Gly Lys Leu Leu Pro Ala Ile Pro Val Leu Ser Ala Leu Val  
 225 230 235

<210> 13  
 <211> 1989  
 <212> DNA  
 <213> Mus musculus

<220>  
 <221> CDS  
 <222> (1)...(1989)  
 <221> misc\_feature  
 <222> (1)...(1989)  
 <223> mouse IL-31RA

<400> 13  
 atg ctg agc agc cag aag gga tcc tgc agc cag gaa cca ggg gca gcc 48  
 Met Leu Ser Ser Gln Lys Gly Ser Cys Ser Gln Glu Pro Gly Ala Ala  
 1 5 10 15

|                                                                 |     |
|-----------------------------------------------------------------|-----|
| cac gtc cag cct ctg ggt gtg aac gct gga ata atg tgg acc ttg gca | 96  |
| His Val Gln Pro Leu Gly Val Asn Ala Gly Ile Met Trp Thr Leu Ala |     |
| 20 25 30                                                        |     |
| ctg tgg gca ttc tct ttc ctc tgc aaa ttc agc ctg gca gtc ctg ccg | 144 |
| Leu Trp Ala Phe Ser Phe Leu Cys Lys Phe Ser Leu Ala Val Leu Pro |     |
| 35 40 45                                                        |     |
| act aag cca gag aac att tcc tgc gtc ttt tac ttc gac aga aat ctg | 192 |
| Thr Lys Pro Glu Asn Ile Ser Cys Val Phe Tyr Phe Asp Arg Asn Leu |     |
| 50 55 60                                                        |     |
| act tgc act tgg aga cca gag aag gaa acc aat gat acc agc tac att | 240 |
| Thr Cys Thr Trp Arg Pro Glu Lys Glu Thr Asn Asp Thr Ser Tyr Ile |     |
| 65 70 75 80                                                     |     |
| gtg act ttg act tac tcc tat gga aaa agc aat tat agt gac aat gct | 288 |
| Val Thr Leu Thr Tyr Ser Tyr Gly Lys Ser Asn Tyr Ser Asp Asn Ala |     |
| 85 90 95                                                        |     |
| aca gag gct tca tat tct ttt ccc cgt tcc tgt gca atg ccc cca gac | 336 |
| Thr Glu Ala Ser Tyr Ser Phe Pro Arg Ser Cys Ala Met Pro Pro Asp |     |
| 100 105 110                                                     |     |
| atc tgc agt gtt gaa gta caa gct caa aat gga gat ggt aaa gtt aaa | 384 |
| Ile Cys Ser Val Glu Val Gln Ala Gln Asn Gly Asp Gly Lys Val Lys |     |
| 115 120 125                                                     |     |
| tct gac atc aca tat tgg cat tta atc tcc ata gca aaa acc gaa cca | 432 |
| Ser Asp Ile Thr Tyr Trp His Leu Ile Ser Ile Ala Lys Thr Glu Pro |     |
| 130 135 140                                                     |     |
| cct ata att tta agt gtg aat cca att tgt aat aga atg ttc cag ata | 480 |
| Pro Ile Ile Leu Ser Val Asn Pro Ile Cys Asn Arg Met Phe Gln Ile |     |
| 145 150 155 160                                                 |     |
| caa tgg aaa ccg cgt gaa aag act cgt ggg ttt cct tta gta tgc atg | 528 |
| Gln Trp Lys Pro Arg Glu Lys Thr Arg Gly Phe Pro Leu Val Cys Met |     |
| 165 170 175                                                     |     |
| ctt cgg ttc aga act gtc aac agt agc cgc tgg acg gaa gtc aat ttt | 576 |
| Leu Arg Phe Arg Thr Val Asn Ser Ser Arg Trp Thr Glu Val Asn Phe |     |
| 180 185 190                                                     |     |
| gaa aac tgt aaa cag gtc tgc aac ctc aca gga ctt cag gct ttc aca | 624 |
| Glu Asn Cys Lys Gln Val Cys Asn Leu Thr Gly Leu Gln Ala Phe Thr |     |
| 195 200 205                                                     |     |
| gaa tat gtc ctg gct cta cga ttc agg ttc aat gac tca aga tat tgg | 672 |
| Glu Tyr Val Leu Ala Leu Arg Phe Arg Phe Asn Asp Ser Arg Tyr Trp |     |
| 210 215 220                                                     |     |
| agc aag tgg agc aaa gaa gaa acc aga gtg act atg gag gaa gtt cca | 720 |
| Ser Lys Trp Ser Lys Glu Glu Thr Arg Val Thr Met Glu Glu Val Pro |     |
| 225 230 235 240                                                 |     |
| cat gtc ctg gac ctg tgg aga att ctg gaa cca gca gac atg aac gga | 768 |
| His Val Leu Asp Leu Trp Arg Ile Leu Glu Pro Ala Asp Met Asn Gly |     |
| 245 250 255                                                     |     |
| gac agg aag gtg cga ttg ctg tgg aag aag gca aga gga gcc ccc gtc | 816 |
| Asp Arg Lys Val Arg Leu Leu Trp Lys Lys Ala Arg Gly Ala Pro Val |     |
| 260 265 270                                                     |     |
| ttg gag aaa aca ttt ggc tac cac ata cag tac ttt gca gag aac agc | 864 |
| Leu Glu Lys Thr Phe Gly Tyr His Ile Gln Tyr Phe Ala Glu Asn Ser |     |

| 275                                                                                                                                                   | 280 | 285 |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|------|
| act aac ctc aca gag ata aac aac atc acc acc cag cag tat gaa ctg<br>Thr Asn Leu Thr Glu Ile Asn Asn Ile Thr Thr Gln Gln Tyr Glu Leu<br>290 295 300     |     |     | 912  |
| ctt ctg atg agc cag gca cac tct gtg tcc gtg act tct ttt aat tct<br>Leu Leu Met Ser Gln Ala His Ser Val Ser Val Thr Ser Phe Asn Ser<br>305 310 315 320 |     |     | 960  |
| ctt ggc aag tcc caa gag acc atc ctg agg atc cca gat gtc cat gag<br>Leu Gly Lys Ser Gln Glu Thr Ile Leu Arg Ile Pro Asp Val His Glu<br>325 330 335     |     |     | 1008 |
| aag acc ttc cag tac att aag agc atg cag gcc tac ata gcc gag ccc<br>Lys Thr Phe Gln Tyr Ile Lys Ser Met Gln Ala Tyr Ile Ala Glu Pro<br>340 345 350     |     |     | 1056 |
| ctg ttg gtg gtg aac tgg caa agc tcc att cct gcg gtg gac act tgg<br>Leu Leu Val Val Asn Trp Gln Ser Ser Ile Pro Ala Val Asp Thr Trp<br>355 360 365     |     |     | 1104 |
| ata gtg gag tgg ctc cca gaa gct gcc atg tgc aag ttc cct gcc ctt<br>Ile Val Glu Trp Leu Pro Glu Ala Ala Met Ser Lys Phe Pro Ala Leu<br>370 375 380     |     |     | 1152 |
| tcc tgg gaa tct gtg tct cag gtc acg aac tgg acc atc gag caa gat<br>Ser Trp Glu Ser Val Ser Gln Val Thr Asn Trp Thr Ile Glu Gln Asp<br>385 390 395 400 |     |     | 1200 |
| aaa cta aaa cct ttc aca tgc tat aat ata tca gtg tat cca gtg ttg<br>Lys Leu Lys Pro Phe Thr Cys Tyr Asn Ile Ser Val Tyr Pro Val Leu<br>405 410 415     |     |     | 1248 |
| gga cac cga gtt gga gag ccg tat tca atc caa gct tat gcc aaa gaa<br>Gly His Arg Val Gly Glu Pro Tyr Ser Ile Gln Ala Tyr Ala Lys Glu<br>420 425 430     |     |     | 1296 |
| gga act cca tta aaa ggt cct gag acc agg gtg gag aac atc ggt ctg<br>Gly Thr Pro Leu Lys Gly Pro Glu Thr Arg Val Glu Asn Ile Gly Leu<br>435 440 445     |     |     | 1344 |
| agg aca gcc acg atc aca tgg aag gag att cct aag agt gct agg aat<br>Arg Thr Ala Thr Ile Thr Trp Lys Glu Ile Pro Lys Ser Ala Arg Asn<br>450 455 460     |     |     | 1392 |
| gga ttt atc aac aat tac act gta ttt tac caa gct gaa ggt gga aaa<br>Gly Phe Ile Asn Asn Tyr Thr Val Phe Tyr Gln Ala Glu Gly Gly Lys<br>465 470 475 480 |     |     | 1440 |
| gaa ctc tcc aag act gtt aac tct cat gcc ctg cag tgt gac ctg gag<br>Glu Leu Ser Lys Thr Val Asn Ser His Ala Leu Gln Cys Asp Leu Glu<br>485 490 495     |     |     | 1488 |
| tct ctg aca cga agg acc tct tat act gtt tgg gtc atg gcc agc acc<br>Ser Leu Thr Arg Arg Thr Ser Tyr Thr Val Trp Val Met Ala Ser Thr<br>500 505 510     |     |     | 1536 |
| aga gct gga ggt acc aac ggg gtg aga ata aac ttc aag aca ttg tca<br>Arg Ala Gly Gly Thr Asn Gly Val Arg Ile Asn Phe Lys Thr Leu Ser<br>515 520 525     |     |     | 1584 |
| atc agt gtg ttt gaa att gtc ctt cta aca tct cta gtt gga gga ggc<br>Ile Ser Val Phe Glu Ile Val Leu Leu Thr Ser Leu Val Gly Gly Gly<br>530 535 540     |     |     | 1632 |

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ctt ctt cta ctt agc atc aaa aca gtg act ttt ggc ctc aga aag cca 1680
Leu Leu Leu Leu Ser Ile Lys Thr Val Thr Phe Gly Leu Arg Lys Pro
545 550 555 560

aac cgg ttg act ccc ctg tgt tgt cct gat gtt ccc aac cct gct gaa 1728
Asn Arg Leu Thr Pro Leu Cys Cys Pro Asp Val Pro Asn Pro Ala Glu
565 570 575

agt agt tta gcc aca tgg ctc gga gat ggt ttc aag aag tca aat atg 1776
Ser Ser Leu Ala Thr Trp Leu Gly Asp Gly Phe Lys Lys Ser Asn Met
580 585 590

aag gag act gga aac tct ggg aac aca gaa gac gtg gtc cta aaa cca 1824
Lys Glu Thr Gly Asn Ser Gly Asn Thr Glu Asp Val Val Leu Lys Pro
595 600 605

tgt ccc gtc ccc gcg gat ctc att gac aag ctg gta gtg aac ttt gag 1872
Cys Pro Val Pro Ala Asp Leu Ile Asp Lys Leu Val Val Asn Phe Glu
610 615 620

aat ttt ctg gaa gta gtt ttg aca gag gaa gct gga aag ggt cag gcg 1920
Asn Phe Leu Glu Val Val Leu Thr Glu Glu Ala Gly Lys Gly Gln Ala
625 630 635 640

agc att ttg gga gga gaa gcg aat gag tat atc tta tcc cag gaa cca 1968
Ser Ile Leu Gly Gly Glu Ala Asn Glu Tyr Ile Leu Ser Gln Glu Pro
645 650 655

agc tgt cct ggc cat tgc tga 1989
Ser Cys Pro Gly His Cys *
660

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&lt;210&gt; 14

&lt;211&gt; 662

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 14

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

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|                                                                 |     |     |
|-----------------------------------------------------------------|-----|-----|
| 210                                                             | 215 | 220 |
| Ser Lys Trp Ser Lys Glu Glu Thr Arg Val Thr Met Glu Glu Val Pro |     |     |
| 225                                                             | 230 | 235 |
| His Val Leu Asp Leu Trp Arg Ile Leu Glu Pro Ala Asp Met Asn Gly |     | 240 |
|                                                                 | 245 | 250 |
| Asp Arg Lys Val Arg Leu Leu Trp Lys Lys Ala Arg Gly Ala Pro Val |     | 255 |
|                                                                 | 260 | 265 |
| Leu Glu Lys Thr Phe Gly Tyr His Ile Gln Tyr Phe Ala Glu Asn Ser |     | 270 |
|                                                                 | 275 | 280 |
| Thr Asn Leu Thr Glu Ile Asn Asn Ile Thr Thr Gln Gln Tyr Glu Leu |     | 285 |
|                                                                 | 290 | 295 |
| Leu Leu Met Ser Gln Ala His Ser Val Ser Val Thr Ser Phe Asn Ser |     | 300 |
| 305                                                             | 310 | 315 |
| Leu Gly Lys Ser Gln Glu Thr Ile Leu Arg Ile Pro Asp Val His Glu |     | 320 |
|                                                                 | 325 | 330 |
| Lys Thr Phe Gln Tyr Ile Lys Ser Met Gln Ala Tyr Ile Ala Glu Pro |     | 335 |
|                                                                 | 340 | 345 |
| Leu Leu Val Val Asn Trp Gln Ser Ser Ile Pro Ala Val Asp Thr Trp |     | 350 |
|                                                                 | 355 | 360 |
| Ile Val Glu Trp Leu Pro Glu Ala Ala Met Ser Lys Phe Pro Ala Leu |     | 365 |
| 370                                                             | 375 | 380 |
| Ser Trp Glu Ser Val Ser Gln Val Thr Asn Trp Thr Ile Glu Gln Asp |     | 385 |
| 385                                                             | 390 | 395 |
| Lys Leu Lys Pro Phe Thr Cys Tyr Asn Ile Ser Val Tyr Pro Val Leu |     | 400 |
|                                                                 | 405 | 410 |
| Gly His Arg Val Gly Glu Pro Tyr Ser Ile Gln Ala Tyr Ala Lys Glu |     | 415 |
|                                                                 | 420 | 425 |
| Gly Thr Pro Leu Lys Gly Pro Glu Thr Arg Val Glu Asn Ile Gly Leu |     | 430 |
|                                                                 | 435 | 440 |
| Arg Thr Ala Thr Ile Thr Trp Lys Glu Ile Pro Lys Ser Ala Arg Asn |     | 445 |
|                                                                 | 450 | 455 |
| Gly Phe Ile Asn Asn Tyr Thr Val Phe Tyr Gln Ala Glu Gly Gly Lys |     | 460 |
| 465                                                             | 470 | 475 |
| Glu Leu Ser Lys Thr Val Asn Ser His Ala Leu Gln Cys Asp Leu Glu |     | 480 |
|                                                                 | 485 | 490 |
| Ser Leu Thr Arg Arg Thr Ser Tyr Thr Val Trp Val Met Ala Ser Thr |     | 495 |
|                                                                 | 500 | 505 |
| Arg Ala Gly Gly Thr Asn Gly Val Arg Ile Asn Phe Lys Thr Leu Ser |     | 510 |
|                                                                 | 515 | 520 |
| Ile Ser Val Phe Glu Ile Val Leu Leu Thr Ser Leu Val Gly Gly Gly |     | 525 |
|                                                                 | 530 | 535 |
| Leu Leu Leu Leu Ser Ile Lys Thr Val Thr Phe Gly Leu Arg Lys Pro |     | 540 |
| 545                                                             | 550 | 555 |
| Asn Arg Leu Thr Pro Leu Cys Cys Pro Asp Val Pro Asn Pro Ala Glu |     | 560 |
|                                                                 | 565 | 570 |
| Ser Ser Leu Ala Thr Trp Leu Gly Asp Gly Phe Lys Lys Ser Asn Met |     | 575 |
|                                                                 | 580 | 585 |
| Lys Glu Thr Gly Asn Ser Gly Asn Thr Glu Asp Val Val Leu Lys Pro |     | 590 |
|                                                                 | 595 | 600 |
| Cys Pro Val Pro Ala Asp Leu Ile Asp Lys Leu Val Val Asn Phe Glu |     | 605 |
|                                                                 | 610 | 615 |
| Asn Phe Leu Glu Val Val Leu Thr Glu Glu Ala Gly Lys Gly Gln Ala |     | 620 |
| 625                                                             | 630 | 635 |
| Ser Ile Leu Gly Gly Glu Ala Asn Glu Tyr Ile Leu Ser Gln Glu Pro |     | 640 |
|                                                                 | 645 | 650 |
| Ser Cys Pro Gly His Cys                                         |     | 655 |
|                                                                 | 660 |     |

<210> 15  
 <211> 2940  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS

&lt;222&gt; (1)...(2940)

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2940)

&lt;223&gt; human OSMRbeta receptor

&lt;400&gt; 15

|                                                                 |     |
|-----------------------------------------------------------------|-----|
| atg gct cta ttt gca gtc ttt cag aca aca ttc ttc tta aca ttg ctg | 48  |
| Met Ala Leu Phe Ala Val Phe Gln Thr Thr Phe Phe Leu Thr Leu Leu |     |
| 1 5 10 15                                                       |     |
| tcc ttg agg act tac cag agt gaa gtc ttg gct gaa cgt tta cca ttg | 96  |
| Ser Leu Arg Thr Tyr Gln Ser Glu Val Leu Ala Glu Arg Leu Pro Leu |     |
| 20 25 30                                                        |     |
| act cct gta tca ctt aaa gtt tcc acc aat tct acg cgt cag agt ttg | 144 |
| Thr Pro Val Ser Leu Lys Val Thr Asn Ser Thr Arg Gln Ser Leu     |     |
| 35 40 45                                                        |     |
| cac tta caa tgg act gtc cac aac ctt cct tat cat cag gaa ttg aaa | 192 |
| His Leu Gln Trp Thr Val His Asn Leu Pro Tyr His Gln Glu Leu Lys |     |
| 50 55 60                                                        |     |
| atg gta ttt cag atc cag atc agt agg att gaa aca tcc aat gtc atc | 240 |
| Met Val Phe Gln Ile Gln Ile Ser Arg Ile Glu Thr Ser Asn Val Ile |     |
| 65 70 75 80                                                     |     |
| tgg gtg ggg aat tac agc acc act gtg aag tgg aac cag gtt ctg cat | 288 |
| Trp Val Gly Asn Tyr Ser Thr Thr Val Lys Trp Asn Gln Val Leu His |     |
| 85 90 95                                                        |     |
| tgg agc tgg gaa tct gag ctc cct ttg gaa tgt gcc aca cac ttt gta | 336 |
| Trp Ser Trp Glu Ser Glu Leu Pro Leu Glu Cys Ala Thr His Phe Val |     |
| 100 105 110                                                     |     |
| aga ata aag agt ttg gtg gac gat gcc aag ttc cct gag cca aat ttc | 384 |
| Arg Ile Lys Ser Leu Val Asp Asp Ala Lys Phe Pro Glu Pro Asn Phe |     |
| 115 120 125                                                     |     |
| tgg agc aac tgg agt tcc tgg gag gaa gtc agt gta caa gat tct act | 432 |
| Trp Ser Asn Trp Ser Ser Trp Glu Glu Val Ser Val Gln Asp Ser Thr |     |
| 130 135 140                                                     |     |
| gga cag gat ata ttg ttc gtt ttc cct aaa gat aag ctg gtg gaa gaa | 480 |
| Gly Gln Asp Ile Leu Phe Val Phe Pro Lys Asp Lys Leu Val Glu Glu |     |
| 145 150 155 160                                                 |     |
| ggc acc aat gtt acc att tgt tac gtt tct agg aac att caa aat aat | 528 |
| Gly Thr Asn Val Thr Ile Cys Tyr Val Ser Arg Asn Ile Gln Asn Asn |     |
| 165 170 175                                                     |     |
| gta tcc tgt tat ttg gaa ggg aaa cag att cat gga gaa caa ctt gat | 576 |
| Val Ser Cys Tyr Leu Glu Gly Lys Gln Ile His Gly Glu Gln Leu Asp |     |
| 180 185 190                                                     |     |
| cca cat gta act gca ttc aac ttg aat agt gtg cct ttc att agg aat | 624 |
| Pro His Val Thr Ala Phe Asn Leu Asn Ser Val Pro Phe Ile Arg Asn |     |
| 195 200 205                                                     |     |
| aaa ggg aca aat atc tat tgt gag gca agt caa gga aat gtc agt gaa | 672 |
| Lys Gly Thr Asn Ile Tyr Cys Glu Ala Ser Gln Gly Asn Val Ser Glu |     |
| 210 215 220                                                     |     |
| ggc atg aaa ggc atc gtt ctt ttt gtc tca aaa gta ctt gag gag ccc | 720 |
| Gly Met Lys Gly Ile Val Leu Phe Val Ser Lys Val Leu Glu Glu Pro |     |
| 225 230 235 240                                                 |     |

|                                                                 |      |
|-----------------------------------------------------------------|------|
| aag gac ttt tct tgt gaa acc gag gac ttc aag act ttg cac tgt act | 768  |
| Lys Asp Phe Ser Cys Glu Thr Glu Asp Phe Lys Thr Leu His Cys Thr |      |
| 245 250 255                                                     |      |
| tgg gat cct ggg acg gac act gcc ttg ggg tgg tct aaa caa cct tcc | 816  |
| Trp Asp Pro Gly Thr Asp Thr Ala Leu Gly Trp Ser Lys Gln Pro Ser |      |
| 260 265 270                                                     |      |
| caa agc tac act tta ttt gaa tca ttt tct ggg gaa aag aaa ctt tgt | 864  |
| Gln Ser Tyr Thr Leu Phe Glu Ser Phe Ser Gly Glu Lys Lys Leu Cys |      |
| 275 280 285                                                     |      |
| aca cac aaa aac tgg tgt aat tgg caa ata act caa gac tca caa gaa | 912  |
| Thr His Lys Asn Trp Cys Asn Trp Gln Ile Thr Gln Asp Ser Gln Glu |      |
| 290 295 300                                                     |      |
| acc tat aac ttc aca ctc ata gct gaa aat tac tta agg aag aga agt | 960  |
| Thr Tyr Asn Phe Thr Leu Ile Ala Glu Asn Tyr Leu Arg Lys Arg Ser |      |
| 305 310 315 320                                                 |      |
| gtc aat atc ctt ttt aac ctg act cat cga gtt tat tta atg aat cct | 1008 |
| Val Asn Ile Leu Phe Asn Leu Thr His Arg Val Tyr Leu Met Asn Pro |      |
| 325 330 335                                                     |      |
| ttt agt gtc aac ttt gaa aat gta aat gcc aca aat gcc atc atg acc | 1056 |
| Phe Ser Val Asn Phe Glu Asn Val Asn Ala Thr Asn Ala Ile Met Thr |      |
| 340 345 350                                                     |      |
| tgg aag gtg cac tcc ata agg aat aat ttc aca tat ttg tgt cag att | 1104 |
| Trp Lys Val His Ser Ile Arg Asn Asn Phe Thr Tyr Leu Cys Gln Ile |      |
| 355 360 365                                                     |      |
| gaa ctc cat ggt gaa gga aaa atg atg caa tac aat gtt tcc atc aag | 1152 |
| Glu Leu His Gly Glu Gly Lys Met Met Gln Tyr Asn Val Ser Ile Lys |      |
| 370 375 380                                                     |      |
| gtg aac ggt gag tac ttc tta agt gaa ctg gaa cct gcc aca gag tac | 1200 |
| Val Asn Gly Glu Tyr Phe Leu Ser Glu Leu Glu Pro Ala Thr Glu Tyr |      |
| 385 390 395 400                                                 |      |
| atg gcg cga gta cgg tgt gct gat gcc agc cac ttc tgg aaa tgg agt | 1248 |
| Met Ala Arg Val Arg Cys Ala Asp Ala Ser His Phe Trp Lys Trp Ser |      |
| 405 410 415                                                     |      |
| gaa tgg agt ggt cag aac ttc acc aca ctt gaa gct gct ccc tca gag | 1296 |
| Glu Trp Ser Gly Gln Asn Phe Thr Thr Leu Glu Ala Ala Pro Ser Glu |      |
| 420 425 430                                                     |      |
| gcc cct gat gtc tgg aga att gtg agc ttg gag cca gga aat cat act | 1344 |
| Ala Pro Asp Val Trp Arg Ile Val Ser Leu Glu Pro Gly Asn His Thr |      |
| 435 440 445                                                     |      |
| gtg acc tta ttc tgg aag cca tta tca aaa ctg cat gcc aat gga aag | 1392 |
| Val Thr Leu Phe Trp Lys Pro Leu Ser Lys Leu His Ala Asn Gly Lys |      |
| 450 455 460                                                     |      |
| atc ctg ttc tat aat gta gtt gta gaa aac cta gac aaa cca tcc agt | 1440 |
| Ile Leu Phe Tyr Asn Val Val Val Glu Asn Leu Asp Lys Pro Ser Ser |      |
| 465 470 475 480                                                 |      |
| tca gag ctc cat tcc att cca gca cca gcc aac agc aca aaa cta atc | 1488 |
| Ser Glu Leu His Ser Ile Pro Ala Pro Ala Asn Ser Thr Lys Leu Ile |      |
| 485 490 495                                                     |      |
| ctt gac agg tgt tcc tac caa atc tgc gtc ata gcc aac aac agt gtg | 1536 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Leu | Asp | Arg | Cys | Ser | Tyr | Gln | Ile | Cys | Val | Ile | Ala | Asn | Asn | Ser | Val |      |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |      |
| ggt | gct | tct | cct | gct | tct | gta | ata | gtc | atc | tct | gca | gac | ccc | gaa | aac | 1584 |
| Gly | Ala | Ser | Pro | Ala | Ser | Val | Ile | Val | Ile | Ser | Ala | Asp | Pro | Glu | Asn |      |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |      |
| aaa | gag | gtt | gag | gaa | gaa | aga | att | gca | ggc | aca | gag | ggt | gga | ttc | tct | 1632 |
| Lys | Glu | Val | Glu | Glu | Glu | Arg | Ile | Ala | Gly | Thr | Glu | Gly | Gly | Phe | Ser |      |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |      |
| ctg | tct | tgg | aaa | ccc | caa | cct | gga | gat | gtt | ata | ggc | tat | gtt | gtg | gac | 1680 |
| Leu | Ser | Trp | Lys | Pro | Gln | Pro | Gly | Asp | Val | Ile | Gly | Tyr | Val | Val | Asp |      |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |      |
| tgg | tgt | gac | cat | acc | cag | gat | gtg | ctc | ggt | gat | ttc | cag | tgg | aag | aat | 1728 |
| Trp | Cys | Asp | His | Thr | Gln | Asp | Val | Leu | Gly | Asp | Phe | Gln | Trp | Lys | Asn |      |
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |      |
| gta | ggt | ccc | aat | acc | aca | agc | aca | gtc | att | agc | aca | gat | gct | ttt | agg | 1776 |
| Val | Gly | Pro | Asn | Thr | Thr | Ser | Thr | Val | Ile | Ser | Thr | Asp | Ala | Phe | Arg |      |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |      |
| cca | gga | gtt | cga | tat | gac | ttc | aga | att | tat | ggg | tta | tct | aca | aaa | agg | 1824 |
| Pro | Gly | Val | Arg | Tyr | Asp | Phe | Arg | Ile | Tyr | Gly | Leu | Ser | Thr | Lys | Arg |      |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |      |
| att | gct | tgt | tta | tta | gag | aaa | aaa | aca | gga | tac | tct | cag | gaa | ctt | gct | 1872 |
| Ile | Ala | Cys | Leu | Leu | Glu | Lys | Lys | Thr | Gly | Tyr | Ser | Gln | Glu | Leu | Ala |      |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |      |
| cct | tca | gac | aac | cct | cac | gtg | ctg | gtg | gat | aca | ttg | aca | tcc | cac | tcc | 1920 |
| Pro | Ser | Asp | Asn | Pro | His | Val | Leu | Val | Asp | Thr | Leu | Thr | Ser | His | Ser |      |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |      |
| ttc | act | ctg | agt | tgg | aaa | gat | tac | tct | act | gaa | tct | caa | cct | ggt | ttt | 1968 |
| Phe | Thr | Leu | Ser | Trp | Lys | Asp | Tyr | Ser | Thr | Glu | Ser | Gln | Pro | Gly | Phe |      |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |      |
| ata | caa | ggg | tac | cat | gtc | tat | ctg | aaa | tcc | aag | gcg | agg | cag | tgc | cac | 2016 |
| Ile | Gln | Gly | Tyr | His | Val | Tyr | Leu | Lys | Ser | Lys | Ala | Arg | Gln | Cys | His |      |
|     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |      |
| cca | cga | ttt | gaa | aag | gca | gtt | ctt | tca | gat | ggt | tca | gaa | tgt | tgc | aaa | 2064 |
| Pro | Arg | Phe | Glu | Lys | Ala | Val | Leu | Ser | Asp | Gly | Ser | Glu | Cys | Cys | Lys |      |
|     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |      |
| tac | aaa | att | gac | aac | ccg | gaa | gaa | aag | gca | ttg | att | gtg | gac | aac | cta | 2112 |
| Tyr | Lys | Ile | Asp | Asn | Pro | Glu | Glu | Lys | Ala | Leu | Ile | Val | Asp | Asn | Leu |      |
|     | 690 |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |      |
| aag | cca | gaa | tcc | ttc | tat | gag | ttt | ttc | atc | act | cca | ttc | act | agt | gct | 2160 |
| Lys | Pro | Glu | Ser | Phe | Tyr | Glu | Phe | Phe | Ile | Thr | Pro | Phe | Thr | Ser | Ala |      |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     |     | 720 |      |
| ggt | gaa | ggc | ccc | agt | gct | acg | ttc | acg | aag | gtc | acg | act | ccg | gat | gaa | 2208 |
| Gly | Glu | Gly | Pro | Ser | Ala | Thr | Phe | Thr | Lys | Val | Thr | Thr | Pro | Asp | Glu |      |
|     |     |     |     | 725 |     |     |     |     | 730 |     |     |     |     | 735 |     |      |
| cac | tcc | tcg | atg | ctg | att | cat | atc | cta | ctg | ccc | atg | gtt | ttc | tgc | gtc | 2256 |
| His | Ser | Ser | Met | Leu | Ile | His | Ile | Leu | Leu | Pro | Met | Val | Phe | Cys | Val |      |
|     |     |     | 740 |     |     |     |     | 745 |     |     |     |     | 750 |     |     |      |
| ttg | ctc | atc | atg | gtc | atg | tgc | tac | ttg | aaa | agt | cag | tgg | atc | aag | gag | 2304 |
| Leu | Leu | Ile | Met | Val | Met | Cys | Tyr | Leu | Lys | Ser | Gln | Trp | Ile | Lys | Glu |      |
|     |     | 755 |     |     |     |     | 760 |     |     |     |     | 765 |     |     |     |      |

acc tgt tat cct gac atc cct gac cct tac aag agc agc atc ctg tca 2352  
 Thr Cys Tyr Pro Asp Ile Pro Asp Pro Tyr Lys Ser Ser Ile Leu Ser  
 770 775 780

tta ata aaa ttc aag gag aac cct cac cta ata ata atg aat gtc agt 2400  
 Leu Ile Lys Phe Lys Glu Asn Pro His Leu Ile Ile Met Asn Val Ser  
 785 790 795 800

gac tgt atc cca gat gct att gaa gtt gta agc aag cca gaa ggg aca 2448  
 Asp Cys Ile Pro Asp Ala Ile Glu Val Val Ser Lys Pro Glu Gly Thr  
 805 810 815

aag ata cag ttc cta ggc act agg aag tca ctc aca gaa acc gag ttg 2496  
 Lys Ile Gln Phe Leu Gly Thr Arg Lys Ser Leu Thr Glu Thr Glu Leu  
 820 825 830

act aag cct aac tac ctt tat ctc ctt cca aca gaa aag aat cac tct 2544  
 Thr Lys Pro Asn Tyr Leu Tyr Leu Leu Pro Thr Glu Lys Asn His Ser  
 835 840 845

ggc cct 'ggc ccc tgc atc tgt ttt gag aac ttg acc tat aac cag gca 2592  
 Gly Pro Gly Pro Cys Ile Cys Phe Glu Asn Leu Thr Tyr Asn Gln Ala  
 850 855 860

gct tct gac tct ggc tct tgt ggc cat gtt cca gta tcc cca aaa gcc 2640  
 Ala Ser Asp Ser Gly Ser Cys Gly His Val Pro Val Ser Pro Lys Ala  
 865 870 875 880

cca agt atg ctg gga cta atg acc tca cct gaa aat gta cta aag gca 2688  
 Pro Ser Met Leu Gly Leu Met Thr Ser Pro Glu Asn Val Leu Lys Ala  
 885 890 895

cta gaa aaa aac tac atg aac tcc ctg gga gaa atc cca gct gga gaa 2736  
 Leu Glu Lys Asn Tyr Met Asn Ser Leu Gly Glu Ile Pro Ala Gly Glu  
 900 905 910

aca agt ttg aat tat gtg tcc cag ttg gct tca ccc atg ttt gga gac 2784  
 Thr Ser Leu Asn Tyr Val Ser Gln Leu Ala Ser Pro Met Phe Gly Asp  
 915 920 925

aag gac agt ctc cca aca aac cca gta gag gca cca cac tgt tca gag 2832  
 Lys Asp Ser Leu Pro Thr Asn Pro Val Glu Ala Pro His Cys Ser Glu  
 930 935 940

tat aaa atg caa atg gca gtc tcc ctg cgt ctt gcc ttg cct ccc ccg 2880  
 Tyr Lys Met Gln Met Ala Val Ser Leu Arg Leu Ala Leu Pro Pro Pro  
 945 950 955 960

acc gag aat agc agc ctc tcc tca att acc ctt tta gat cca ggt gaa 2928  
 Thr Glu Asn Ser Ser Leu Ser Ser Ile Thr Leu Leu Asp Pro Gly Glu  
 965 970 975

cac tac tgc taa 2940  
 His Tyr Cys \*

&lt;210&gt; 16

&lt;211&gt; 979

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

Met Ala Leu Phe Ala Val Phe Gln Thr Thr Phe Phe Leu Thr Leu Leu

1

5

10

15

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | Arg | Thr | Tyr | Gln | Ser | Glu | Val | Leu | Ala | Glu | Arg | Leu | Pro | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Thr | Pro | Val | Ser | Leu | Lys | Val | Ser | Thr | Asn | Ser | Thr | Arg | Gln | Ser | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| His | Leu | Gln | Trp | Thr | Val | His | Asn | Leu | Pro | Tyr | His | Gln | Glu | Leu | Lys |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Met | Val | Phe | Gln | Ile | Gln | Ile | Ser | Arg | Ile | Glu | Thr | Ser | Asn | Val | Ile |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |
| Trp | Val | Gly | Asn | Tyr | Ser | Thr | Thr | Val | Lys | Trp | Asn | Gln | Val | Leu | His |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Trp | Ser | Trp | Glu | Ser | Glu | Leu | Pro | Leu | Glu | Cys | Ala | Thr | His | Phe | Val |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Arg | Ile | Lys | Ser | Leu | Val | Asp | Asp | Ala | Lys | Phe | Pro | Glu | Pro | Asn | Phe |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Trp | Ser | Asn | Trp | Ser | Ser | Trp | Glu | Glu | Val | Ser | Val | Gln | Asp | Ser | Thr |
|     |     | 130 |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Gly | Gln | Asp | Ile | Leu | Phe | Val | Phe | Pro | Lys | Asp | Lys | Leu | Val | Glu | Glu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Gly | Thr | Asn | Val | Thr | Ile | Cys | Tyr | Val | Ser | Arg | Asn | Ile | Gln | Asn | Asn |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Val | Ser | Cys | Tyr | Leu | Glu | Gly | Lys | Gln | Ile | His | Gly | Glu | Gln | Leu | Asp |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Pro | His | Val | Thr | Ala | Phe | Asn | Leu | Asn | Ser | Val | Pro | Phe | Ile | Arg | Asn |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Lys | Gly | Thr | Asn | Ile | Tyr | Cys | Glu | Ala | Ser | Gln | Gly | Asn | Val | Ser | Glu |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Gly | Met | Lys | Gly | Ile | Val | Leu | Phe | Val | Ser | Lys | Val | Leu | Glu | Glu | Pro |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Lys | Asp | Phe | Ser | Cys | Glu | Thr | Glu | Asp | Phe | Lys | Thr | Leu | His | Cys | Thr |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Trp | Asp | Pro | Gly | Thr | Asp | Thr | Ala | Leu | Gly | Trp | Ser | Lys | Gln | Pro | Ser |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     |     | 270 |     |
| Gln | Ser | Tyr | Thr | Leu | Phe | Glu | Ser | Phe | Ser | Gly | Glu | Lys | Lys | Leu | Cys |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Thr | His | Lys | Asn | Trp | Cys | Asn | Trp | Gln | Ile | Thr | Gln | Asp | Ser | Gln | Glu |
|     |     | 290 |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Thr | Tyr | Asn | Phe | Thr | Leu | Ile | Ala | Glu | Asn | Tyr | Leu | Arg | Lys | Arg | Ser |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Val | Asn | Ile | Leu | Phe | Asn | Leu | Thr | His | Arg | Val | Tyr | Leu | Met | Asn | Pro |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Phe | Ser | Val | Asn | Phe | Glu | Asn | Val | Asn | Ala | Thr | Asn | Ala | Ile | Met | Thr |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Trp | Lys | Val | His | Ser | Ile | Arg | Asn | Asn | Phe | Thr | Tyr | Leu | Cys | Gln | Ile |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Glu | Leu | His | Gly | Glu | Gly | Lys | Met | Met | Gln | Tyr | Asn | Val | Ser | Ile | Lys |
|     |     | 370 |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Val | Asn | Gly | Glu | Tyr | Phe | Leu | Ser | Glu | Leu | Glu | Pro | Ala | Thr | Glu | Tyr |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Met | Ala | Arg | Val | Arg | Cys | Ala | Asp | Ala | Ser | His | Phe | Trp | Lys | Trp | Ser |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Glu | Trp | Ser | Gly | Gln | Asn | Phe | Thr | Thr | Leu | Glu | Ala | Ala | Pro | Ser | Glu |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Ala | Pro | Asp | Val | Trp | Arg | Ile | Val | Ser | Leu | Glu | Pro | Gly | Asn | His | Thr |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Val | Thr | Leu | Phe | Trp | Lys | Pro | Leu | Ser | Lys | Leu | His | Ala | Asn | Gly | Lys |
|     |     | 450 |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ile | Leu | Phe | Tyr | Asn | Val | Val | Val | Glu | Asn | Leu | Asp | Lys | Pro | Ser | Ser |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Ser | Glu | Leu | His | Ser | Ile | Pro | Ala | Pro | Ala | Asn | Ser | Thr | Lys | Leu | Ile |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Leu | Asp | Arg | Cys | Ser | Tyr | Gln | Ile | Cys | Val | Ile | Ala | Asn | Asn | Ser | Val |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Gly | Ala | Ser | Pro | Ala | Ser | Val | Ile | Val | Ile | Ser | Ala | Asp | Pro | Glu | Asn |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Lys | Glu | Val | Glu | Glu | Glu | Arg | Ile | Ala | Gly | Thr | Glu | Gly | Gly | Phe | Ser |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |

Leu Ser Trp Lys Pro Gln Pro Gly Asp Val Ile Gly Tyr Val Val Asp  
 545 550 555 560  
 Trp Cys Asp His Thr Gln Asp Val Leu Gly Asp Phe Gln Trp Lys Asn  
 565 570 575  
 Val Gly Pro Asn Thr Thr Ser Thr Val Ile Ser Thr Asp Ala Phe Arg  
 580 585 590  
 Pro Gly Val Arg Tyr Asp Phe Arg Ile Tyr Gly Leu Ser Thr Lys Arg  
 595 600 605  
 Ile Ala Cys Leu Leu Glu Lys Lys Thr Gly Tyr Ser Gln Glu Leu Ala  
 610 615 620  
 Pro Ser Asp Asn Pro His Val Leu Val Asp Thr Leu Thr Ser His Ser  
 625 630 635 640  
 Phe Thr Leu Ser Trp Lys Asp Tyr Ser Thr Glu Ser Gln Pro Gly Phe  
 645 650 655  
 Ile Gln Gly Tyr His Val Tyr Leu Lys Ser Lys Ala Arg Gln Cys His  
 660 665 670  
 Pro Arg Phe Glu Lys Ala Val Leu Ser Asp Gly Ser Glu Cys Cys Lys  
 675 680 685  
 Tyr Lys Ile Asp Asn Pro Glu Glu Lys Ala Leu Ile Val Asp Asn Leu  
 690 695 700  
 Lys Pro Glu Ser Phe Tyr Glu Phe Phe Ile Thr Pro Phe Thr Ser Ala  
 705 710 715 720  
 Gly Glu Gly Pro Ser Ala Thr Phe Thr Lys Val Thr Thr Pro Asp Glu  
 725 730 735  
 His Ser Ser Met Leu Ile His Ile Leu Leu Pro Met Val Phe Cys Val  
 740 745 750  
 Leu Leu Ile Met Val Met Cys Tyr Leu Lys Ser Gln Trp Ile Lys Glu  
 755 760 765  
 Thr Cys Tyr Pro Asp Ile Pro Asp Pro Tyr Lys Ser Ser Ile Leu Ser  
 770 775 780  
 Leu Ile Lys Phe Lys Glu Asn Pro His Leu Ile Ile Met Asn Val Ser  
 785 790 795 800  
 Asp Cys Ile Pro Asp Ala Ile Glu Val Val Ser Lys Pro Glu Gly Thr  
 805 810 815  
 Lys Ile Gln Phe Leu Gly Thr Arg Lys Ser Leu Thr Glu Thr Glu Leu  
 820 825 830  
 Thr Lys Pro Asn Tyr Leu Tyr Leu Leu Pro Thr Glu Lys Asn His Ser  
 835 840 845  
 Gly Pro Gly Pro Cys Ile Cys Phe Glu Asn Leu Thr Tyr Asn Gln Ala  
 850 855 860  
 Ala Ser Asp Ser Gly Ser Cys Gly His Val Pro Val Ser Pro Lys Ala  
 865 870 875 880  
 Pro Ser Met Leu Gly Leu Met Thr Ser Pro Glu Asn Val Leu Lys Ala  
 885 890 895  
 Leu Glu Lys Asn Tyr Met Asn Ser Leu Gly Glu Ile Pro Ala Gly Glu  
 900 905 910  
 Thr Ser Leu Asn Tyr Val Ser Gln Leu Ala Ser Pro Met Phe Gly Asp  
 915 920 925  
 Lys Asp Ser Leu Pro Thr Asn Pro Val Glu Ala Pro His Cys Ser Glu  
 930 935 940  
 Tyr Lys Met Gln Met Ala Val Ser Leu Arg Leu Ala Leu Pro Pro Pro  
 945 950 955 960  
 Thr Glu Asn Ser Ser Leu Ser Ser Ile Thr Leu Leu Asp Pro Gly Glu  
 965 970 975  
 His Tyr Cys

&lt;210&gt; 17

&lt;211&gt; 5

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; WSXWS peptide motif

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<223> Xaa = any amino acid

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Trp Ser Xaa Trp Ser  
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<211> 12  
<212> DNA  
<213> Artificial Sequence

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