(12) STANDARD PATENT (11) Application No. **AU 2005266892 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Use of IL-28 and IL-29 to treat cancer and autoimmune disorders

(51) International Patent Classification(s)
C07K 14/54 (2006.01) ***A61P 35/00*** (2006.01)
A61K 38/20 (2006.01)

(21) Application No: **2005266892** (22) Date of Filing: **2005.07.29**

(87) WIPO No: **WO06/012644**

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/629,702	**2004.11.19**	**US**
60/592,069	**2004.07.29**	**US**
60/676,047	**2005.04.29**	**US**

(43) Publication Date: **2006.02.02**
(44) Accepted Journal Date: **2011.03.03**

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(56) Related Art
US 2002/039763 A1
WO 2002/086087 A
WO 2005/023862
WO 2002/092762 A
WO 2003/0660020 A2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2006 (02.02.2006)

PCT

(10) International Publication Number
WO 2006/012644 A2

(51) International Patent Classification:
A61K 38/00 (2006.01)

(21) International Application Number:
PCT/US2005/026951

(22) International Filing Date: 29 July 2005 (29.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/592,069	29 July 2004 (29.07.2004)	US
60/629,702	19 November 2004 (19.11.2004)	US
60/676,047	29 April 2005 (29.04.2005)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

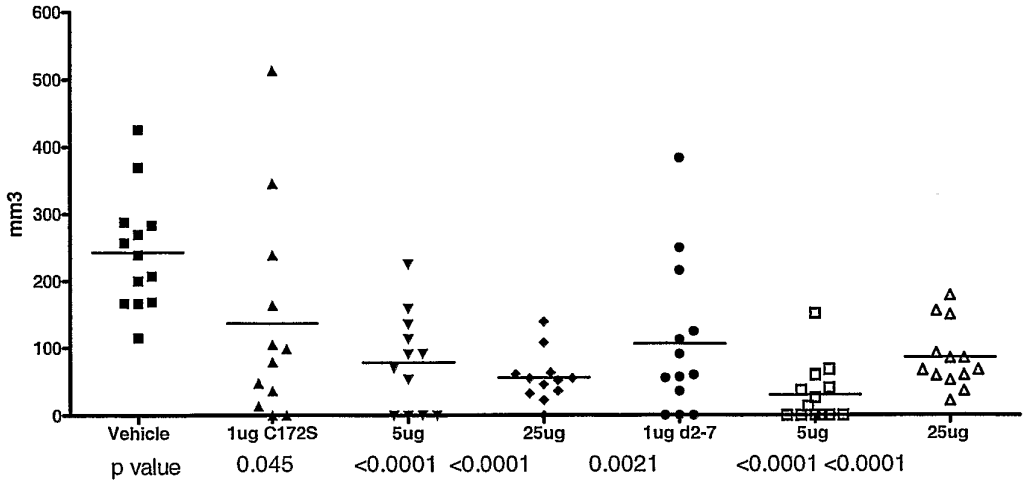
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian*

[Continued on next page]

(54) Title: USE OF IL-28 AND IL-29 TO TREAT CANCER AND AUTOIMMUNE DISORDERS



(57) Abstract: Methods for treating patients with cancer and autoimmune disorders using IL-28 and IL-29 molecules. The IL-28 and IL-29 molecules include polypeptides that have homology to the human IL-28 or IL-29 polypeptide sequence and proteins fused to a polypeptide with IL-28 and IL-29 functional activity. The molecules can be used as a monotherapy or in combination with other known cancer and/or autoimmune therapeutics.

WO 2006/012644 A2

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

- *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

USE OF IL-28 AND IL-29 TO TREAT CANCER AND AUTOIMMUNE DISORDERS

BACKGROUND OF THE INVENTION

Cytokines generally stimulate proliferation or differentiation of cells of the hematopoietic lineage or participate in the immune and inflammatory response mechanisms of the body. Examples of cytokines which affect hematopoiesis are erythropoietin (EPO), which stimulates the development of red blood cells; thrombopoietin (TPO), which stimulates development of cells of the megakaryocyte lineage; and granulocyte-colony stimulating factor (G-CSF), which stimulates development of neutrophils. These cytokines are useful in restoring normal blood cell levels in patients suffering from anemia, thrombocytopenia, and neutropenia or receiving chemotherapy for cancer.

The interleukins are a family of cytokines that mediate immunological responses. Central to an immune response is the T cell, which produce many cytokines and adaptive immunity to antigens. Cytokines produced by the T cell have been classified as type 1 and type 2 (Kelso, A. Immun. Cell Biol. 76:300-317, 1998). Type 1 cytokines include IL-2, IFN-γ, LT-α, and are involved in inflammatory responses, viral immunity, intracellular parasite immunity and allograft rejection. Type 2 cytokines include IL-4, IL-5, IL-6, IL-10 and IL-13, and are involved in humoral responses, helminth immunity and allergic response. Shared cytokines between Type 1 and 2 include IL-3, GM-CSF and TNF-α. There is some evidence to suggest that Type 1 and Type 2 producing T cell populations preferentially migrate into different types of inflamed tissue.

The immune system is the body's primary defense against diseases caused by pathogens, namely bacteria, viruses, fungi etc, as well as against diseases caused by abnormal growth of the body's own cells and tissues (*i.e.* cancerous tumors). Normally, the immune system is able to distinguish between the body's normal cells or "self" and foreign pathogens or abnormal cells or "non-self". The processes by which the immune system refrains from reacting to one's own body is called tolerance.

Sometimes, the immune system loses the ability to recognize "self" as normal and the subsequent response directed against the tissue or cells, results in loss of tolerance, a state of autoimmunity. The pathologies resulting from autoimmunity often have serious clinical consequences and are one of the major health problems in the world, especially in developed nations.

One example of such an autoimmune disorder is multiple sclerosis (MS), a progressive disease of the central nervous system (CNS). In MS patients, the patient's own immune system destroys myelin, the protective layer that surrounds and insulates the nerve fibers in the brain and spinal cord. The destruction of the myelin sheath leads to disruption of neurotransmission and scarring damage to the nerve fibers. The end result is the manifestation of numerous symptoms in the affected patient including tingling or numbness, slurred speech, impaired vision, vertigo etc. Over the course of the disease, there is loss of strength in the extremities, leading to problems with movement and in the most severe cases, leading to paralysis of the limbs. Based on clinical diagnosis, there are currently four types of MS classifications, based on which part of the brain or spinal cord are affected, severity, frequency of attacks etc.

Current therapies for MS include corticosteroid drugs (to alleviate symptoms of acute episodes), as well as other drugs like IFN-β and Novantrone®. Novantrone® has been approved for late stage MS patients, specifically for whom other therapies have not worked. Novantrone® is cytotoxic to most cells and therefore as one would expect, has an array of side effects and is toxic at doses required for the maximal therapeutic effects. IFN-β is also toxic, limiting dosage of the drug in MS patients. Furthermore, continuous use of these drugs has been shown to desensitize patients to further use of the same drug, thereby limiting the ability to use these drugs as long term therapeutics.

Of particular interest, from a therapeutic standpoint, are the interferons (reviews on interferons are provided by De Maeyer and De Maeyer-Guignard, "Interferons," in *The Cytokine Handbook, 3rd Edition*, Thompson (ed.), pages 491-516 (Academic Press Ltd. 1998), and by Walsh, *Biopharmaceuticals: Biochemistry and Biotechnology*, pages 158-188 (John Wiley & Sons 1998)). Interferons exhibit a variety of biological activities, and are useful for the treatment of certain autoimmune diseases, particular cancers, and the enhancement of the immune response against

infectious agents, including viruses, bacteria, fungi, and protozoa. To date, six forms of interferon have been identified, which have been classified into two major groups. The so-called "type I" IFNs include IFN-α, IFN-β, IFN-ω, IFN-δ, and interferon-τ. Currently, IFN-γ and one subclass of IFN-α are the only type II IFNs.

Type I IFNs, which are thought to be derived from the same ancestral gene, have retained sufficient similar structure to act by the same cell surface receptor. The α-chain of the human IFN-α/β receptor comprises an extracellular N-terminal domain, which has the characteristics of a class II cytokine receptor. IFN-γ does not share significant homology with the type I IFN or with the type II IFN-α subtype, but shares a number of biological activities with the type I IFN.

Clinicians are taking advantage of the multiple activities of interferons by using the proteins to treat a wide range of conditions. For example, one form of IFN-α has been approved for use in more than 50 countries for the treatment of medical conditions such as hairy cell leukemia, renal cell carcinoma, basal cell carcinoma, malignant melanoma, AIDS-related Kaposi's sarcoma, multiple myeloma, chronic myelogenous leukemia, non-Hodgkin's lymphoma, laryngeal papillomatosis, mycosis fungoides, condyloma acuminata, chronic hepatitis B, hepatitis C, chronic hepatitis D, and chronic non-A, non-B/C hepatitis. The U.S. Food and Drug Administration has approved the use of IFN-β to treat multiple sclerosis, a chronic disease of the nervous system. IFN-γ is used to treat chronic granulomatous diseases, in which the interferon enhances the patient's immune response to destroy infectious bacterial, fungal, and protozoal pathogens. Clinical studies also indicate that IFN-γ may be useful in the treatment of AIDS, leishmaniasis, and lepromatous leprosy.

IL-28A, IL-28B, and IL-29 comprise a recently discovered new family of proteins that have sequence homology to type I interferons and genomic homology to IL-10. This new family is fully described in co-owned PCT application WO 02/086087 and Sheppard et al., Nature Immunol. 4:63-68, 2003; both incorporated by reference herein. Functionally, IL-28 and IL-29 resemble type I INFs in their ability to induce an antiviral state in cells but, unlike type I IFNs, they do not display antiproliferative activity against certain B cell lines.

Mature T cells can be activated, i.e., by an antigen or other stimulus, to produce, for example, cytokines, biochemical signaling molecules, or receptors that further influence the fate of the T cell population.

B cells can be activated via receptors on their cell surface including B cell receptor and other accessory molecules to perform accessory cell functions, such as production of cytokines. B cell activation results in the production of antibodies that can bind to immunogenic cell-surface proteins on tumor cells and initiate complement-mediated cell lysis, bridge NK cells or macrophages to the tumor for antibody-dependent cell-mediated cytotoxicity (ADCC), interfere with tumor cell growth by blocking survival or inducing apoptotic signals, or increase immunogenicity by facilitating the uptake and presentation of tumor antigens by APCs. Thus, enhancing B cell responses in vivo has the potential to promote antitumor activity (Blattman et al., Science, 305:200-205 (July 9, 2004)).

Therefore, agents which can augment natural host defenses against tumor induction or progression may increase remission rates and enhance survival of patients, without the cytotoxic side effects of prior methods.

The present invention provides such methods for treating solid tumors, lymphomas, and autoimmune disorders by administrating IL-28A, IL-28B, or IL-29 compositions that may be used as a monotherapy or in combination with chemotherapy, radiation therapy, small molecules or other biologics. These and other uses should be apparent to those skilled in the art from the teachings herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows mice injected with mouse IL-28 plasmid on Days 5 and 12 inhibit RENCA tumor growth *in vivo*.

Figure 2 shows mice injected with mouse IL-28 plasmid, mouse IFN-α plasmid, and human IL-29 C172S polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol propionaldehyde inhibit RENCA tumor growth *in vivo*. Plasmid injections are on Days 5 and 12. Protein was given every other day from day 5-21.

Figure 3 shows mice injected with 1μg, 5 μg and 25 μg of human IL-29 C172S polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol

propionaldehyde and human IL-29 C172S d2-7 polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol propionaldehyde inhibit RENCA tumor growth *in vivo*. All protein given every other day from days 5-23.

Figure 4 shows mice injected with vehicle (■), 5μg human IL-29 C172S d2-7 polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol propionaldehyde (▼), and 25μg human IL-29 C172S d2-7 polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol proprionaldehyde (♦) every-other-day for 20 days once tumor volume reached 100mm^3, 5μg human IL-29 C172S d2-7 polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol propionaldehyde everyday for 20 days once a tumor volume reached 100mm^3 (●), and 5μg human IL-29 C172S d2-7 polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol propionaldehyde administered prophylatically every other day for 20 days starting on day 5 of tumor injection (▲).

Figure 5A shows mice injected with 25μg human IL-29 C172S d2-7 polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol propionaldehyde or vehicle beginning on Day 0 and ten subsequent i.p. injections every-other-day prolongs survival of the mice in the E.G7 thymoma model.

Figure 5B shows mice injected with 25μg human IL-29 C172S d2-7 polypeptide N-terminally conjugated to a 20kD methoxy-polyethylene glycol propionaldehyde or vehicle beginning on Day 0 and ten subsequent i.p. injections every-other-day inhibits tumor growth in the E.G7 thymoma model.

DESCRIPTION OF THE INVENTION

In the description that follows, a number of terms are used extensively. The following definitions are provided to facilitate understanding of the invention.

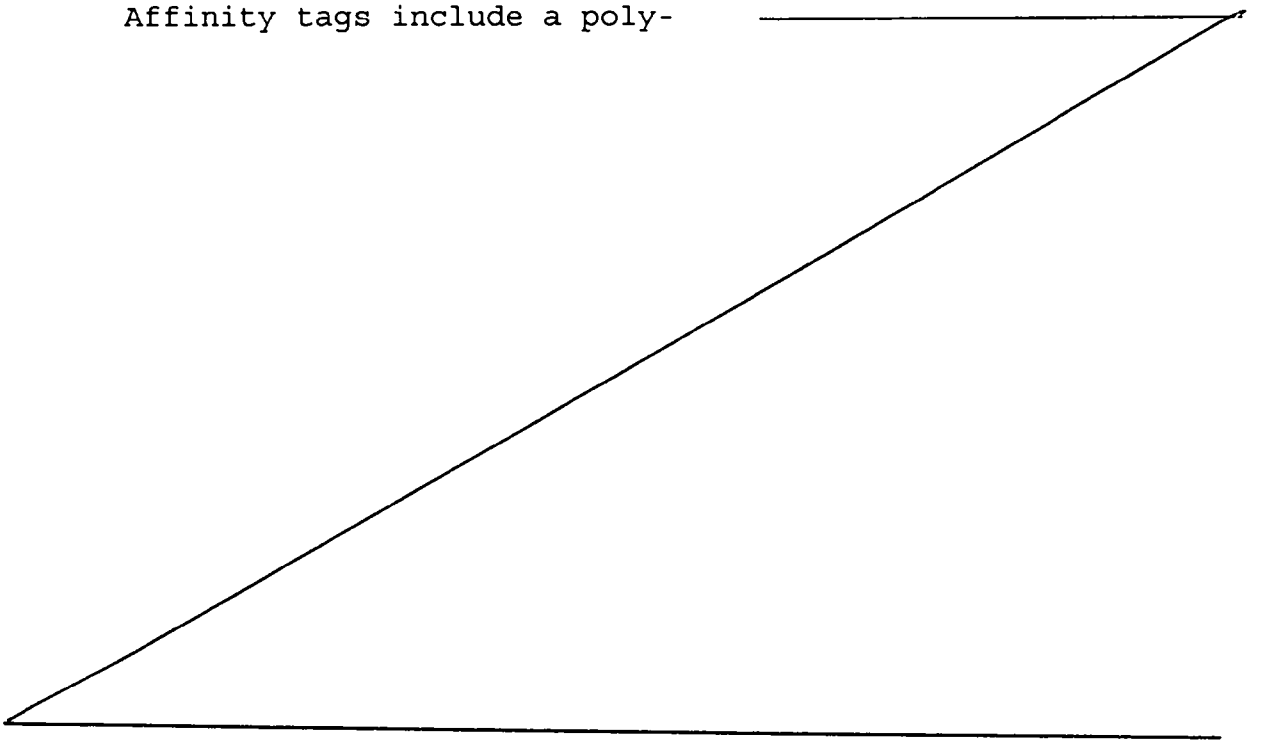
In the claims which follow and in the preceding description of the invention, except where the context

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.

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.

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

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™ 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).

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.

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.

The term “cancer” or “cancer cell” is used herein to denote a tissue or cell found in a neoplasm which possesses characteristics which differentiate it from normal tissue or tissue cells. Among such characteristics include but are not limited to: degree of anaplasia, irregularity in shape, indistinctness of cell outline, nuclear size, changes in structure of nucleus or cytoplasm, other phenotypic changes, presence of cellular proteins indicative of a cancerous or pre-cancerous state, increased number of mitoses, and ability to metastasize. Words pertaining to “cancer” include carcinoma, sarcoma, tumor, epithelioma, leukemia, lymphoma, polyp, and scirrus, transformation, neoplasm, and the like.

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 $<10^9$ M^{-1}.

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.

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).

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.

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).

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

The term "level" when referring to immune cells, such as NK cells, T cells, in particular cytotoxic T cells, B cells and the like, an increased level is either increased number of cells or enhanced activity of cell function.

The term "neoplastic", when referring to cells, indicates cells undergoing new and abnormal proliferation, particularly in a tissue where in the proliferation is uncontrolled and progressive, resulting in a neoplasm. The neoplastic cells can be either malignant, i.e. invasive and metastatic, or benign.

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.

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.

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".

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.

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.

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).

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.

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 ±10%.

"zcyto20", "zcyto21", "zcyto22" are the previous designations for human IL-28A, human IL-29, and human IL-28B, respectively, and are used interchangeably herein. The nucleotide and amino acid sequence for IL-28A are shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. The nucleotide and amino acid sequences for IL-29 are shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. The nucleotide and amino acid sequence for IL-28B are shown in SEQ ID NO:5 and SEQ ID NO:6, respectively. These sequences are fully described in PCT application WO 02/086087 commonly assigned to ZymoGenetics, Inc., incorporated herein by reference.

"zcyto24" and "zcyto25" are the previous designations for mouse IL-28, and are shown in SEQ ID NOs: 7, 8, 9, 10, respectively. The polynucleotide and polypeptides are fully described in PCT application WO 02/086087 commonly assigned to ZymoGenetics, Inc., incorporated herein by reference.

"zcytor19" is the previous designation for IL-28 receptor α-subunit, and is shown in SEQ ID NO: 11. The polynucleotides and polypeptides are described in PCT application WO 02/20569 on behalf of Schering, Inc., and WO 02/44209 assigned to ZymoGenetics, Inc and incorporated herein by reference. "IL-28 receptor" denotes the IL-28 α-subunit and CRF2-4 subunit forming a heterodimeric receptor.

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

A. IL-28, IL-29 and its Receptor

When referring to IL-28, the term shall mean both IL-28A and IL-28B. Previously IL-28A was designated zcyto20 (SEQ ID NOs: 1 and 2) and the terms are used interchangeably herein, IL-29 was designated zcyto21 (SEQ ID NOs: 3 and 4) and the terms are used interchangeably herein, and IL-28B was designated zcyto22 (SEQ

ID NOs:5 and 6) and the terms are used interchangeably herein (See, PCT application WO 02/086087 and Sheppard et al., supra.). The mouse orthologs for IL-28 were previously designated as zcyto24 (SEQ ID NOs:7 and 8), zcyto25 (SEQ ID NOs: 9 and 10).

Wildtype IL-28A gene encodes a polypeptide of 200 amino acids, as shown in SEQ ID NO:2. The signal sequence for IL-28A can be predicted as comprising amino acid residue -25 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:2. The mature peptide for IL-28A begins at amino acid residue 1 (Val). IL-28A helices are predicted as follow: helix A is defined by amino acid residues 24 (Leu) to 40 (Glu); helix B by amino acid residues 58 (Thr) to 65 (Gln); helix C by amino acid residues 69 (Arg) to 85 (Ala); helix D by amino acid residues 95 (Val) to 114 (Ala); helix E by amino acid residues 126 (Thr) to 142 (Lys); and helix F by amino acid residues 148 (Cys) to 169 (Ala); as shown in SEQ ID NO: 2.

Wildtype IL-29 gene encodes a polypeptide of 200 amino acids, as shown in SEQ ID NO:4. The signal sequence for IL-29 can be predicted as comprising amino acid residue -19 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:4, SEQ ID NO:119, or SEQ ID NO:121. The mature peptide for IL-29 begins at amino acid residue 1 (Gly). IL-29 has been described in PCT application WO 02/02627. IL-29 helices are predicted as follows: helix A is defined by amino acid residues 30 (Ser) to 44 (Leu); helix B by amino acid residues 57 (Asn) to 65 (Val); helix C by amino acid residues 70(Val) to 85 (Ala); helix D by amino acid residues 92 (Glu) to 114 (Gln); helix E by amino acid residues 118 (Thr) to 139 (Lys); and helix F by amino acid residues 144 (Gly) to 170 (Leu); as shown in SEQ ID NO: 4.

Wildtype IL-28B gene encodes a polypeptide of 200 amino acids, as shown in SEQ ID NO:6. The signal sequence for IL-28B can be predicted as comprising amino acid residue -21 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:6. The mature peptide for IL-28B begins at amino acid residue 1 (Val). IL-28B helices are predicted as follow: helix A is defined by amino acid residues 8 (Leu) to 41 (Glu); helix B by amino acid residues 58 (Trp) to 65 (Gln); helix C by amino acid residues 69 (Arg) to 86 (Ala); helix D by amino acid residues 95 (Gly) to 114 (Ala); helix E by amino acid residues 126 (Thr) to 142 (Lys); and helix F by amino acid residues 148 (Cys) to 169 (Ala); as shown in SEQ ID NO: 6.

The present invention provides mutations in the IL-28 and IL-29 wildtype sequences as shown in SEQ ID NOs: 1, 2, 3, 4, 5, and 6, that result in expression of single forms of the IL-28 or IL-29 molecule. Because the heterogeneity of forms is believed to be a result of multiple intramolecular disulfide bonding patterns, specific embodiments of the present invention includes mutations to the cysteine residues within the wildtype IL-28 and IL-29 sequences. When IL-28 and IL-29 are expressed in *E. coli*, an N-terminal Methionine is present. SEQ ID NOs:12-17, for example, show the nucleotide and amino acid residue numbering for IL-28A, IL-29 and IL-28B when the N-terminal Met is present. Table 1 shows the possible combinations of intramolecular disulfide bonded cysteine pairs for wildtype IL-28A, IL-28B, and IL-29.

Table 1

IL-28A SEQ ID NO:2	C_{16}-C_{115}	C_{48}-C_{148}	C_{50}-C_{148}	C_{167}-C_{174}	C_{16}-C_{48}	C_{16}-C_{50}	C_{48}-C_{115}	C_{50}-C_{115}	C_{115}-C_{148}
Met IL-28A SEQ ID NO:13	C_{17}-C_{116}	C_{49}-C_{149}	C_{51}-C_{1498}	C_{168}-C_{175}	C_{17}-C_{49}	C_{17}-C_{51}	C_{49}-C_{116}	C_{51}-C_{116}	C_{116}-C_{149}
IL-29 SEQ ID NO:4	C_{15}-C_{112}	C_{49}-C_{145}	C_{112}-C_{171}						
Met IL-29 SEQ ID NO:15	C_{16}-C_{113}	C_{50}-C_{146}	C_{113}-C_{172}						
IL-28B SEQ ID NO:6	C_{16}-C_{115}	C_{48}-C_{148}	C_{50}-C_{148}	C_{167}-C_{174}	C_{16}-C_{48}	C_{16}-C_{50}	C_{48}-C_{115}	C_{50}-C_{115}	C_{115}-C_{148}
Met IL-28B SEQ ID NO:17	C_{17}-C_{116}	C_{49}-C_{149}	C_{51}-C_{1498}	C_{168}-C_{175}	C_{17}-C_{49}	C_{17}-C_{51}	C_{49}-C_{116}	C_{51}-C_{116}	C_{116}-C_{149}

The polynucleotide and polypeptide molecules of the present invention may have a mutation at one or more of the Cysteines present in the wildtype IL-28A, IL-29 or IL-28B molecules, yet retain some biological activity as described herein. Table 2 illustrates exemplary Cysteine mutants, in particular point mutations of cysteine (C) to serine (S).

Table 2

IL-28A C48S	SEQ ID NO:19
Met IL-28A C49S	SEQ ID NO:21
IL-28A C50S	SEQ ID NO:23
Met IL-28A C51S	SEQ ID NO:25
IL-29 C171S	SEQ ID NO:27
Met IL-29 C172S	SEQ ID NO:29

All the members of the family have been shown to bind to the same class II cytokine receptor, IL-28R. IL-28 α-subunit was previously designated zcytor19 receptor. While not wanting to be bound by theory, these molecules appear to all signal through IL-28R receptor via the same pathway. IL-28 receptor is described in a commonly assigned PCT patent application WO 02/44209, incorporated by reference herein; Sheppard et al., supra; Kotenko et al., Nature Immunol. 4:69-77, 2003; and PCT WO/03/040345. IL-28R is a member of the Class II cytokine receptors which is characterized by the presence of one or more cytokine receptor modules (CRM) in their extracellular domains. Other class II cytokine receptors include zcytor11 (commonly owned US Patent No. 5,965,704), CRF2-4 (Genbank Accession No. Z17227), IL-10R (Genbank Accession No.s U00672 and NM_001558), DIRS1, zcytor7 (commonly owned US Patent No. 5,945,511), and tissue factor. IL-28 receptor, like all known class II receptors except interferon-alpha/beta receptor alpha chain, has only a single class II CRM in its extracellular domain.

Four-helical bundle cytokines are also grouped by the length of their component helices. "Long-helix" form cytokines generally consist of between 24-30 residue helices, and include IL-6, ciliary neutrotrophic factor (CNTF), leukemia inhibitory factor (LIF) and human growth hormone (hGH). "Short-helix" form cytokines generally consist of between 18-21 residue helices and include IL-2, IL-4 and GM-CSF. Studies using CNTF and IL-6 demonstrated that a CNTF helix can be

exchanged for the equivalent helix in IL-6, conferring CTNF-binding properties to the chimera. Thus, it appears that functional domains of four-helical cytokines are determined on the basis of structural homology, irrespective of sequence identity, and can maintain functional integrity in a chimera (Kallen et al., J. Biol. Chem. 274:11859-11867, 1999). Therefore, IL-28 and IL-29 polypeptides will be useful for preparing chimeric fusion molecules, particularly with other interferons to determine and modulate receptor binding specificity. Of particular interest are fusion proteins that combine helical and loop domains from interferons and cytokines such as INF-α, IL-10, human growth hormone.

The present invention provides polynucleotide molecules, including DNA and RNA molecules, that encode IL-28 or IL-29 polypeptides. For example, the present invention provides degenerate nucleotide sequences encoding IL-28A C48S, Met IL-28A C49S, IL-28A C50S, Met IL-28A C51S, IL-29 C171S and Met IL-29 C172S polypeptides disclosed herein. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. SEQ ID NOs:30, 31, 32, 33, 34, and 35 are a degenerate DNA sequences that encompasses all DNAs that encode IL-28A C48S, Met IL-28A C49S, IL-28A C50S, Met IL-28A C51S, IL-29 C171S and Met IL-29 C172S, respectively. Those skilled in the art will recognize that the degenerate sequence of SEQ ID NOs:30, 31, 32, 33, 34, and 35 also provides all RNA sequences encoding SEQ ID NOs:30, 31, 32, 33, 34, and 35 by substituting U for T and are thus contemplated by the present invention.

A zcyto20 or IL-28A gene encodes a polypeptide of 205 amino acids, as shown in SEQ ID NO:2. The signal sequence for IL-28A comprises amino acid residue -25 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:2, or alternatively amino acid residues -21 (Met) through amino acid residue -1 (Ala) of SEQ ID NO:2. The mature peptide for IL-28A begins at amino acid residue 1 (Val) of SEQ ID NO:2. Zcyto20 helices are predicted as follow: helix A is defined by amino acid residues 52 (Ala) to 66 (Leu); helix B by amino acid residues 78 (Arg) to 87 (Val); helix C by amino acid residues 91 (Pro) to 108 (Thr); helix D by amino acid residues 116 (Val) to 138 (Ser); helix E by amino acid residues 151 (Thr) to 172 (Lys); and helix F by amino acid residues 177 (Gly) to 197 (Cys); as shown in SEQ ID NO:2. Further analysis of

Zcyto20 based on multiple alignments predicts that cysteines at amino acid residues 37 and 136; 69 and 197; and 71 and 178 (as shown in SEQ ID NO:2) will form intramolecular disulfide bonds. The corresponding polynucleotides encoding the Zcyto20 polypeptide regions, domains, motifs, residues and sequences described herein are as shown in SEQ ID NO:1. When a polynucleotide sequence encoding the mature polypeptide is expressed in a prokaryotic system, such as *E. coli*, the a secretory signal sequence may not be required and the an N-terminal Met will be present, resulting in expression of a polypeptide such as is shown in SEQ ID NO:13.

IL-28A polypeptides of the present invention also include a mutation at the second cysteine, C2, of the mature polypeptide. For example, C2 from the N-terminus of the polypeptide of SEQ ID NO:2 is the cysteine at amino acid position 48, or position 49 (additional N-terminal Met) if expressed in *E coli* (see, for example, SEQ ID NO:13). This second cysteine (of which there are seven, like IL-28B) or C2 of IL-28A can be mutated to any amino acid that will not form a disulfide bond, for example, to a serine, alanine, threonine, valine, or asparagine. IL-28A C2 mutant molecules of the present invention include, for example, polynucleotide molecules as shown in SEQ ID NOs:18 and 20, including DNA and RNA molecules, that encode IL-28A C2 mutant polypeptides as shown in SEQ ID NOs:19 and 21, respectively. Additional IL-28A C2 mutant molecules of the present invention include polypeptides as shown in SEQ ID NOs:36 and 37.

In addition to the IL-28A C2 mutants, the present invention also includes IL-28A polypeptides comprising a mutation at the third cysteine position, C3, of the mature polypeptide. For example, C3 from the N-terminus of the polypeptide of SEQ ID NO:2, is the cysteine at position 50, or position 51 (additional N-terminal Met) if expressed in *E. coli* (see, for example, SEQ ID NO:13). IL-28A C3 mutant molecules of the present invention include, for example, polynucleotide molecules as shown in SEQ ID NOs:22 and 24, including DNA and RNA molecules, that encode IL-28A C3 mutant polypeptides as shown in SEQ ID NOs:23 and 25, respectively. Additional IL-28A C3 mutant molecules of the present invention include polypeptides as shown in SEQ ID NOs:38 and 39.

The IL-28A polypeptides of the present invention include, for example, SEQ ID NOs:2, 13, 19, 21, 23, 25, which are encoded by IL-28A polynucleotide

molecules as shown in SEQ ID NOs:1, 12, 18, 20, 22 and 24, respectively. In addition, the present invention also provides for IL-28A polypeptides as shown in SEQ ID NOs:36, 37, 38, and 39.

A Zcyto22 or IL-28B gene encodes a polypeptide of 205 amino acids, as shown in SEQ ID NO:6. The signal sequence for IL-28B comprises amino acid residue -25 (Met) through amino acid residue 0 (Ala) of SEQ ID NO:6, or alternatively amino acid residues -21 (Met) through amino acid residue 0 (Ala) of SEQ ID NO:6. The mature peptide for IL-28B begins at amino acid residue 1 (Val) of SEQ ID NO:6. IL-28B helices are predicted as follow: helix A is defined by amino acid residues 8 (Leu) to 41 (Glu); helix B by amino acid residues 58 (Trp) to 65 (Gln); helix C by amino acid residues 69 (Arg) to 86 (Ala); helix D by amino acid residues 95 (Gly) to 114 (Ala); helix E by amino acid residues 126 (Thr) to 142 (Lys); and helix F by amino acid residues 148 (Cys) to 169 (Ala); as shown in SEQ ID NO:6. When a polynucleotide sequence encoding the mature polypeptide is expressed in a prokaryotic system, such as *E. coli*, the a secretory signal sequence may not be required and the an N-terminal Met will be present, resulting in expression of a polypeptide such as is shown in SEQ ID NO:17.

IL-28B polypeptides of the present invention also include a mutation at the second cysteine, C2, of the mature polypeptide. For example, C2 from the N-terminus of the polypeptide of SEQ ID NO:6 is the cysteine at amino acid position 48, or position 49 (additional N-terminal Met) if expressed in *E. coli* (see, for example, SEQ ID NO:17). This second cysteine (of which there are seven, like IL-28A) or C2 of IL-28B can be mutated to any amino acid that will not form a disulfide bond, for example, to a serine, alanine, threonine, valine, or asparagine. IL-28B C2 mutant molecules of the present invention include, for example, polynucleotide molecules as shown in SEQ ID NOs:122 and 124, including DNA and RNA molecules, that encode IL-28B C2 mutant polypeptides as shown in SEQ ID NOs:123 and 125, respectively. Additional IL-28B C2 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:130 and 132 including DNA and RNA molecules, that encode IL-28B C2 mutant polypeptides as shown in SEQ ID NOs:131 and 133, respectively (PCT publication WO 03/066002 (Kotenko et al.)).

In addition to the IL-28B C2 mutants, the present invention also includes IL-28B polypeptides comprising a mutation at the third cysteine position, C3, of the mature polypeptide. For example, C3 from the N-terminus of the polypeptide of SEQ ID NO:6, is the cysteine at position 50, or position 51 (additional N-terminal Met) if expressed in *E. coli* (see, for example, SEQ ID NO:17). IL-28B C3 mutant molecules of the present invention include, for example, polynucleotide molecules as shown in SEQ ID NOs:126 and 128, including DNA and RNA molecules, that encode IL-28B C3 mutant polypeptides as shown in SEQ ID NOs:127 and 129, respectively (PCT publication WO 03/066002 (Kotenko et al.)). Additional IL-28B C3 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:134 and 136 including DNA and RNA molecules, that encode IL-28B C3 mutant polypeptides as shown in SEQ ID NOs:135 and 137, respectively (PCT publication WO 03/066002 (Kotenko et al.)).

The IL-28B polypeptides of the present invention include, for example, SEQ ID NOs:6, 17, 123, 125, 127, 129, 131, 133, 135, and 137, which are encoded by IL-28B polynucleotide molecules as shown in SEQ ID NOs:5, 16, 122, 124, 126, 128, 130, 132, 134, and 136, respectively.

Zcyto21 or IL-29 polypeptides of the present invention also include a mutation at the fifth cysteine, C5, of the mature polypeptide. For example, C5 from the N-terminus of the polypeptide of SEQ ID NO:4, is the cysteine at position 171, or position 172 (additional N-terminal Met) if expressed in E. coli. (see, for example, SEQ ID NO:15). This fifth cysteine or C5 of IL-29 can be mutated to any amino acid that will not form a disulfide bond, for example, to a serine, alanine, threonine, valine, or asparagine. These IL-29 C5 mutant polypeptides have a disulfide bond pattern of C1(Cys15 of SEQ ID NO:4)/C3(Cys112 of SEQ ID NO:4) and C2(Cys49 of SEQ ID NO:4)/C4(Cys145 of SEQ ID NO:4). Additional IL-29 C5 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:26, 28, 82, 84, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, and 160, including DNA and RNA molecules, that encode IL-29 C5 mutant polypeptides as shown in SEQ ID NOs:27, 29, 83, 85, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, and 161, respectively. Additional IL-29 C5 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:86, 88, 94, and 96, including DNA

and RNA molecules, that encode IL-29 C5 mutant polypeptides as shown in SEQ ID NOs:87, 89, 95, and 97, respectively (PCT publication WO 03/066002 (Kotenko et al.)). Additional, IL-29 C5 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:102, 104, 110, and 112, including DNA and RNA molecules, that encode IL-29 C5 mutant polypeptides as shown in SEQ ID NOs:103, 105, 111, and 113, respectively (PCT publication WO 02/092762 (Baum et al.)).

In addition to the IL-29 C5 mutants, the present invention also includes IL-29 polypeptides comprising a mutation at the first cysteine position, C1, of the mature polypeptide. For example, C1 from the N-terminus of the polypeptide of SEQ ID NO:4, is the cysteine at position 15, or position 16 (additional N-terminal Met) if expressed in *E. coli* (see, for example, SEQ ID NO:15). These IL-29 C1 mutant polypeptides will thus have a predicted disulfide bond pattern of C2(Cys49 of SEQ ID NO:4)/C4(Cys145 of SEQ ID NO:4) and C3(Cys112 of SEQ ID NO:4)/C5(Cys171 of SEQ ID NO:4). Additional IL-29 C1 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:74, 76, 78, and 80, including DNA and RNA molecules, that encode IL-29 C1 mutant polypeptides as shown in SEQ ID NOs:75, 77, 79 and 81, respectively. Additional IL-29 C1 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:90, 92, 98, and 100, including DNA and RNA molecules, that encode IL-29 C1 mutant polypeptides as shown in SEQ ID NOs:91, 93, 99, and 101, respectively (PCT publication WO 03/066002 (Kotenko et al.)). Additional, IL-29 C1 mutant molecules of the present invention include polynucleotide molecules as shown in SEQ ID NOs:106, 108, 114, and 116, including DNA and RNA molecules, that encode IL-29 C1 mutant polypeptides as shown in SEQ ID NOs:107, 109, 115, and 117, respectively (PCT publication WO 02/092762 (Baum et al.)).

The IL-29 polypeptides of the present invention include, for example, SEQ ID NOs:4, 15, 27, 29, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, and 161, which are encoded by IL-29 polynucleotide molecules as shown in SEQ ID NOs:3, 14, 26, 28, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158,

and 160, may further include a signal sequence as shown in SEQ ID NO:119 or a signal sequence as shown in SEQ ID NO:121. Additional IL-29 polypeptides include SEQ ID NOs:40 and 41. A polynucleotide molecule encoding the signal sequence polypeptide of SEQ ID NO:119 is shown as SEQ ID NO:118. A polynucleotide molecule encoding the signal sequence polypeptide of SEQ ID NO:120 is shown as SEQ ID NO:121.

Table 3 sets forth the one-letter codes used within SEQ ID NOS: 30, 31, 32, 33, 34, and 35 to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, with A being complementary to T, and G being complementary to C.

Table 3

Nucleotide	Resolution	Complement	Resolution
A	A	T	T
C	C	G	G
G	G	C	C
T	T	A	A
R	A|G	Y	C|T
Y	C|T	R	A|G
M	A|C	K	G|T
K	G|T	M	A|C
S	C|G	S	C|G
W	A|T	W	A|T
H	A|C|T	D	A|G|T
B	C|G|T	V	A|C|G
V	A|C|G	B	C|G|T
D	A|G|T	H	A|C|T
N	A|C|G|T	N	A|C|G|T

The degenerate codons used in SEQ ID NOs: 30, 31, 32, 33, 34, and 35, encompassing all possible codons for a given amino acid, are set forth in Table 4.

Table 4

Amino Acid	One Letter Code	Codons	Degenerate Codon
Cys	C	TGC TGT	TGY
Ser	S	AGC AGT TCA TCC TCG TCT	WSN
Thr	T	ACA ACC ACG ACT	ACN
Pro	P	CCA CCC CCG CCT	CCN
Ala	A	GCA GCC GCG GCT	GCN
Gly	G	GGA GGC GGG GGT	GGN
Asn	N	AAC AAT	AAY
Asp	D	GAC GAT	GAY
Glu	E	GAA GAG	GAR
Gln	Q	CAA CAG	CAR
His	H	CAC CAT	CAY
Arg	R	AGA AGG CGA CGC CGG CGT	MGN
Lys	K	AAA AAG	AAR
Met	M	ATG	ATG
Ile	I	ATA ATC ATT	ATH
Leu	L	CTA CTC CTG CTT TTA TTG	YTN
Val	V	GTA GTC GTG GTT	GTN
Phe	F	TTC TTT	TTY
Tyr	Y	TAC TAT	TAY
Trp	W	TGG	TGG
Ter	.	TAA TAG TGA	TRR
Asn|Asp	B		RAY
Glu|Gln	Z		SAR
Any	X		NNN

One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequence may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant

sequences by reference to the amino acid sequence of SEQ ID NOS:19, 21, 23, 25, 27, and 29. Variant sequences can be readily tested for functionality as described herein.

One of ordinary skill in the art will also appreciate that different species can exhibit "preferential codon usage." In general, see, Grantham, et al., Nuc. Acids Res. 8:1893-912, 1980; Haas, et al. Curr. Biol. 6:315-24, 1996; Wain-Hobson, et al., Gene 13:355-64, 1981; Grosjean and Fiers, Gene 18:199-209, 1982; Holm, Nuc. Acids Res. 14:3075-87, 1986; Ikemura, J. Mol. Biol. 158:573-97, 1982. As used herein, the term "preferential codon usage" or "preferential codons" is a term of art referring to protein translation codons that are most frequently used in cells of a certain species, thus favoring one or a few representatives of the possible codons encoding each amino acid (See Table 4). For example, the amino acid Threonine (Thr) may be encoded by ACA, ACC, ACG, or ACT, but in mammalian cells ACC is the most commonly used codon; in other species, for example, insect cells, yeast, viruses or bacteria, different Thr codons may be preferential. Preferential codons for a particular species can be introduced into the polynucleotides of the present invention by a variety of methods known in the art. Introduction of preferential codon sequences into recombinant DNA can, for example, enhance production of the protein by making protein translation more efficient within a particular cell type or species. Therefore, the degenerate codon sequence disclosed in SEQ ID NOS: 30, 31, 32, 33, 34, and 35 serves as a template for optimizing expression of polynucleotides in various cell types and species commonly used in the art and disclosed herein. Sequences containing preferential codons can be tested and optimized for expression in various species, and tested for functionality as disclosed herein.

As previously noted, the isolated polynucleotides of the present invention include DNA and RNA. Methods for preparing DNA and RNA are well known in the art. In general, RNA is isolated from a tissue or cell that produces large amounts of IL-28 or IL-29 RNA. Such tissues and cells are identified by Northern blotting (Thomas, Proc. Natl. Acad. Sci. USA 77:5201, 1980), or by screening conditioned medium from various cell types for activity on target cells or tissue. Once the activity or RNA producing cell or tissue is identified, total RNA can be prepared using guanidinium isothiocyanate extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., Biochemistry 18:52-94, 1979). Poly $(A)^+$ RNA is

prepared from total RNA using the method of Aviv and Leder (Proc. Natl. Acad. Sci. USA 69:1408-12, 1972). Complementary DNA (cDNA) is prepared from poly(A)$^+$ RNA using known methods. In the alternative, genomic DNA can be isolated. Polynucleotides encoding IL-28 or IL-29 polypeptides are then identified and isolated by, for example, hybridization or PCR.

A full-length clones encoding IL-28 or IL-29 can be obtained by conventional cloning procedures. Complementary DNA (cDNA) clones are preferred, although for some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for preparing cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequence disclosed herein, or parts thereof, for probing or priming a library. Expression libraries can be probed with antibodies to IL-28 receptor fragments, or other specific binding partners.

Those skilled in the art will recognize that the sequence disclosed in, for example, SEQ ID NOs:1, 3, and 5, respectively, represent mutations of single alleles of human IL-28 and IL-29 bands, and that allelic variation and alternative splicing are expected to occur. For example, an IL-29 variant has been identified where amino acid residue 169 (Asn) as shown in SEQ ID NO:4 is an Arg residue, as described in WO 02/086087. Such allelic variants are included in the present invention. Allelic variants of this sequence can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Allelic variants of the DNA sequence shown in SEQ ID NOs:1, 3 and 5, including those containing silent mutations and those in which mutations result in amino acid sequence changes, in addition to the cysteine mutations, are within the scope of the present invention, as are proteins which are allelic variants of SEQ ID NOs:2, 4, and 6. cDNAs generated from alternatively spliced mRNAs, which retain the properties of IL-28 or IL-29 polypeptides, are included within the scope of the present invention, as are polypeptides encoded by such cDNAs and mRNAs. Allelic variants and splice variants of these sequences can be cloned by probing cDNA or genomic libraries from different individuals or tissues according to standard procedures known in the art, and mutations to the

polynucleotides encoding cysteines or cysteine residues can be introduced as described herein.

Within embodiments of the invention, isolated IL-28- and IL-29-encoding nucleic acid molecules can hybridize under stringent conditions to nucleic acid molecules having the nucleotide sequence of SEQ ID NOs:1, 3, 5, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160 or to nucleic acid molecules having a nucleotide sequence complementary to SEQ ID NOs:1, 3, 5, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160. In general, stringent conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe.

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_m 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.

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_m 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_m 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_m 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.

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, cysteine mutant, or IL-28 or IL-29 polypeptides hybridize with a nucleic acid molecule having the nucleotide sequence of SEQ ID NOs:1, 3, 5, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158 or 160, respectively (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.

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 of a IL-28 or IL-29 polypeptide hybridize with a nucleic acid molecule having the nucleotide sequence of SEQ ID

NOs:1, 3, 5, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158 or 160, (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.

The present invention also provides IL-28 or IL-29 polypeptides that have a substantially similar sequence identity to the polypeptides of the present invention, for example SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161, respectively. The term "substantially similar sequence identity" is used herein to denote polypeptides comprising at least 80%, at least 90%, at least 95%, or greater than 95%, 96%, 97%, 98%, 99%, or 99.5% sequence identity to the sequences shown in SEQ ID NOs: 2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161, respectively, or their orthologs. The present invention also includes polypeptides that comprise an amino acid sequence having 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 a polypeptide or fragment thereof of the present invention. The present invention further includes nucleic acid molecules that encode such polypeptides. The IL-28 and IL-29 polypeptides of the present invention are preferably recombinant polypeptides. In another aspect, the IL-28 and IL-29 polypeptides of the present invention have at least 15, at least 30, at least 45, or at least 60 sequential amino acids. For example, an IL-29 polypeptide of the present invention relates to a polypeptide having at least 15, at least 30, at least 45, or at least 60 sequential amino acids from SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161. Methods for determining percent identity are described below.

The present invention also contemplates variant nucleic acid molecules that can be identified using two criteria: a determination of the similarity between the encoded polypeptide with the amino acid sequence of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161 respectively, and/or a hybridization assay, as described above. Such variants include nucleic acid molecules: (1) that hybridize with a nucleic acid molecule having the nucleotide sequence of SEQ ID NOs:1, 3, 5, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158 or 160, respectively (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; or (2) that encode a polypeptide having at least 80%, at least 90%, at least 95% or greater than 95%, 96%, 97%, 98%, 99% or 99.5% sequence identity to the amino acid sequence of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161. Alternatively, variants can be characterized as nucleic acid molecules: (1) that hybridize with a nucleic acid molecule having the nucleotide sequence of SEQ ID NOs:1, 3, 5, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158 or 160, (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; and (2) that encode a polypeptide having at least 80%, at least 90%, at least 95% or greater than 95%, 96%, 97%, 98%, 99% or 99.5% sequence identity to the amino acid sequence of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161 respectively.

The present invention further provides a polynucleotide encoding a polypeptide that treats, prevents, inhibits the progession of, delay the onset of, and/or

reduce the severity or inhibit at least one of the conditions or symptoms of a cancer as disclosed herein wherein the encoded polypeptide is a sequence selected from the group of SEQ ID NOs:36-41.

Percent sequence identity is determined by conventional methods. See, for example, Altschul et al., Bull. Math. Bio. 48:603 (1986), and Henikoff and Henikoff, Proc. Natl. Acad. Sci. USA 89:10915 (1992). Briefly, two amino acid sequences are aligned to optimize the alignment scores using a gap opening penalty of 10, a gap extension penalty of 1, and the "BLOSUM62" scoring matrix of Henikoff and Henikoff (*ibid.*) as shown in Table 5 (amino acids are indicated by the standard one-letter codes).

$$\frac{\text{Total number of identical matches}}{\text{[length of the longer sequence plus the number of gaps introduced into the longer sequence in order to align the two sequences]}} \times 100$$

Table 5

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4																			
R	-1	5																		
N	-2	0	6																	
D	-2	-2	1	6																
C	0	-3	-3	-3	9															
Q	-1	1	0	0	-3	5														
E	-1	0	0	2	-4	2	5													
G	0	-2	0	-1	-3	-2	-2	6												
H	-2	0	1	-1	-3	0	0	-2	8											
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

Those skilled in the art appreciate that there are many established algorithms available to align two amino acid sequences. The "FASTA" similarity search algorithm of Pearson and Lipman is a suitable protein alignment method for examining the level of identity shared by an amino acid sequence disclosed herein and the amino acid sequence of a putative variant IL-28 or IL-29. The FASTA algorithm is described by Pearson and Lipman, Proc. Nat'l Acad. Sci. USA 85:2444 (1988), and by Pearson, Meth. Enzymol. 183:63 (1990).

Briefly, FASTA first characterizes sequence similarity by identifying regions shared by the query sequence (*e.g.*, SEQ ID NO:2) and a test sequence that have either the highest density of identities (if the ktup variable is 1) or pairs of identities (if ktup=2), without considering conservative amino acid substitutions, insertions, or deletions. The ten regions with the highest density of identities are then rescored by comparing the similarity of all paired amino acids using an amino acid substitution matrix, and the ends of the regions are "trimmed" to include only those residues that contribute to the highest score. If there are several regions with scores greater than the "cutoff" value (calculated by a predetermined formula based upon the length of the sequence and the ktup value), then the trimmed initial regions are examined to determine whether the regions can be joined to form an approximate alignment with gaps. Finally, the highest scoring regions of the two amino acid sequences are aligned using a modification of the Needleman-Wunsch-Sellers algorithm (Needleman and Wunsch, J. Mol. Biol. 48:444 (1970); Sellers, SIAM J. Appl. Math. 26:787 (1974)), which allows for amino acid insertions and deletions. Preferred parameters for FASTA analysis are: ktup=1, gap opening penalty=10, gap extension penalty=1, and substitution matrix=BLOSUM62. These parameters can be introduced into a FASTA program by modifying the scoring matrix file ("SMATRIX"), as explained in Appendix 2 of Pearson, Meth. Enzymol. 183:63 (1990).

FASTA can also be used to determine the sequence identity of nucleic acid molecules using a ratio as disclosed above. For nucleotide sequence comparisons, the ktup value can range between one to six, preferably from three to six, most preferably three, with other parameters set as default.

Variant IL-28 or IL-29 polypeptides or polypeptides with substantially similar sequence identity are characterized as having one or more amino acid

substitutions, deletions or additions. These changes are preferably of a minor nature, that is conservative amino acid substitutions (see Table 6) and other substitutions that do not significantly affect the folding or activity of the polypeptide; small deletions, typically of one to about 30 amino acids; and amino- or carboxyl-terminal extensions, such as an amino-terminal methionine residue, a small linker peptide of up to about 20-25 residues, or an affinity tag. The present invention thus includes polypeptides that comprise a sequence that is at least 80%, preferably at least 90%, and more preferably at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5% or greater than 99.5% identical to the corresponding region of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161. Polypeptides comprising affinity tags can further comprise a proteolytic cleavage site between the IL-28 and IL-29 polypeptide and the affinity tag. Preferred such sites include thrombin cleavage sites and factor Xa cleavage sites.

Table 6

Conservative amino acid substitutions

Basic:	arginine
	lysine
	histidine
Acidic:	glutamic acid
	aspartic acid
Polar:	glutamine
	asparagine
Hydrophobic:	leucine
	isoleucine
	valine
Aromatic:	phenylalanine
	tryptophan
	tyrosine
Small:	glycine
	alanine
	serine
	threonine
	methionine

Determination of amino acid residues that comprise regions or domains that are critical to maintaining structural integrity can be determined. Within these regions one can determine specific residues that will be more or less tolerant of change and maintain the overall tertiary structure of the molecule. Methods for analyzing sequence structure include, but are not limited to alignment of multiple sequences with high amino acid or nucleotide identity, secondary structure propensities, binary patterns, complementary packing and buried polar interactions (Barton, Current Opin. Struct. Biol. 5:372-376, 1995 and Cordes et al., Current Opin. Struct. Biol. 6:3-10, 1996). In general, when designing modifications to molecules or identifying specific

fragments determination of structure will be accompanied by evaluating activity of modified molecules.

Amino acid sequence changes are made in IL-28 or IL-29 polypeptides so as to minimize disruption of higher order structure essential to biological activity. For example, where the IL-28 or IL-29 polypeptide comprises one or more helices, changes in amino acid residues will be made so as not to disrupt the helix geometry and other components of the molecule where changes in conformation abate some critical function, for example, binding of the molecule to its binding partners. The effects of amino acid sequence changes can be predicted by, for example, computer modeling as disclosed above or determined by analysis of crystal structure (see, e.g., Lapthorn et al., Nat. Struct. Biol. 2:266-268, 1995). Other techniques that are well known in the art compare folding of a variant protein to a standard molecule (e.g., the native protein). For example, comparison of the cysteine pattern in a variant and standard molecules can be made. Mass spectrometry and chemical modification using reduction and alkylation provide methods for determining cysteine residues which are associated with disulfide bonds or are free of such associations (Bean et al., Anal. Biochem. 201:216-226, 1992; Gray, Protein Sci. 2:1732-1748, 1993; and Patterson et al., Anal. Chem. 66:3727-3732, 1994). It is generally believed that if a modified molecule does not have the same cysteine pattern as the standard molecule folding would be affected. Another well known and accepted method for measuring folding is circular dichrosism (CD). Measuring and comparing the CD spectra generated by a modified molecule and standard molecule is routine (Johnson, Proteins 7:205-214, 1990). Crystallography is another well known method for analyzing folding and structure. Nuclear magnetic resonance (NMR), digestive peptide mapping and epitope mapping are also known methods for analyzing folding and structurally similarities between proteins and polypeptides (Schaanan et al., Science 257:961-964, 1992).

A Hopp/Woods hydrophilicity profile of the IL-28 or IL-29 polypeptide sequence as shown in SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159 or 161 can be generated (Hopp et al., Proc. Natl. Acad. Sci.78:3824-3828, 1981; Hopp, J. Immun. Meth. 88:1-18, 1986 and Triquier et al., Protein Engineering

11:153-169, 1998). The profile is based on a sliding six-residue window. Buried G, S, and T residues and exposed H, Y, and W residues were ignored. Those skilled in the art will recognize that hydrophilicity or hydrophobicity will be taken into account when designing modifications in the amino acid sequence of a IL-28 or IL-29 polypeptide, so as not to disrupt the overall structural and biological profile. Of particular interest for replacement are hydrophobic residues selected from the group consisting of Val, Leu and Ile or the group consisting of Met, Gly, Ser, Ala, Tyr and Trp.

The identities of essential amino acids can also be inferred from analysis of sequence similarity between IFN-α and members of the family of IL-28A, IL-28B, and IL-29 (as shown in Tables 1 and 2). Using methods such as "FASTA" analysis described previously, regions of high similarity are identified within a family of proteins and used to analyze amino acid sequence for conserved regions. An alternative approach to identifying a variant polynucleotide on the basis of structure is to determine whether a nucleic acid molecule encoding a potential variant IL-28 or IL-29 gene can hybridize to a nucleic acid molecule as discussed above.

Other methods of identifying essential amino acids in the polypeptides of the present invention are procedures known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, Science 244:1081 (1989), Bass et al., Proc. Natl Acad. Sci. USA 88:4498 (1991), Coombs and Corey, "Site-Directed Mutagenesis and Protein Engineering," in Proteins: Analysis and Design, Angeletti (ed.), pages 259-311 (Academic Press, Inc. 1998)). In the latter technique, single alanine mutations are introduced at every residue in the molecule, and the resultant molecules are tested for biological or biochemical activity as disclosed below to identify amino acid residues that are critical to the activity of the molecule. See also, Hilton *et al.*, J. Biol. Chem. 271:4699 (1996).

The present invention also includes functional fragments of IL-28 or IL-29 polypeptides and nucleic acid molecules encoding such functional fragments. A "functional" IL-28 or IL-29 or fragment thereof as defined herein is characterized by its proliferative or differentiating activity, by its ability to induce or inhibit specialized cell functions, or by its ability to bind specifically to an anti- IL-28 or IL-29 antibody or IL-28 receptor (either soluble or immobilized). The specialized activities of IL-28 or IL-29 polypeptides and how to test for them are disclosed herein. As previously described

herein, IL-28 and IL-29 polypeptides are characterized by a six-helical-bundle. Thus, the present invention further provides fusion proteins encompassing: (a) polypeptide molecules comprising one or more of the helices described above; and (b) functional fragments comprising one or more of these helices. The other polypeptide portion of the fusion protein may be contributed by another helical-bundle cytokine or interferon, such as IFN-α, or by a non-native and/or an unrelated secretory signal peptide that facilitates secretion of the fusion protein.

The IL-28 or IL-29 polypeptides of the present invention, including full-length polypeptides, cysteine mutant polypeptides, biologically active fragments, and fusion polypeptides can be produced according to conventional techniques using cells into which have been introduced an expression vector encoding the polypeptide. As used herein, "cells into which have been introduced an expression vector" include both cells that have been directly manipulated by the introduction of exogenous DNA molecules and progeny thereof that contain the introduced DNA. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., Current Protocols in Molecular Biology, John Wiley and Sons, Inc., NY, 1987.

In general, a DNA sequence encoding a IL-28 or IL-29 polypeptide of the present invention is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers may be provided on separate vectors, and replication of the exogenous DNA may be provided by integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

To direct a IL-28 or IL-29 polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be, for example, that of Cysteine mutant IL-28 or IL-29, e.g., SEQ ID NO:119 or SEQ ID NO:121, or may be derived from another secreted protein (e.g., t-PA; see, U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the IL-28 or IL-29 DNA sequence, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized polypeptide into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the polypeptide of interest, although certain signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

A wide variety of suitable recombinant host cells includes, but is not limited to, gram-negative prokaryotic host organisms. Suitable strains of *E. coli* include W3110, K12-derived strains MM294, TG-1, JM-107, BL21, and UT5600. Other suitable strains include: BL21(DE3), BL21(DE3)pLysS, BL21(DE3)pLysE, DH1, DH4I, DH5, DH5I, DH5IF', DH5IMCR, DH10B, DH10B/p3, DH11S, C600, HB101, JM101, JM105, JM109, JM110, K38, RR1, Y1088, Y1089, CSH18, ER1451, ER1647, *E. coli* K12, *E. coli* K12 RV308, *E. coli* K12 C600, *E. coli*HB101, *E. coli* K12 C600 R.sub.k-M.sub.k-, *E. coli* K12 RR1 (see, for example, Brown (ed.), Molecular Biology Labfax (Academic Press 1991)). Other gram-negative prokaryotic hosts can include *Serratia*, *Pseudomonas*, *Caulobacter*. Prokaryotic hosts can include gram-positive organisms such as *Bacillus*, for example, *B. subtilis* and *B. thuringienesis*, and *B. thuringienesis* var. *israelensis*, as well as *Streptomyces*, for example, *S. lividans*, *S. ambofaciens*, *S. fradiae*, and *S. griseofuscus*. Suitable strains of *Bacillus subtilus* include BR151, YB886, MI119, MI120, and B170 (see, for example, Hardy, "Bacillus Cloning Methods," in DNA Cloning: A Practical Approach, Glover (ed.) (IRL Press 1985)). Standard techniques for propagating vectors in prokaryotic hosts are well-known to those of skill in the art (see, for example, Ausubel *et al.* (eds.), Short Protocols in Molecular Biology, *3rd Edition* (John Wiley & Sons 1995); Wu *et al.*, Methods in Gene Biotechnology (CRC Press, Inc. 1997)). In one embodiment, the methods of the present

invention use IL-28 or IL-29 expressed in the W3110 strain, which has been deposited at the American Type Culture Collection (ATCC) as ATCC # 27325.

When large scale production of IL-28 or IL-29 using the expression system of the present invention is required, batch fermentation can be used. Generally, batch fermentation comprises that a first stage seed flask is prepared by growing *E. coli* strains expressing IL-28 or IL-29 in a suitable medium in shake flask culture to allow for growth to an optical density (OD) of between 5 and 20 at 600 nm. A suitable medium would contain nitrogen from a source(s) such as ammonium sulfate, ammonium phosphate, ammonium chloride, yeast extract, hydrolyzed animal proteins, hydrolyzed plant proteins or hydrolyzed caseins. Phosphate will be supplied from potassium phosphate, ammonium phosphate, phosphoric acid or sodium phosphate. Other components would be magnesium chloride or magnesium sulfate, ferrous sulfate or ferrous chloride, and other trace elements. Growth medium can be supplemented with carbohydrates, such as fructose, glucose, galactose, lactose, and glycerol, to improve growth. Alternatively, a fed batch culture is used to generate a high yield of IL-28 or IL-29 protein. The IL-28 or IL-29 producing *E. coli* strains are grown under conditions similar to those described for the first stage vessel used to inoculate a batch fermentation.

Following fermentation the cells are harvested by centrifugation, re-suspended in homogenization buffer and homogenized, for example, in an APV-Gaulin homogenizer (Invensys APV, Tonawanda, New York) or other type of cell disruption equipment, such as bead mills or sonicators. Alternatively, the cells are taken directly from the fermentor and homogenized in an APV-Gaulin homogenizer. The washed inclusion body prep can be solubilized using guanidine hydrochloride (5-8 M) or urea (7 – 8 M) containing a reducing agent such as beta mercaptoethanol (10 – 100 mM) or dithiothreitol (5-50 mM). The solutions can be prepared in Tris, phopshate, HEPES or other appropriate buffers. Inclusion bodies can also be solubilized with urea (2-4 M) containing sodium lauryl sulfate (0.1-2%). In the process for recovering purified IL-28 or IL-29 from transformed *E. coli* host strains in which the IL-28 or IL-29 is accumulates as refractile inclusion bodies, the cells are disrupted and the inclusion bodies are recovered by centrifugation. The inclusion bodies are then solubilized and denatured in 6 M guanidine hydrochloride containing a reducing agent. The reduced

IL-28 or IL-29 is then oxidized in a controlled renaturation step. Refolded IL-28 or IL-29 can be passed through a filter for clarification and removal of insoluble protein. The solution is then passed through a filter for clarification and removal of insoluble protein. After the IL-28 or IL-29 protein is refolded and concentrated, the refolded IL-28 or IL-29 protein is captured in dilute buffer on a cation exchange column and purified using hydrophobic interaction chromatography.

Cultured mammalian cells are suitable hosts within the present invention. Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-5, 1982), DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 1993, and viral vectors (Miller and Rosman, BioTechniques 7:980-90, 1989; Wang and Finer, Nature Med. 2:714-6, 1996). The production of recombinant polypeptides in cultured mammalian cells is disclosed, for example, by Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Manassas, VA. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and are able to pass the gene of interest to their progeny are referred to as "stable transfectants." A preferred selectable marker is a gene encoding resistance to the

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

Other higher eukaryotic cells can also be used as hosts, including plant cells, insect cells and avian cells. The use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., J. Biosci. (Bangalore) 11:47-58, 1987. Transformation of insect cells and production of foreign polypeptides therein is disclosed by Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463. Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica nuclear polyhedrosis virus* (AcNPV). See, King, L.A. and Possee, R.D., The Baculovirus Expression System: A Laboratory Guide, London, Chapman & Hall; O'Reilly, D.R. et al., Baculovirus Expression Vectors: A Laboratory Manual, New York, Oxford University Press., 1994; and, Richardson, C. D., Ed., Baculovirus Expression Protocols. Methods in Molecular Biology, Totowa, NJ, Humana Press, 1995. The second method of making recombinant baculovirus utilizes a transposon-based system described by Luckow (Luckow, V.A, et al., J Virol 67:4566-79, 1993). This system is sold in the Bac-to-Bac kit (Life Technologies, Rockville, MD). This system utilizes a transfer vector, pFastBac1™ (Life Technologies) containing a Tn7 transposon to move the DNA encoding the IL-28 or IL-29 polypeptide into a baculovirus genome maintained in E. coli as a large plasmid called a "bacmid." The pFastBac1™ transfer vector utilizes the AcNPV polyhedrin promoter to drive the expression of the gene of interest, in this case

IL-28 or IL-29. However, pFastBac1™ can be modified to a considerable degree. The polyhedrin promoter can be removed and substituted with the baculovirus basic protein promoter (also known as P*cor*, p6.9 or MP promoter) which is expressed earlier in the baculovirus infection, and has been shown to be advantageous for expressing secreted proteins. See, Hill-Perkins, M.S. and Possee, R.D., J. Gen. Virol. 71:971-6, 1990; Bonning, B.C. et al., J. Gen. Virol. 75:1551-6, 1994; and, Chazenbalk, G.D., and Rapoport, B., J. Biol. Chem. 270:1543-9, 1995. In such transfer vector constructs, a short or long version of the basic protein promoter can be used. Moreover, transfer vectors can be constructed which replace the native IL-28 or IL-29 secretory signal sequences with secretory signal sequences derived from insect proteins. For example, a secretory signal sequence from Ecdysteroid Glucosyltransferase (EGT), honey bee Melittin (Invitrogen, Carlsbad, CA), or baculovirus gp67 (PharMingen, San Diego, CA) can be used in constructs to replace the native IL-28 or IL-29 secretory signal sequence. In addition, transfer vectors can include an in-frame fusion with DNA encoding an epitope tag at the C- or N-terminus of the expressed IL-28 or IL-29 polypeptide, for example, a Glu-Glu epitope tag (Grussenmeyer, T. et al., Proc. Natl. Acad. Sci. 82:7952-4, 1985). Using techniques known in the art, a transfer vector containing IL-28 or IL-29 is transformed into *E. Coli*, and screened for bacmids which contain an interrupted lacZ gene indicative of recombinant baculovirus. The bacmid DNA containing the recombinant baculovirus genome is isolated, using common techniques, and used to transfect *Spodoptera frugiperda* cells, e.g. Sf9 cells. Recombinant virus that expresses IL-28 or IL-29 is subsequently produced. Recombinant viral stocks are made by methods commonly used the art.

The recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda*. See, in general, Glick and Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994. Another suitable cell line is the High FiveO™ cell line (Invitrogen) derived from *Trichoplusia ni* (U.S. Patent No. 5,300,435)..

Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include *Saccharomyces cerevisiae*, *Pichia pastoris*, and *Pichia methanolica*. Methods for transforming *S.*

cerevisiae cells with exogenous DNA and producing recombinant polypeptides therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in *Saccharomyces cerevisiae* is the *POT1* vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454. Transformation systems for other yeasts, including *Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii* and *Candida maltosa* are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-65, 1986 and Cregg, U.S. Patent No. 4,882,279. *Aspergillus* cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming *Acremonium chrysogenum* are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming *Neurospora* are disclosed by Lambowitz, U.S. Patent No. 4,486,533. The use of *Pichia methanolica* as host for the production of recombinant proteins is disclosed in U.S. Patent Nos. 5,955,349, 5,888,768 and 6,001,597, U.S. Patent No. 5,965,389, U.S. Patent No. 5,736,383, and U.S. Patent No. 5,854,039.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥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 or protein is substantially free of other polypeptides or proteins, particularly those of animal origin.

Expressed recombinant IL-28 or IL-29 proteins (including chimeric polypeptides and multimeric proteins) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography according to conventional procedures. See, for example, Grussenmeyer et al., supra. Maltose binding protein fusions are purified on an amylose column according to methods known in the art.

IL-28 or IL-29 polypeptides can also be prepared through chemical synthesis according to methods known in the art, including exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, J. Am. Chem. Soc. 85:2149, 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, *Chem. Pept. Prot.* 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989. In vitro synthesis is particularly advantageous for the preparation of smaller polypeptides.

Using methods known in the art, IL-28 or IL-29 proteins can be prepared as monomers or multimers; glycosylated or non-glycosylated; pegylated or non-pegylated; fusion proteins; and may or may not include an initial methionine amino acid residue. IL-28 or IL-29 conjugates used for therapy may comprise pharmaceutically acceptable water-soluble polymer moieties. Conjugation of interferons with water-soluble polymers has been shown to enhance the circulating half-life of the interferon, and to reduce the immunogenicity of the polypeptide (see, for example, Nieforth *et al.*, Clin. Pharmacol. Ther. 59:636 (1996), and Monkarsh *et al.*, Anal. Biochem. 247:434 (1997)).

Suitable water-soluble polymers include polyethylene glycol (PEG), monomethoxy-PEG, mono-(C1-C10)alkoxy-PEG, aryloxy-PEG, poly-(N-vinyl pyrrolidone)PEG, tresyl monomethoxy PEG, monomethoxy-PEG propionaldehyde,

PEG propionaldehyde, *bis*-succinimidyl carbonate PEG, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (*e.g.*, glycerol), monomethoxy-PEG butyraldehyde, PEG butyraldehyde, monomethoxy-PEG acetaldehyde, PEG acetaldehyde, methoxyl PEG-succinimidyl propionate, methoxyl PEG-succinimidyl butanoate, polyvinyl alcohol, dextran, cellulose, or other carbohydrate-based polymers. Suitable PEG may have a molecular weight from about 600 to about 60,000, including, for example, 5,000 daltons, 12,000 daltons, 20,000 daltons, 30,000 daltons, and 40,000 daltons, which can be linear or branched. A IL-28 or IL-29 conjugate can also comprise a mixture of such water-soluble polymers.

One example of a IL-28 or IL-29 conjugate comprises a IL-28 or IL-29 moiety and a polyalkyl oxide moiety attached to the *N*-terminus of the IL-28 or IL-29 moiety. PEG is one suitable polyalkyl oxide. As an illustration, IL-28 or IL-29 can be modified with PEG, a process known as "PEGylation." PEGylation of IL-28 or IL-29 can be carried out by any of the PEGylation reactions known in the art (see, for example, EP 0 154 316, Delgado *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems 9:249 (1992), Duncan and Spreafico, Clin. Pharmacokinet. 27:290 (1994), and Francis *et al.*, Int J Hematol 68:1 (1998)). For example, PEGylation can be performed by an acylation reaction or by an alkylation reaction with a reactive polyethylene glycol molecule. In an alternative approach, IL-28 or IL-29 conjugates are formed by condensing activated PEG, in which a terminal hydroxy or amino group of PEG has been replaced by an activated linker (see, for example, Karasiewicz *et al.*, U.S. Patent No. 5,382,657).

PEGylation by acylation typically requires reacting an active ester derivative of PEG with a IL-28 or IL-29 polypeptide. An example of an activated PEG ester is PEG esterified to *N*-hydroxysuccinimide. As used herein, the term "acylation" includes the following types of linkages between IL-28 or IL-29 and a water-soluble polymer: amide, carbamate, urethane, and the like. Methods for preparing PEGylated IL-28 or IL-29 by acylation will typically comprise the steps of (a) reacting an IL-28 or IL-29 polypeptide with PEG (such as a reactive ester of an aldehyde derivative of PEG) under conditions whereby one or more PEG groups attach to IL-28 or IL-29, and (b) obtaining the reaction product(s). Generally, the optimal reaction conditions for

acylation reactions will be determined based upon known parameters and desired results. For example, the larger the ratio of PEG: IL-28 or IL-29, the greater the percentage of polyPEGylated IL-28 or IL-29 product.

PEGylation by alkylation generally involves reacting a terminal aldehyde, e.g., propionaldehyde, butyraldehyde, acetaldehyde, and the like, derivative of PEG with IL-28 or IL-29 in the presence of a reducing agent. PEG groups are preferably attached to the polypeptide via a $-CH_2-NH_2$ group.

Derivatization via reductive alkylation to produce a monoPEGylated product takes advantage of the differential reactivity of different types of primary amino groups available for derivatization. Typically, the reaction is performed at a pH that allows one to take advantage of the pKa differences between the ε-amino groups of the lysine residues and the α-amino group of the *N*-terminal residue of the protein. By such selective derivatization, attachment of a water-soluble polymer that contains a reactive group such as an aldehyde, to a protein is controlled. The conjugation with the polymer occurs predominantly at the *N*-terminus of the protein without significant modification of other reactive groups such as the lysine side chain amino groups.

Reductive alkylation to produce a substantially homogenous population of monopolymer IL-28 or IL-29 conjugate molecule can comprise the steps of: (a) reacting a IL-28 or IL-29 polypeptide with a reactive PEG under reductive alkylation conditions at a pH suitable to permit selective modification of the α-amino group at the amino terminus of the IL-28 or IL-29, and (b) obtaining the reaction product(s). The reducing agent used for reductive alkylation should be stable in aqueous solution and preferably be able to reduce only the Schiff base formed in the initial process of reductive alkylation. Preferred reducing agents include sodium borohydride, sodium cyanoborohydride, dimethylamine borane, trimethylamine borane, and pyridine borane.

For a substantially homogenous population of monopolymer IL-28 or IL-29 conjugates, the reductive alkylation reaction conditions are those that permit the selective attachment of the water-soluble polymer moiety to the *N*-terminus of IL-28 or IL-29. Such reaction conditions generally provide for pKa differences between the lysine amino groups and the α-amino group at the *N*-terminus. The pH also affects the ratio of polymer to protein to be used. In general, if the pH is lower, a larger excess of polymer to protein will be desired because the less reactive the *N*-terminal α-group, the

more polymer is needed to achieve optimal conditions. If the pH is higher, the polymer: IL-28 or IL-29 need not be as large because more reactive groups are available. Typically, the pH will fall within the range of 3 - 9, or 3 - 6. Another factor to consider is the molecular weight of the water-soluble polymer. Generally, the higher the molecular weight of the polymer, the fewer number of polymer molecules which may be attached to the protein. For PEGylation reactions, the typical molecular weight is about 2 kDa to about 100 kDa, about 5 kDa to about 50 kDa, about 12 kDa to about 40 kDa, or about 20kDa to about 30 kDa. The molar ratio of water-soluble polymer to IL-28 or IL-29 will generally be in the range of 1:1 to 100:1. Typically, the molar ratio of water-soluble polymer to IL-28 or IL-29 will be 1:1 to 20:1 for polyPEGylation, and 1:1 to 5:1 for monoPEGylation.

General methods for producing conjugates comprising interferon and water-soluble polymer moieties are known in the art. See, for example, Karasiewicz *et al.*, U.S. Patent No. 5,382,657, Greenwald *et al.,* U.S. Patent No. 5,738, 846, Nieforth *et al.,* Clin. Pharmacol. Ther. 59:636 (1996), Monkarsh *et al.,* Anal. Biochem. 247:434 (1997). PEGylated species can be separated from unconjugated IL-28 or IL-29 polypeptides using standard purification methods, such as dialysis, ultrafiltration, ion exchange chromatography, affinity chromatography, size exclusion chromatography, and the like.

The IL-28 or IL-29 molecules of the present invention are capable of specifically binding the IL-28 receptor and/or acting as an antumor agent. The binding of IL-28 or Il-29 polypeptides to the IL-28 receptor can be assayed using established approaches. IL-28 or IL-29 can be iodinated using an iodobead (Pierce, Rockford, IL) according to manufacturer``s directions, and the ^{125}I-IL-28 or ^{125}I-IL-29 can then be used as described below.

In a first approach fifty nanograms of ^{125}I-IL-28 or ^{125}I-IL-29 can be combind with 1000ng of IL-28 receptor human IgG fusion protein, in the presence or absence of possible binding competitors including unlabeled IL-28 or IL-29. The same binding reactions would also be performed substituting other cytokine receptor human IgG fusions as controlsfor specificity. Following incubation at 4°C, protein–G (Zymed, SanFransisco, CA) is added to the reaction, to capture the receptor-IgG fusions and any proteins bound to them, and the reactions are incubated another hour at 4°C. The

protein-G sepharose is then collected, washed three times with PBS and ^{125}I-IL-28 or ^{125}I-IL-29 bound is measure by gamma counter (Packard Instruments, Downers Grove,IL).

In a second approach, the ability of molecules to inhibit the binding of ^{125}I-IL-28 or ^{125}I-IL-29 to plate bound receptors can be assayed. A fragment of the IL-28 receptor, representing the extracellular, ligand binding domain, can be adsorbed to the wells of a 96 well plate by incubating 100 μl of 1 g/mL solution of receptor in the plate overnight. In a second form, a receptor-human IgG fusion can be bound to the wells of a 96 well plate that has been coated with an antibody directed against the human IgG portion of the fusion protein. Following coating of the plate with receptor the plate is washed, blocked with SUPERBLOCK (Pierce, Rockford, IL) and washed again. Solutions containing a fixed concentration of ^{125}I-IL-28 or ^{125}I-IL-29 with or without increasing concentrations of potential binding competitors including, IL-28, IL-29, IL-28 and IL-29, and 100 μl of the solution added to appropriate wells of the plate. Following a one hour incubation at 4°C the plate is washed and the amount ^{125}I-IL-28 or ^{125}I-IL-29 bound determined by counting (Topcount, Packard Instruments, Downers grove, IL). The specificity of binding of ^{125}I-IL-28 or ^{125}I-IL-29 can be defined by receptor molecules used in these binding assays as well as by the molecules used as inhibitors.

In addition to pegylation, human albumin can be genetically coupled to a polypeptide of the present invention to prolong its half-life. Human albumin is the most prevalent naturally occurring blood protein in the human circulatory system, persisting in circulation in the body for over twenty days. Research has shown that therapeutic proteins genetically fused to human albumin have longer half-lives. An IL28 or IL29 albumin fusion protein, like pegylation, may provide patients with long-acting treatment options that offer a more convenient administration schedule, with similar or improved efficacy and safety compared to currently available treatments (U.S. Patent No. 6,165,470; Syed et al., Blood, 89(9):3243-3253 (1997); Yeh et al., Proc. Natl. Acad. Sci. USA, 89:1904-1908 (1992); and Zeisel et al., Horm. Res., 37:5-13 (1992)).

Like the aforementioned peglyation and human albumin, an Fc portion of the human IgG molecule can be fused to a polypeptide of the present invention. The

resultant fusion protein may have an increased circulating half-life due to the Fc moiety (U.S. Patent No. 5,750,375, U.S. Patent No. 5843,725, U.S. Patent No. 6,291,646; Barouch et al., Journal of Immunology, 61:1875-1882 (1998); Barouch et al., Proc. Natl. Acad. Sci. USA, 97(8):4192-4197 (April 11, 2000); and Kim et al., Transplant Proc., 30(8):4031-4036 (Dec. 1998)).

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as $F(ab')_2$ and Fab fragments, single chain antibodies, and the like, including genetically engineered antibodies. 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. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains. Antibodies are defined to be specifically binding if they bind to IL-28 or IL-29 polypeptide or protein with an affinity at least 10-fold greater than the binding affinity to control (non- IL-28 and IL-29) polypeptide or protein. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, Ann. NY Acad. Sci. 51: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982, which is incorporated herein by reference). The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-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.

A variety of assays known to those skilled in the art can be utilized to detect antibodies which specifically bind to IL-28 or IL-29 polypeptides. Exemplary assays are described in detail in Using Antibodies: A Laboratory Manual, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1999. Representative examples of such assays include: concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

For certain applications, including *in vitro* and *in vivo* diagnostic uses, it is advantageous to employ labeled antibodies. 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 of the present invention 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(e.g., inhibition of cell proliferation). See, in general, Ramakrishnan et al., Cancer Res. 56:1324-1330, 1996.

Administration of a pharmaceutical formulation to a patient can be topical, 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. In general, pharmaceutical formulations will include a IL-28 or IL-29 polypeptide in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, etc. Methods of formulation are well known in the art and are disclosed, for example, in *Remington: The Science and Practice of Pharmacy,* Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. An IL-28 or IL-29 polypeptide will preferably be used in a concentration of about 10 to 100 μg/ml of total volume, although concentrations in the range of 1 ng/ml to 1000 μg/ml may be used. For topical application, such as for the promotion of wound healing, the protein will be applied in the range of 0.1-10 μg/cm^2 of wound area, with the exact dose determined by

the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Determination of dose is within the level of ordinary skill in the art. Dosing is daily or intermittently over the period of treatment. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. Sustained release formulations can also be employed. In general, a therapeutically effective amount of IL-28 or IL-29 is an amount sufficient to produce a clinically significant change in the treated condition, such as a clinically significant change in hematopoietic or immune function, a significant reduction in morbidity, or a significantly increased histological score.

As an illustration, pharmaceutical formulations may be supplied as a kit comprising a container that comprises an IL-28 or IL29 polypeptide of the present invention. Therapeutic polypeptides can be provided in the form of an injectable solution for single or multiple doses, or as a sterile powder that will be reconstituted before injection. Alternatively, such a kit can include a dry-powder disperser, liquid aerosol generator, or nebulizer for administration of a therapeutic polypeptide. Such a kit may further comprise written information on indications and usage of the pharmaceutical composition. Moreover, such information may include a statement that the IL-28 or IL29 polypeptide formulation is contraindicated in patients with known hypersensitivity to IL-28 or IL29 polypeptide.

B. The Use of IL-28 and IL-29 to Treat Cancer

IL-28 and IL-29 polypeptides of the present invention have been shown to have an antiviral effect that is similar to interferon-α (See WO 04/037995). Interferon has been approved in the United States for treatment of autoimmune diseases, condyloma acuminatum, chronic hepatitis C, bladder carcinoma, cervical carcinoma, laryngeal papillomatosis, fungoides mycosis, chronic hepatitis B, Kaposi's sarcoma in patients infected with human immunodeficiency virus, malignant melanoma, hairy cell leukemia, and multiple sclerosis. In addition, IL-28 and IL-29 polypeptides may be used to treat forms of arteriosclerosis, such as atherosclerosis, by inhibiting cell proliferation. Accordingly, the present invention contemplates the use of IL-28 or IL-29 polypeptides, fusion proteins, and fragments thereof having IL-28 and IL-29 activity to treat such conditions, as well as to treat retinopathy. The present

invention provides for the use of IL-28 and IL-29 proteins, polypeptides, and peptides having IL-28 and IL-29 activity to treat, prevent, inhibit the progression of, delay the onset of, and/or reduce at least one of the conditions or symptoms associated with the lymphoproliferative disorders, including for instance, B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia. In addition, the present invention further provides for the use of IL-28 and IL-29 proteins, polypeptides, and peptides having IL-28 and IL-29 activity to treat, prevent, inhibit the progression of, delay the onset of, and/or reduce the severity or inhibit at least one of the conditions or symptoms associated with the following cancers selected from the group of renal cell carcinoma, cervical cancer (e.g., squamous type and adenocarcinoma), head and neck tumours (e.g., Hypopharyngeal Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Metastatic Squamous Neck Cancer with Occult Primary, Nasopharyngeal Cancer, Oropharyngeal Cancer, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, and Salivary Gland Cancer), melanoma (e.g., malignant melanoma such as Superficial spreading melanoma, Nodular melanoma, and Lentigo maligna melanoma), thyroid carcinoma (e.g., Papillary, Follicular, Medullary, and Anaplastic), malignant gliomas (e.g., gliobastoma multiforme and anaplastic astrocytoma), breast cancer (e.g., ductal carcinoma), colon cancer, lung cancer (e.g., small cell lung cancer, non-small cell lung cancer such as Squamous cell carcinoma, Adenocarcinoma and Large cell carcinoma, and mesothelioma), pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer (e.g., Osteosarcoma, Ewing's sarcoma, Chondrosarcoma, Spindle cell sarcoma, and Chordoma).

Interferons have also been shown to induce the expression of antigens by cultured cells (see, for example, Auth *et al.*, Hepatology 18:546 (1993), Guadagni *et al.*, Int. J. Biol. Markers 9:53 (1994), Girolomoni *et al.*, Eur. J. Immunol. 25:2163 (1995), and Maciejewski *et al.*, Blood 85:3183 (1995). This activity enhances the ability to identify new tumor associated antigens *in vitro*. Moreover, the ability of interferons to augment the level of expression of human tumor antigens indicates that interferons can be useful in an adjuvant setting for immunotherapy or enhance immunoscintigraphy using anti-tumor antigen antibodies (Guadagni *et al.*, Cancer

Immunol. Immunother. 26:222 (1988); Guadagni *et al.*, Int. J. Biol. Markers 9:53 (1994)). Thus, the present invention includes the use of IL-28 or IL-29 proteins, polypeptides and peptides having IL-28 and IL-29 activity as an adjuvant for immunotherapy or to improve immunoscintigraphy using anti-tumor antigen antibodies.

The activity and effect of an IL-28 or IL-29 polypeptide on tumor progression and metastasis can be measured *in vivo*. Several syngeneic mouse models have been developed to study the influence of polypeptides, compounds or other treatments on tumor progression. In these models, tumor cells passaged in culture are implanted into mice of the same strain as the tumor donor. The cells will develop into tumors having similar characteristics in the recipient mice, and metastasis will also occur in some of the models. Appropriate tumor models for our studies include the Lewis lung carcinoma (ATCC No. CRL-1642) and B16 melanoma (ATCC No. CRL-6323), amongst others. These are both commonly used tumor lines, syngeneic to the C57BL6 mouse, that are readily cultured and manipulated *in vitro*. Tumors resulting from implantation of either of these cell lines are capable of metastasis to the lung in C57BL6 mice. The Lewis lung carcinoma model has recently been used in mice to identify an inhibitor of angiogenesis (O'Reilly MS, et al. Cell 79: 315-328,1994). C57BL6/J mice are treated with an experimental agent either through daily injection of recombinant protein, agonist or antagonist or a one-time injection of recombinant adenovirus. Three days following this treatment, 10^5 to 10^6 cells are implanted under the dorsal skin. Alternatively, the cells themselves may be infected with recombinant adenovirus, such as one expressing IL-28 and IL-29, before implantation so that the protein is synthesized at the tumor site or intracellularly, rather than systemically. The mice normally develop visible tumors within 5 days. The tumors are allowed to grow for a period of up to 3 weeks, during which time they may reach a size of 1500 - 1800 mm^3 in the control treated group. Tumor size and body weight are carefully monitored throughout the experiment. At the time of sacrifice, the tumor is removed and weighed along with the lungs and the liver. The lung weight has been shown to correlate well with metastatic tumor burden. As an additional measure, lung surface metastases are counted. The resected tumor, lungs and liver are prepared for histopathological examination, immunohistochemistry, and *in situ* hybridization, using methods known in

the art and described herein. The influence of the expressed polypeptide in question, e.g., Cysteine mutant IL-28 and IL-29, on the ability of the tumor to recruit vasculature and undergo metastasis can thus be assessed. In addition, aside from using adenovirus, the implanted cells can be transiently transfected with IL-28 and IL-29. Use of stable IL-28 or IL-29 transfectants as well as use of induceable promoters to activate IL-28 or IL-29 expression *in vivo* are known in the art and can be used in this system to assess induction of metastasis. Moreover, purified IL-28 or IL-29 conditioned media can be directly injected in to this mouse model, and hence be used in this system. For general reference see, O'Reilly MS, et al. Cell 79:315-328, 1994; and Rusciano D, et al. Murine Models of Liver Metastasis. Invasion Metastasis 14:349-361, 1995.

The present invention provides for a method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161 wherein the cancer is selected from the group of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, malignant gliomas, breast cancer, colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39,

40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161, wherein the cancer is selected from the group of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, malignant gliomas, breast cancer, colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; and a pharmaceutically acceptable vehicle; and wherein the cancer is selected from the group of renal cell carcinoma, cervical cancer (e.g., squamous type and adenocarcinoma), head and neck tumours (e.g., Hypopharyngeal Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Metastatic Squamous Neck Cancer with Occult Primary, Nasopharyngeal Cancer, Oropharyngeal Cancer, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, and Salivary Gland Cancer), melanoma (e.g., malignant

melanoma such as Superficial spreading melanoma, Nodular melanoma, and Lentigo maligna melanoma), thyroid carcinoma (e.g., Papillary, Follicular, Medullary, and Anaplastic), malignant gliomas (e.g., gliobastoma multiforme and anaplastic astrocytoma), breast cancer (e.g., ductal carcinoma), colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer (e.g., Osteosarcoma, Ewing's sarcoma, Chondrosarcoma, Spindle cell sarcoma, and Chordoma). The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a second polypeptide; a pharmaceutically acceptable vehicle; and wherein the cancer is selected from the group of renal cell carcinoma, cervical cancer (e.g., squamous type and adenocarcinoma), head and neck tumours (e.g., Hypopharyngeal Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Metastatic Squamous Neck Cancer with Occult Primary, Nasopharyngeal Cancer, Oropharyngeal Cancer, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, and Salivary Gland Cancer), melanoma (e.g.,

malignant melanoma such as Superficial spreading melanoma, Nodular melanoma, and Lentigo maligna melanoma), thyroid carcinoma (e.g., Papillary, Follicular, Medullary, and Anaplastic), malignant gliomas (e.g., gliobastoma multiforme and anaplastic astrocytoma), breast cancer (e.g., ductal carcinoma), colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer (e.g., Osteosarcoma, Ewing's sarcoma, Chondrosarcoma, Spindle cell sarcoma, and Chordoma). The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of inhibiting the progressive of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161, wherein the cancer is selected from the group of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, malignant gliomas, breast cancer, colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer. The polypeptide may have at

least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of inhibiting the progression of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a second polypeptide; a pharmaceutically acceptable vehicle; and wherein the cancer is selected from the group of renal cell carcinoma, cervical cancer (e.g., squamous type and adenocarcinoma), head and neck tumours (e.g., Hypopharyngeal Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Metastatic Squamous Neck Cancer with Occult Primary, Nasopharyngeal Cancer, Oropharyngeal Cancer, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, and Salivary Gland Cancer), melanoma (e.g., malignant melanoma such as Superficial spreading melanoma, Nodular melanoma, and Lentigo maligna melanoma), thyroid carcinoma (e.g., Papillary, Follicular, Medullary, and Anaplastic), malignant gliomas (e.g., gliobastoma multiforme and anaplastic astrocytoma), breast cancer (e.g., ductal carcinoma), colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer (e.g., Osteosarcoma, Ewing's sarcoma, Chondrosarcoma, Spindle cell sarcoma, and Chordoma). The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37,

38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of delaying the onset of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161, wherein the cancer is selected from the group of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, malignant gliomas, breast cancer, colon cancer, lung, cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The

patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of delaying the onset of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a second polypeptide; a pharmaceutically acceptable vehicle; and wherein the cancer is selected from the group of renal cell carcinoma, cervical cancer (e.g., squamous type and adenocarcinoma), head and neck tumours (e.g., Hypopharyngeal Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Metastatic Squamous Neck Cancer with Occult Primary, Nasopharyngeal Cancer, Oropharyngeal Cancer, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, and Salivary Gland Cancer), melanoma (e.g., malignant melanoma such as Superficial spreading melanoma, Nodular melanoma, and Lentigo maligna melanoma), thyroid carcinoma (e.g., Papillary, Follicular, Medullary, and Anaplastic), malignant gliomas (e.g., gliobastoma multiforme and anaplastic astrocytoma), breast cancer (e.g., ductal carcinoma), colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer (e.g., Osteosarcoma, Ewing's sarcoma, Chondrosarcoma, Spindle cell sarcoma, and Chordoma). The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an

Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of reducing the severity of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161, wherein the cancer is selected from the group of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, malignant gliomas, breast cancer, colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of reducing the severity of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a

second polypeptide; a pharmaceutically acceptable vehicle; and wherein the cancer is selected from the group of renal cell carcinoma, cervical cancer (e.g., squamous type and adenocarcinoma), head and neck tumours (e.g., Hypopharyngeal Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Metastatic Squamous Neck Cancer with Occult Primary, Nasopharyngeal Cancer, Oropharyngeal Cancer, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, and Salivary Gland Cancer), melanoma (e.g., malignant melanoma such as Superficial spreading melanoma, Nodular melanoma, and Lentigo maligna melanoma), thyroid carcinoma (e.g., Papillary, Follicular, Medullary, and Anaplastic), malignant gliomas (e.g., gliobastoma multiforme and anaplastic astrocytoma), breast cancer (e.g., ductal carcinoma), colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer (e.g., Osteosarcoma, Ewing's sarcoma, Chondrosarcoma, Spindle cell sarcoma, and Chordoma). The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161,

wherein the cancer is selected from the group of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, malignant gliomas, breast cancer, colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of cancer comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a second polypeptide; a pharmaceutically acceptable vehicle; and wherein the cancer is selected from the group of renal cell carcinoma, cervical cancer (e.g., squamous type and adenocarcinoma), head and neck tumours (e.g., Hypopharyngeal Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Metastatic Squamous Neck Cancer with Occult Primary, Nasopharyngeal Cancer, Oropharyngeal Cancer, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, and Salivary Gland Cancer), melanoma (e.g., malignant melanoma such as Superficial spreading melanoma, Nodular melanoma, and Lentigo maligna melanoma), thyroid carcinoma (e.g., Papillary, Follicular, Medullary, and Anaplastic), malignant gliomas (e.g.,

gliobastoma multiforme and anaplastic astrocytoma), breast cancer (e.g., ductal carcinoma), colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer (e.g., Osteosarcoma, Ewing's sarcoma, Chondrosarcoma, Spindle cell sarcoma, and Chordoma). The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of non-Hogkin's lymphoma comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161, wherein the at least one of the conditions or symptoms is selected from the group of painless swelling of a lymph node in the neck, armpit or groin, night sweats, unexplained fever, weight loss, and excessive tiredness. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol

moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of non-Hodgkin's lymphoma comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a second polypeptide; and a pharmaceutically acceptable vehicle; wherein the at least one of the conditions or symptoms is selected from the group of painless swelling of a lymph node in the neck, armpit or groin, night sweats, unexplained fever, weight loss, and excessive tiredness. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of multiple myeloma comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at

least 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161, wherein the at least one of the conditions or symptoms is selected from the group of back pain, loss of height, anaemia, kidney damage, repeated respiratory infections, and hypercalcaemia. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of multiple myeloma comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a second polypeptide; and a pharmaceutically acceptable vehicle; wherein the at least one of the conditions or symptoms is selected from the group of back pain, loss of height, anaemia, kidney damage, repeated respiratory infections, and hypercalcaemia. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The

polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of head and neck tumours comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161, wherein the at least one of the conditions or symptoms is selected from the group of an ulcer or sore area in the head or neck that does not heal within a few weeks, difficulty in swallowing, trouble with breathing or speaking, a numb feeling in the mouth, nose bleeds, persistent earache, difficulty in hearing, and swelling or lump in the mouth or neck. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

The present invention also provides a method of inhibiting at least one of the conditions or symptoms of head and neck tumours comprising administering to a

patient in need thereof a therapeutically effective amount of a formulation comprising: a polypeptide having at least 90% or 95% sequence identity with a sequence selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161; a second polypeptide; and a pharmaceutically acceptable vehicle; wherein the at least one of the conditions or symptoms is selected from the group of an ulcer or sore area in the head or neck that does not heal within a few weeks, difficulty in swallowing, trouble with breathing or speaking, a numb feeling in the mouth, nose bleeds, persistent earache, difficulty in hearing, and swelling or lump in the mouth or neck. The polypeptide may have at least 15, at least 30, at least 45, or at least 60 sequential amino acids to SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human. The second polypeptide may be an Interferon molecule, such as Interferon-alpha, Interferon-beta, or Interferon-gamma, another therapeutic agent, such as IL-2 and/or IL-21, or combination thereof.

There are four main types of malignant melanoma which occur in the skin. These are known as cutaneous melanoma:

Superficial spreading melanoma is the most common type of melanoma. About 7 out of 10 (70%) are this type. They occur mostly in middle-aged people. The most common place in women is on the legs, while in men it is more common on the trunk, particularly the back. They tend to start by spreading out across the surface of the skin: this is known as the radial growth phase. If the melanoma is removed at this stage there is a very high chance of cure. If the melanoma is not removed, it will start to grow down deeper into the layers of the skin. There is then a risk that it will spread

in the bloodstream or lymph system to other parts of the body. Nodular melanoma occurs most often on the chest or back. It is most commonly found in middle-aged people. It tends to grow deeper into the skin quite quickly if it is not removed. This type of melanoma is often raised above the rest of the skin surface and feels like a bump. It may be very dark brown-black or black. Lentigo maligna melanoma is most commonly found on the face, particularly in older people. It grows slowly and may take several years to develop. Acral melanoma is usually found on the palms of the hands, soles of the feet or around the toenails. Other very rare types of melanoma of the skin include amelanotic melanoma (in which the melanoma loses its pigment and appears as a white area) and desmoplastic melanoma (which contains fibrous scar tissue). Malignant melanoma can start in parts of the body other than the skin but this is very rare. The parts of the body that may be affected are the eye, the mouth, under the fingernails (known as subungual melanoma) the vulval or vaginal tissues, or internally (cancerbacup internet website).

Most melanomas start with a change in the appearance of normal skin. This can look like an abnormal new mole. Less than a third develop in existing moles. It can be difficult to tell the difference between a mole and a melanoma, but the following checklist can be used to help. It is known as the ABCD list. Asymmetry – Ordinary moles are usually symmetrical in shape. Melanomas are likely to be irregular or asymmetrical. Border – Moles usually have a well-defined regular border. Melanomas are more likely to have an irregular border with jagged edges. Colour – Moles are usually a uniform brown. Melanomas tend to have more than one colour. They may be varying shades of brown mixed with black, red, pink, white or a bluish tint. Diameter – Moles are normally no bigger than the blunt end of a pencil (about 6mm across). Melanomas are usually more than 7mm in diameter. Normal moles can be raised up from the skin and/or may be hairy. Itching, crusting or bleeding may also occur in melanomas – these are less common signs but should not be ignored (cancerbacup internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a murine melanoma model similar to that described in Hermans et al., Cancer Res. 2003 Dec 1;63(23):8408-13; Ramont et al., Exp Cell Res. 2003 Nov 15;291(1):1-10; Safwat et al., J Exp Ther

Oncol. 2003 Jul-Aug;3(4):161-8; and Fidler, I.J., Nat New Biol. 1973 Apr 4;242(118):148-9.

Chronic myeloid leukaemia (CML) is a rare type of cancer affecting mostly adults. It is a cancer of granulocytes (one of the main types of white blood cells). In CML too many granulocytes are produced and they are released into the blood when they are immature and unable to work properly. The immature white blood cells are known as blasts. The production of other types of blood cells is also disrupted. Normally, white blood cells repair and reproduce themselves in an orderly and controlled manner, but in chronic myeloid leukaemia the process gets out of control and the cells continue to divide and mature abnormally. The disease usually develops very slowly, which is why it is called 'chronic' myeloid leukaemia (cancerbacup internet website).

Because CML develops (progresses) slowly, it is difficult to detect in its early stages. Sometimes it is discovered only when a blood test is done for another reason. The symptoms of CML are often vague and non-specific and are caused by the increased number of abnormal white blood cells in the bone marrow and the reduced number of normal blood cells: a feeling of fullness or a tender lump on the left side of the abdomen. This is because, in CML, the spleen can become enlarged. The spleen is an organ which lies just below the ribs on the left side of the abdomen. It filters the blood and removes worn-out red blood cells. The swelling of the spleen may also cause pressure on the stomach, which can lead to indigestion and poor appetite some people feel tired and look pale, due to a lack of red blood cells (anaemia) due to a lower number of platelets in the blood some people may notice that they bleed or bruise more easily. As well as bruising more easily than normal, a special type of bruising can be seen. This consists of small blood-like spots usually seen on the legs or in the mouth and is called petechiae. Women may find that their periods become very much heavier. However, these symptoms and signs are rare some people may notice a generalised itching. Chronic myeloid leukaemia can occur at any age, but it more commonly affects middle-aged and older people. It is rare in children (cancerbacup internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a murine chronic myeloid leukaemia model similar to that described in Ren, R., Oncogene. 2002 Dec 9;21(56):8629-42; Wertheim et al.,

Oncogene. 2002 Dec 9;21(56):8612-28; and Wolff et al., Blood. 2001 Nov 1;98(9):2808-16.

Non-Hodgkin's lymphomas are a type of cancer of the lymphatic system. There are two main types of lymphoma. One is called Hodgkin's disease (named after Dr Hodgkin, who first described it). The other is called non-Hodgkin's lymphoma. There are about 20 different types of non-Hodgkin's lymphoma. In most cases of Hodgkin's disease, a particular cell known as the Reed-Sternberg cell is found in the biopsies. This cell is not usually found in other lymphomas, so they are called non-Hodgkin's lymphoma. This may not seem a very big difference, but it is important because the treatment for Hodgkin's and non-Hodgkin's lymphomas can be very different (cancerbacup internet website).

Often, the first sign of a non-Hodgkin's lymphoma is a painless swelling of a lymph node in the neck, armpit or groin. Other symptoms may include any of the following: night sweats or unexplained high temperatures (fever); loss of appetite, unexplained weight loss and excessive tiredness; children may develop a cough or breathlessness. They may also complain of abdominal pain or you may notice a lump in your child's abdomen persistent itching of the skin all over the body (cancerbacup internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a murine non-Hodgkin's lymphoma model similar to that described in Ansell et al., Leukemia. 2004 Mar;18(3):616-23; De Jonge et al., J Immunol. 1998 Aug 1;161(3):1454-61; and Slavin et al., Nature. 1978 Apr 13;272(5654):624-6.

Renal cell carcinoma, a form of kidney cancer that involves cancerous changes in the cells of the renal tubule, is the most common type of kidney cancer in adults. Why the cells become cancerous is not known. A history of smoking greatly increases the risk for developing renal cell carcinoma. Some people may also have inherited an increased risk to develop renal cell carcinoma, and a family history of kidney cancer increases the risk. People with von Hippel-Lindau disease, a hereditary disease that affects the capillaries of the brain, commonly also develop renal cell carcinoma. Kidney disorders that require dialysis for treatment also increase the risk for developing renal cell carcinoma. The first symptom is usually blood in the urine. Sometimes both kidneys are involved. The cancer metastasizes or spreads easily, most

often to the lungs and other organs, and about one-third of patients have metastasis at the time of diagnosis (Medline Plus Medical Encyclopedia Internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a murine renal cell carcinoma model similar to that described in Sayers et al., Cancer Res. 1990 Sep 1;50(17):5414-20; Salup et al., Immunol. 1987 Jan 15;138(2):641-7; and Luan et al., Transplantation. 2002 May 27;73(10):1565-72.

The cervix is the neck of the uterus that opens into the vagina. Cervical cancer, also called cervical carcinoma, develops from abnormal cells on the surface of the cervix. Cervical cancer is one of the most common cancers affecting women. Cervical cancer is usually preceded by dysplasia, precancerous changes in the cells on the surface of the cervix. These abnormal cells can progress to invasive cancer. Once the cancer appears it can progress through four stages. The stages are defined by the extent of spread of the cancer. The more the cancer has spread, the more extensive the treatment is likely to be. There are 2 main types of cervical cancer: (1) Squamous type (epidermoid cancer): This is the most common type, accounting for about 80% to 85% of cervical cancers. This cancer may be caused by sexually transmitted diseases. One such sexual disease is the human papillomavirus, which causes venereal warts. The cancerous tumor grows on and into the cervix. This cancer generally starts on the surface of the cervix and may be diagnosed at an early stage by a Pap smear. (2) Adenocarcinoma: This type of cervical cancer develops from the tissue in the cervical glands in the canal of the cervix. Early cervical cancer usually causes no symptoms. The cancer is usually detected by a Pap smear and pelvic exam. This is why you should start having Pap smears and pelvic exams as soon as you become sexually active. Healthy young women who have never been sexually active should have their first annual pelvic exam by age 18. Later stages of cervical cancer cause abnormal vaginal bleeding or a bloodstained discharge at unexpected times, such as between menstrual periods, after intercourse, or after menopause. Abnormal vaginal discharge may be cloudy or bloody or may contain mucus with a bad odor. Advanced stages of the cancer may cause pain (University of Michigan Health System Internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a murine cervical cancer model similar to that described in Ahn et

al., Hum Gene Ther. 2003 Oct 10;14(15):1389-99; Hussain et al., Oncology. 1992;49(3):237-40; and Sengupta et al., Oncology. 1991;48(3):258-61.

Most cancers of the head and neck are of a type called carcinoma (in particular squamous cell carcinoma). Carcinomas of the head and neck start in the cells that form the lining of the mouth, nose, throat or ear, or the surface layer covering the tongue. However, cancers of the head and neck can develop from other types of cells. Lymphoma develops from the cells of the lymphatic system. Sarcoma develops from the supportive cells which make up muscles, cartilage or blood vessels. Melanoma starts from cells called melanocytes, which give colour to the eyes and skin. The symptoms of a head and neck cancer will depend on where it is - for example, cancer of the tongue may cause some slurring of speech. The most common symptoms are an ulcer or sore area in the head or neck that does not heal within a few weeks; difficulty in swallowing, or pain when chewing or swallowing; trouble with breathing or speaking, such as persistent noisy breathing, slurred speech or a hoarse voice; a numb feeling in the mouth; a persistent blocked nose, or nose bleeds; persistent earache, ringing in the ear, or difficulty in hearing; a swelling or lump in the mouth or neck; pain in the face or upper jaw; in people who smoke or chew tobacco, pre-cancerous changes can occur in the lining of the mouth, or on the tongue. These can appear as persistent white patches (leukoplakia) or red patches (erythroplakia). They are usually painless but can sometimes be sore and may bleed (Cancerbacup Internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a murine head and neck tumor model similar to that described in Kuriakose et al., Head Neck. 2000 Jan;22(1):57-63; Cao et al., Clin Cancer Res. 1999 Jul;5(7):1925-34; Hier et al., Laryngoscope. 1995 Oct;105(10):1077-80; Braakhuis et al., Cancer Res. 1991 Jan 1;51(1):211-4; Baker, S.R., Laryngoscope. 1985 Jan;95(1):43-56; and Dong et al., Cancer Gene Ther. 2003 Feb;10(2):96-104.

Papillary and follicular thyroid cancers account for 80 to 90 percent of all thyroid cancers. Both types begin in the follicular cells of the thyroid. Most papillary and follicular thyroid cancers tend to grow slowly. If they are detected early, most can be treated successfully. Medullary thyroid cancer accounts for 5 to 10 percent of thyroid cancer cases. It arises in C cells, not follicular cells. Medullary thyroid cancer is easier to control if it is found and treated before it spreads to other parts of the

body. Anaplastic thyroid cancer is the least common type of thyroid cancer (only 1 to 2 percent of cases). It arises in the follicular cells. The cancer cells are highly abnormal and difficult to recognize. This type of cancer is usually very hard to control because the cancer cells tend to grow and spread very quickly. Early thyroid cancer often does not cause symptoms. But as the cancer grows, symptoms may include: A lump, or nodule, in the front of the neck near the Adam's apple; Hoarseness or difficulty speaking in a normal voice; Swollen lymph nodes, especially in the neck; Difficulty swallowing or breathing; or Pain in the throat or neck (National Cancer Institute's Internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a murine or rat thyroid tumor model similar to that described in Quidville et al., Endocrinology. 2004 May;145(5):2561-71 (mouse model); Cranston et al., Cancer Res. 2003 Aug 15;63(16):4777-80 (mouse model); Zhang et al., Clin Endocrinol (Oxf). 2000 Jun;52(6):687-94 (rat model); and Zhang et al., Endocrinology. 1999 May;140(5):2152-8 (rat model).

Tumors that begin in brain tissue are known as primary tumors of the brain. Primary brain tumors are named according to the type of cells or the part of the brain in which they begin. The most common primary brain tumors are gliomas. They begin in glial cells. There are many types of gliomas. (1) Astrocytoma - The tumor arises from star-shaped glial cells called astrocytes. In adults, astrocytomas most often arise in the cerebrum. In children, they occur in the brain stem, the cerebrum, and the cerebellum. A grade III astrocytoma is sometimes called an anaplastic astrocytoma. A grade IV astrocytoma is usually called a glioblastoma multiforme. (2) Brain stem glioma - The tumor occurs in the lowest part of the brain. Brain stem gliomas most often are diagnosed in young children and middle-aged adults. (3) Ependymoma - The tumor arises from cells that line the ventricles or the central canal of the spinal cord. They are most commonly found in children and young adults. (4) Oligodendroglioma - This rare tumor arises from cells that make the fatty substance that covers and protects nerves. These tumors usually occur in the cerebrum. They grow slowly and usually do not spread into surrounding brain tissue. They are most common in middle-aged adults. The symptoms of brain tumors depend on tumor size, type, and location. Symptoms may be caused when a tumor presses on a nerve or damages a certain area of the brain. They also may be caused when the brain swells or fluid builds up within the skull.

These are the most common symptoms of brain tumors: Headaches (usually worse in the morning); Nausea or vomiting; Changes in speech, vision, or hearing; Problems balancing or walking; Changes in mood, personality, or ability to concentrate; Problems with memory; Muscle jerking or twitching (seizures or convulsions); and Numbness or tingling in the arms or legs (National Cancer Institute's Internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a glioma animal model similar to that described in Schueneman et al., Cancer Res. 2003 Jul 15;63(14):4009-16; Martinet et al., Eur J Surg Oncol. 2003 May;29(4):351-7; Bello et al., Clin Cancer Res. 2002 Nov;8(11):3539-48; Ishikawa et al., Cancer Sci. 2004 Jan;95(1):98-103; Degen et al., J Neurosurg. 2003 Nov;99(5):893-8; Engelhard et al., Neurosurgery. 2001 Mar;48(3):616-24; Watanabe et al., Neurol Res. 2002 Jul;24(5):485-90; and Lumniczky et al., Cancer Gene Ther. 2002 Jan;9(1):44-52.

Multiple myeloma is a type of cancer. It affects certain white blood cells called plasma cells. When cancer involves plasma cells, the body keeps producing more and more of these cells. The unneeded plasma cells -- all abnormal and all exactly alike -- are called myeloma cells. Myeloma cells tend to collect in the bone marrow and in the hard, outer part of bones. Sometimes they collect in only one bone and form a single mass, or tumor, called a plasmacytoma. In most cases, however, the myeloma cells collect in many bones, often forming many tumors and causing other problems. When this happens, the disease is called multiple myeloma. Myeloma cells tend to collect in the bone marrow and in the hard, outer part of bones. Sometimes they collect in only one bone and form a single mass, or tumor, called a plasmacytoma. In most cases, however, the myeloma cells collect in many bones, often forming many tumors and causing other problems. When this happens, the disease is called multiple myeloma. Because people with multiple myeloma have an abnormally large number of identical plasma cells, they also have too much of one type of antibody. These myeloma cells and antibodies can cause a number of serious medical problems: (1) As myeloma cells increase in number, they damage and weaken bones, causing pain and sometimes fractures. Bone pain can make it difficult for patients to move; (2) When bones are damaged, calcium is released into the blood. This may lead to hypercalcemia -- too much calcium in the blood. Hypercalcemia can cause loss of

appetite, nausea, thirst, fatigue, muscle weakness, restlessness, and confusion; (3) Myeloma cells prevent the bone marrow from forming normal plasma cells and other white blood cells that are important to the immune system. Patients may not be able to fight infection and disease; (4) The cancer cells also may prevent the growth of new red blood cells, causing anemia. Patients with anemia may feel unusually tired or weak; and (5) Multiple myeloma patients may have serious problems with their kidneys. Excess antibody proteins and calcium can prevent the kidneys from filtering and cleaning the blood properly. Symptoms of multiple myeloma depend on how advanced the disease is. In the earliest stage of the disease, there may be no symptoms. When symptoms do occur, patients commonly have bone pain, often in the back or ribs. Patients also may have broken bones, weakness, fatigue, weight loss, or repeated infections. When the disease is advanced, symptoms may include nausea, vomiting, constipation, problems with urination, and weakness or numbness in the legs (National Cancer Institute's Internet website). The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a multiple myeloma murine model similar to that described in Oyajobi et al., Blood. 2003 Jul 1;102(1):311-9; Croucher et al., J Bone Miner Res. 2003 Mar;18(3):482-92; Asosingh et al., Hematol J. 2000;1(5):351-6; and Miyakawa et al., Biochem Biophys Res Commun. 2004 Jan 9;313(2):258-62.

The effects of an IL-28 or IL-29 polypeptide, fragment, or fusion protein on tumor response can be evaluated in a human small/non-small cell lung carcinoma xenograft model. Briefly, human tumors are grafted into immunodecicient mice and these mice are treated with IL-28 or IL-29 polypeptide, fragment, or fusion proteins alone or in combination with other agents which can be used to demonstrate the efficacy of the treatment by evaluating tumor growth (Nemati et al., Clin Cancer Res. 2000 May;6(5):2075-86; and Hu et al., Clin Cancer Res. 2004 Nov 15;10(22):7662-70).

The powerful inducer of apoptosis Apo2L/TNF-related apoptosis-inducing ligand (TRAIL) has generated exciting promise as a potential tumour specific cancer therapeutic agent, since it selectively induces apoptosis in transformed versus normal cells. Interferons (IFNs) are important modulators of TRAIL expression, thus the ligand appears to play an important role in surveillance against viral infection and malignant transformation. Fiorucci et al., Curr Pharm Des. 2005;11(7):933-44. IL-28

and IL-29 also appear to be important regulators of TRAIL (See Example 41 where TRAIL is upregulated by IL-29).

C. The Use of IL-28 and IL-29 to Treat Autoimmune Disorders

The present invention provides for a method of treating, preventing, inhibiting the progression of, delaying the onset of, and/or reducing at least one of the conditions or symptoms associated with autoimmune disorder comprising administering to a patient in need thereof a therapeutically effective amount of a polypeptide selected from the group of SEQ ID NOs:2, 4, 6, 13, 15, 17, 19, 21, 23, 25, 27, 29, 36, 37, 38, 39, 40, 41, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, and 161 wherein the autoimmune disorder is selected from the group of selected from the group of multiple sclerosis, arthritis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and psoriasis. The polypeptide may further optionally include a polyethylene glycol moiety, which can be covalently linked to the polypeptide (e.g., amino-terminally). The polyethylene glycol may be linear or branched. The polyethylene glycol may have a molecular weight of about 20kD, 30kD, or 40kD. The polyethylene glycol may be monomethoxy-PEG propionaldehyde. The patient upon which the polypeptide is administered may be a mammal, such as a human.

1. Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disorder where the immune responses of the body are targeted against the body's own proteins, in particular collagen, a protein that is the foundation of multiple tissues, specifically joints. The resulting immune response against collagen leads to destruction of the joints. Over time, the patient can lose the ability to move their fingers and toes and can experience acute pain in the joints and knees. Serum from arthritis patients have increased amounts of TNFα (tumor necrosis factor) and antibodies against collagen, both of which are not only indicators of chronic disease but also contribute towards the pathology of the disease. (Smolen and Stein+er G, Nat. Rev. Drug Discov., 2:473–488, 2003; Firestein, Nature 423:356-361, 2003.) Furthermore, the disease is initiated and mediated by

$CD4^+$ T cells. DCs present collagen as an antigen to $CD4^+$ T cells. The collagen-induced arthritis (CIA) model is a mouse model for rheumatoid arthritis that reflects to large extent the disease seen in humans. (Moore, Methods Mol. Biol. 225:175-179, 2003: Waksman, Scand. J. Immunol., 56:12-34, 2002). Mice are immunized with 2 doses of collagen emulsified in CFA at the base of the tail. This results in swelling of the paws that increases over a period of time and can be both visually scored and measured using calipers. IL-28A, IL-28B, or IL-29 is administered to groups of collagen-immunized mice, and effects on disease scores are evaluated. Inhibition of paw scores and thickness by IL-28A, IL-28B, and IL-29 is indicative of it's inhibitory effect on an ongoing autoimmune response.

2. *Inflammatory Bowel Disease*

Inflammation in the gut resulting from defective immune regulation, known as inflammatory bowel disease (IBD) is characterized into two broad disease definitions, Crohn's disease (CD) and Ulcerative colitis (UC). Generally, CD is thought to be due to dysfunction in the regulation of Th1 responses, and UC is believed to be due to dysfunction in the regulation of Th2 responses. Multiple cytokines, chemokines, and matrix metaloproteinases have beens shown to be upregulated in inflamed lesions from IBD patients. These include IL-1, IL-12, IL-18, IL-15, TNF-α, IFN-γ, MIP1α, MIP1β, and MIP2. Currently REMICADE® (Centocor, Malvern, PA) is the only drug that has successfully been used to target the disease itself when treating CD patients, with other treatments generally improving the quality of life of patients. IL-28A, IL-28B, and IL-29 inhibition of the autoimmune response associated with IBD is demonstrated in IBD models, such as the mouse DSS, TNBS, CD4+CD45Rbhi, mdr1a-/- and graft v. host disease (GVHD) intestinal inflammation models. (Stadnicki A and Colman RW, Arch Immunol Ther Exp 51:149-155, 2003; Pizarro TT et al., Trends in Mol Med 9:218-222, 2003). One experimental model for human IBD is the oral administration of dextran sodium sulfate (DSS) to rodents. DSS induces both acute and chronic ulcerative colitis with features somewhat resembling histological findings in humans. Colitis induced by DSS involves gut bacteria, macrophages and neutrophils, with a minor role for T and B cells (Mahler et al., Am. J. Physiol. 274:G544-G551, 1998; Egger et al., Digestion 62:240-248, 2000). TNBS-induced colitis is considered a

Th1 mediated disease and therefore resembles CD more than UC in humans. Tri-nitro benzene sulfonic acid (TNBS) is infused into mice intra-rectally in varying doses (strain dependent) to induce antigen specific (TNBS) T cell response that involves secretion of Th1-like cytokines IL-12, IL-18 and IFNγ. Colitis involves recruitment of antigen-specific T cells, macrophages and neutrophils to the site of inflammation (Neurath et al., Int. Rev. Immunol., 19:51-62, 2000; Dohi T et al., J. Exp. Med. 189:1169-1179, 1999). Another relatively new model for colitis is the CD4+CD45RB^{hi} transfer model into SCID mice. CD4$^+$ T cells can be divided broadly into 2 categories based on expression of CD45Rb. CD4+CD45RB^{hi} cells are considered naïve T cells whereas CD4+CD45Rb^{lo} cells are considered regulatory T cells. Transfer of whole CD4$^+$ T cells into syngenic SCID mice does not induce symptoms of colitis. However, if only the CD4+CD45RB^{hi} T cells are injected into SCID mice, mice develop colitis over a period of 3-6 weeks. Co-transfer of the CD4+CD45Rb^{lo} regulatory T cells along with the naïve T cells inhibits colitis suggesting that the regulatory T cells play an important role in regulating the immune response (Leach et al., Am. J. Pathol., 148:1503-1515, 1996; Powrie et al., J. Exp. Med., 179:589-600, 1999). This model will demonstrate that IL-28A, IL-28B, and IL-29 inhibit colitis by upregulating T regulatory function via its ability to generate tolerogenic DCs in mice. A clinically relevant model of colitis associated with bone marrow transplantation is GVHD-induced colitis. Graft-versus-host disease (GVHD) develops in immunoincompetent, histocompatible recipients of effector cells, which proliferate and attack host cells. Patients receiving allogeneic bone marrow transplantation or severe aplastic anemia are at risk for GVHD. In both mice and humans, diarrhea is a common and serious symptom of the syndrome. In human, both colonic and small intestinal disease have been observed. Mouse models for GVHD-induced colitis show similar histological disease as seen in humans. These mouse models can therefore be used to assess the efficacy of colitis inhibiting drugs for GVHD (Eigenbrodt et al., Am. J. Pathol., 137:1065-1076, 1990; Thiele et al., J. Clin. Invest., 84:1947-1956, 1989).

3. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an immune-complex related disorder characterized by chronic IgG antibody production directed at ubiquitous self

antigens (anti-dsDNA). The effects of SLE are systemic, rather than localized to a specific organ. Multiple chromosomal loci have been associated with the disease and may contribute towards different aspects of the disease, such as anti-dsDNA antibodies and glomerulonephritis. $CD4^+$ T cells have been shown to play an active part in mouse models of SLE (Horwitz, Lupus 10:319-320, 2001; Yellin and Thienel, Curr. Rheumatol. Rep., 2:24-37, 2000). The role for $CD8^+$ T cells is not clearly defined, but there is evidence to suggest that "suppressor" $CD8^+$ T cell function is impaired in lupus patients (Filaci et al., J. Immunol., 166:6452-6457, 2001; Sakane et al, J. Immunol., 137:3809-3813, 1986).

Sera from human SLE patients and mouse models are assayed for IL-28A, IL-28B, and IL-29 activity. $CD8^+$ T cell suppressor activity in PBLs from human SLE patients after culture with of IL-28A, IL-28B, or IL-29 is evaluated in vitro. Suppressor activity of $CD8^+$ T cells from SLE patients is evaluated by their ability to inhibit anti-CD3 induced proliferation of autologous PBMC. Inhibition function correlates with secretion of IFNγ and IL-6 in the cultures. Increased IFNγ and IL-6 in cultures from IL-28A, IL-28B, or IL-29 treated patients might indicate higher suppressor activity (Filaci et al., J. Immunol. 166:6452-6457, 2001)

4. Psoriasis

Psoriasis is a chronic inflammatory skin disease that is associated with hyperplastic epidermal keratinocytes and infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages (Christophers, Int. Arch. Allergy Immunol., 110:199, 1996). It is currently believed that environmental antigens play a significant role in initiating and contributing to the pathology of the disease. However, it is the loss of tolrance to self antigens that is thought to mediate the pathology of psoriasis. Dendritic cells and $CD4^+$ T cells are thought to play an important role in antigen presentation and recognition that mediate the immune response leading to the pathology. A model of psoriasis based on the CD4+CD45RB transfer model was recently developed (Davenport et al., Internat. Immunopharmacol., 2:653-672 (2002)). IL-28A, IL-28B, or IL-29 is administered to mice that are injected with psoriasis inducing cells and the effects on clinical score (skin disease) is evaluated, showing beneficial effects of IL-28A, IL-28B, and IL-29.

IL-28A, IL-28B, or IL-29 can be administered in combination with other agents already in use in autoimmunity and/or cancer including agents such as interferon-alpha (IFN-α, e.g., PEGASYS®, PEG-INTRON®, INFERGEN®, Albuferon-Alpha™), interferon-beta (INF-β, e.g., AVONEX®, BETASERON®, REBIF®), interferon-gamma (IFNγ, e.g., ACTIMMUNE®), NOVANTRONE®, ENBREL®, REMICADE®, LEUKINE®, APO2L/TNF-Related Apoptosis-Inducing Ligand (TRAIL), IL-21 and IL-2. Establishing the optimal dose level and scheduling for IL-28A, IL-28B, and IL-29 is done by a variety of means, including study of the pharmacokinetics and pharmacodynamics of IL-28A, IL-28B, and IL-29; determination of effective doses in animal models, and evaluation of the toxicity of IL-28A, IL-28B, and IL-29. Direct pharmacokinetic measurements done in primates and clinical trials can then be used to predict theoretical doses in patients that achieve plasma IL-28A, IL-28B, and IL-29 levels that are of sufficient magnitude and duration to achieve a biological response in patients.

The invention is further illustrated by the following non-limiting example.

EXAMPLES

Example 1

Mammalian Expression plasmids

An expression plasmid containing zcyto20 and zcyto21 was constructed via homologous recombination. Fragments of zcyto20 and zcyto21 cDNA were generated using PCR amplification. The primers for PCR were as follows:

zcyto20/pZMP21: zc40923, and zc43152 SEQ ID NOS: 42 and 43, respectively; and zcyto21/pZMP21: zc40922, and zc43153 SEQ ID NOS:72 and 73, respectively.

The PCR reaction mixture was run on a 1% agarose gel and a band corresponding to the size of the insert was gel-extracted using a QIAquick™ Gel Extraction Kit (Qiagen, Valencia, CA).

The plasmid pZMP21, which was cut with BglII, was used for recombination with the PCR insert fragment. Plasmid pZMP21 is a mammalian expression vector containing an expression cassette having the MPSV promoter, and multiple restriction sites for insertion of coding sequences; an *E. coli* origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in *S. cerevisiae*. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (*S. cerevisiae*) cells were independently combined with 10 μl of the insert DNA and 100ng of the cut pZMP21 vector above, and the mix was transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixture was electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, and 25 μF. Six hundred μl of 1.2 M sorbitol was added to the cuvette, and the yeast was plated in a 100-μl and 300μl aliquot onto two URA-D plates and incubated at 30°C. After about 72 hours, the Ura^+ yeast transformants from a single plate were resuspended in 1 ml H_2O and spun briefly to pellet the yeast cells. The cell pellet was resuspended in 0.5 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). The five hundred microliters of the lysis mixture was added to an Eppendorf tube containing 250 μl acid-washed glass beads and 300 μl phenol-chloroform, was vortexed for 3 minutes, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase was transferred to a fresh tube, and the DNA was precipitated with 600 μl ethanol (EtOH) and 30μl 3M sodium acetate, followed by centrifugation for 30 minutes at maximum speed. The DNA pellet was resuspended in 30 μl TE.

Transformation of electrocompetent *E. coli* host cells (MC1061) was done using 5 μl of the yeast DNA prep and 50 μl of cells. The cells were electropulsed at 2.0 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% Bacto™ Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM $MgCl_2$, 10 mM $MgSO_4$, 20 mM glucose) was added and then the cells were plated in a 50 μl and 200 μl aliquot on two LB AMP plates (LB broth (Lennox), 1.8% Bacto™ Agar (Difco), 100 mg/L Ampicillin).

The inserts of three clones for each construct were subjected to sequence analysis and one clone for each construct, containing the correct sequence, was selected. Larger scale plasmid DNA was isolated using a commercially available kit (QIAGEN Plasmid Mega Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct constructs were designated zcyto20/pZMP21 and zcyto21/pZMP21.

Example 2

Expression of Mammalian Constructs in CHO cells

200μg of a zcyto20/pZMP21 and zcyto21/pZMP21 construct were digested with 200 units of Pvu I at 37°C for three hours and then were precipitated with IPA and spun down in a 1.5 mL microfuge tube. The supernatant was decanted off the pellet, and the pellet was washed with 1 mL of 70% ethanol and allowed to incubate for 5 minutes at room temperature. The tube was spun in a microfuge for 10 minutes at 14,000 RPM and the supernatant was aspirated off the pellet. The pellet was then resuspended in 750 μl of PF-CHO media in a sterile environment, and allowed to incubate at 60°C for 30 minutes. CHO cells were spun down and resuspended using the DNA-media solution. The DNA/cell mixture was placed in a 0.4 cm gap cuvette and electroporated using the following parameters: 950 μF, high capacitance, and 300 V. The contents of the cuvette were then removed and diluted to 25 mLs with PF-CHO media and placed in a 125 mL shake flask. The flask was placed in an incubator on a shaker at 37°C, 6% CO_2, and shaking at 120 RPM.

Example 3

Purification and Analysis of zcyto20-CHO Protein

A. Purification of Zcyto20-CHO Protein

Recombinant zcyto20 (IL-28A) protein was produced from a pool of DXB11-CHO cell lines. Cultures were harvested, and the media were sterile filtered using a 0.2 μm filter.

The purification of zcyto20-CHO protein was achieved by the sequential use of a Poros HS 50 column (Applied Biosystems, Framingham, MA), a Monolithic WCX column (Isco, Inc., Lincoln, NE), a ToyoPearl Butyl 650S column (TosoH, Montgomeryville, PA), and a Superdex 75 column (Amersham Biosciences, Piscataway, NJ). Culture media from DXB111-CHO were adjusted to pH 6.0 before loading onto a Poros 50 HS column. The column was washed with 50 mM MES (2-Morpholinoethanesulfonic acid), 100 mM NaCl, pH 6 and the bound protein was eluted with a 10 column volumes (CV) linear gradient to 60% of 50 mM MES, 2 M NaCl, pH 6. The eluting fractions were collected and the presence of zcyto20 protein was confirmed by SDS-PAGE with a Coomassie staining. This fractions containing zcyto20 protein were pooled, diluted with double distilled water to a conductivity of about 20 mS, and loaded onto a Monolithic WCX column. The column was washed with 93% of 50 mM MES, 100 mM NaCl, pH 6, and 7% of 50 mM MES, 2 M NaCl, pH 6. The bound protein was eluted with a 25-CV linear gradient from 7% to 50% of 50 mM MES, 2 M NaCl, pH 6. The eluting fractions were collected and the presence of zcyto20 protein was confirmed by SDS-PAGE with a Coomassie staining. The fractions containing zcyto20 protein were pooled, adjusted to 1 M ammonium sulfate and loaded onto a ToyoPearl Butyl 650S column. Zcyto20 was eluted with a decreasing ammonium sulfate gradient and the fractions containing the pure zcyto20 were pooled and concentrated for injection into a Superdex 75 column. Fractions containing zcyto20 protein from the gel filtration column was pooled, concentrated, filtered through a 0.2 μm filter and frozen at –80°C. The concentration of the final purified protein was determined by a BCA assay (Pierce Chemical Co., Rockford, IL) and HPLC-amino acid analysis.

B. SDS-PAGE and Western blotting analysis of zcyto20-CHO protein

Recombinant zcyto20 protein was analyzed by SDS-PAGE (Nupage 4-12% Bis-Tris, Invitrogen, Carlsbad, CA) and Western blot using rabbit anti-zcyto21-

CEE-BV IgG as the primary antibody that cross-reacts to zcyto20-CHO protein. The gel was electrophoresed using Invitrogen's Xcell II mini-cell (Carlsbad, CA) and transferred to a 0.2 μm nitrocellulose membrane (Bio-Rad Laboratories, Hercules, CA) using Invitrogen's Xcell II blot module according to directions provided in the instrument manual. The transfer was run at 500 mA for 50 minutes in a buffer containing 25 mM Tris base, 200 mM glycine, and 20% methanol. The membrane was blocked with 10% non-fat dry milk in 1x PBS for 10 minutes then probed with the primary antibody in 1x PBS containing 2.5% non-fat dry milk. The blot was labeled for one hour at room temperature while shaking. For the secondary antibody labeling, blot was washed three times for 10 minutes each with PBS and then probed with goat anti-rabbit IgG-HRP (Pierce Chemical Co., Rockford, IL) for one hour. The blot was washed three times with 1x PBS for 10 minutes each and developed using a 1:1 mixture of SuperSignal® ULTRA reagents (Pierce Chemical Co., Rockford, IL) and the signal was captured using a Lumi-Imager (Boehringer Mannheim GmbH, Germany).

C. Summary of protein purification and analysis

The purified zcyto20 protein from the CHO media migrated predominantly as a doublet at approximately 20 kDa and a minor triplet dimer at about 38 kDa on a 4-12% Bis-Tris gel under non-reducing conditions. They all collapsed into a single 20 kDa band under reducing conditions. MS peptide mapping indicated a mixture of two isomers with respect to disulfide linkage and the presence of O-linked glycosylation site.

Example 4

Purification and Analysis of zcyto21-CHO Protein

A. Purification of Zcyto21-CHO Protein

Recombinant zcyto21 was produced from stable DXB11-CHO cell lines. Cultures were harvested, and the media were sterile filtered using a 0.2 μm filter. Proteins were purified from the conditioned media by starting with a combination of cationic and anionic exchange chromatography followed by a hydrophobic interaction chromatography and a size exclusion chromatography. DXB111-CHO culture media were adjusted to pH 6.0 before loading onto a Poros 50 HS column (Applied

Biosystems, Framingham, MA). The column was washed with 1x PBS, pH 6 and the bound protein was eluted with 5x PBS, pH 8.4. The eluting fraction was collected and the presence of zcyto21 protein was confirmed by SDS-PAGE with a Coomassie stain. This fraction was then diluted to a conductivity of 13 mS and its pH adjusted to 8.4 and flowed through a Poros 50 HQ column (Applied Biosystems, Framingham, MA). The flow-through containing zcyto21 protein were then adjusted to about 127 mS with ammonium sulfate and loaded onto a Toyopearl Phenyl 650S column (TosoH, Montgomeryville, PA). Zcyto21 protein was eluted with a decreasing ammonium sulfate gradient and the fractions containing the pure zcyto21 were pooled and concentrated for injection into a Superdex 75 column (Amersham Biosciences, Piscataway, NJ). The concentration of the final purified protein was determined by a BCA assay (Pierce Chemical Co., Rockford, IL) and HPLC-amino acid analysis.

B. SDS-PAGE and Western blotting analysis of zcyto21-CHO protein

Recombinant zcyto21 protein was analyzed by SDS-PAGE (Nupage 4-12% Bis-Tris, Invitrogen, Carlsbad, CA) and Western blot using rabbit anti-zcyto21-CEE-BV IgG as the primary antibody. The gel was electrophoresed using Invitrogen's Xcell II mini-cell (Carlsbad, CA) and transferred to a 0.2 μm nitrocellulose membrane (Bio-Rad Laboratories, Hercules, CA) using Invitrogen's Xcell II blot module according to directions provided in the instrument manual. The transfer was run at 500 mA for 50 minutes in a buffer containing 25 mM Tris base, 200 mM glycine, and 20% methanol. The transferred blot was blocked with 10% non-fat dry milk in 1x PBS for 10 minutes then probed with the primary antibody in 1x PBS containing 2.5% non-fat dry milk. The blot was labeled for one hour at room temperature while shaking. For the secondary antibody labeling, blot was washed three times for 10 minutes each with PBS and then probed with goat anti-rabbit IgG-HRP (Pierce Chemical Co., Rockford, IL) for one hour. The blot was washed three times with 1x PBS for 10 minutes each and developed using a 1:1 mixture of SuperSignal® ULTRA reagents (Pierce Chemical Co., Rockford, IL) and the signal was captured using a Lumi-Imager (Boehringer Mannheim GmbH, Germany).

C. Summary of protein purification and analysis

The purified zcyto21 protein from the CHO media migrated as two or more approximately 28 kDa bands on a 4-12% Bis-Tris gel under both reducing and non-reducing conditions. MS peptide mapping indicated a mixture of two isomers with respect to disulfide linkage and the presence of one N-linked glycosylation and several O-linked glycosylation sites.

Example 5

Identification of IL-29 Forms

Peak fractions from purified pools of IL-29 were digested overnight at 37°C with sequencing grade trypsin (Roche Applied Science, Indianapolis, IN) in phosphate buffer at approximately pH 6.3 to limit disulfide re-arrangement. Each digest was analyzed by reversed-phase HPLC (Agilent, Palo Alto, CA) connected in-line to a quadrupole-time of flight hybrid mass spectrometer (Micromass, Milford MA). Spectra were collected, converted from mass to charge ratio to mass, and compared to all theoretical peptides and disulfide-linked peptide combinations resulting from trypsin digestion of IL-29. Disulfides were assigned by comparing spectra before and after reduction with assignment of appropriate masses to disulfide linked peptides in IL-29. The material from fraction #20 showed the disulfide pattern C15 – C112 and C49 – C145 with C171 observed as a S-glutathionyl cysteine (all referring to SEQ ID NO: 4). The material from fraction #51 showed the disulfide pattern C49 – C145 and C112 – C171 with C15 observed as an S-glutathionyl cysteine (referring to SEQ ID NO:4).

Example 6

E. coli Expression Plasmids

Construction of expression vector, pTAP237

Plasmid pTAP237 was generated by inserting a PCR-generated linker into the SmaI site of pTAP186 by homologous recombination. Plasmid pTAP186 was derived from the plasmids pRS316 (a *Saccharomyces cerevisiae* shuttle vector) and pMAL-c2, an *E. coli* expression plasmid derived from pKK223-3 and comprising the *tac* promoter and the *rrnB* terminator.. Plasmid pTAP186 contains a kanamycin resistance gene in which the Sma I site has been destroyed and has NotI and SfiI sites flanking the yeast ARS-CEN6 and URA3 sequences, facilitating their removal from the

plasmid by digestion with NotI. The PCR-generated linker replaced the expression coupler sequence in pTAP186 with the synthetic RBS II sequence. It was prepared from 100 pmoles each of oligonucleotides zc29,740 and zc29,741, as shown in SEQ ID NOS: 44 and 45, respectively, and approximately 5 pmoles each of oligonucleotides zc29,736 and zc29,738, as shown in SEQ ID NOS: 46 and 47, respectively. These oligonucleotides were combined by PCR for ten cycles of 94°C for 30 seconds, 50°C for 30 seconds, and 72°C for 30 seconds, followed by 4°C soak. The resulting PCR products were concentrated by precipitation with two times the volume of 100% ethanol. Pellet was resuspended in 10 µL water to be used for recombining into the recipient vector pTAP186 digested with SmaI to produce the construct containing the synthetic RBS II sequence. Approximately 1 µg of the PCR-generated linker and 100 ng of pTAP186 digested with SmaI were mixed together and transformed into competent yeast cells (*S. cerevisiae*). The yeast was then plated onto -URA D plates and left at room temperature for about 72 hours. Then the Ura+ transformants from a single plate were resuspended in 1 mL H_2O and spun briefly to pellet the yeast cells. The cell pellet was resuspended in 0.5 mL of lysis buffer. DNA was recovered and transformed into *E. coli* MC1061. Clones were screened by colony PCR as disclosed above using 20 pmoles each of oligonucleotides zc29,740 and zc29,741, as shown in SEQ ID NOS: 44 and 45, respectively. Clones displaying the correct size band on an agarose gel were subject to sequence analysis. The correct plasmid was designated pTAP237.

Example 7

Codon Optimization of IL-29 Cysteine mutant

A. Codon Optimization Generation of the IL-29 wildtype expression construct

Native human IL-29 gene sequence was not well expressed in *E. coli* strain W3110. Examination of the codons used in the IL-29 coding sequence indicated that it contained an excess of the least frequently used codons in *E. coli* with a CAI value equal to 0.206. The CAI is a statistical measure of synonymous codon bias and can be used to predict the level of protein production (Sharp et al., Nucleic Acids Res. 15(3):1281-95, 1987). Genes coding for highly expressed proteins tend to have high CAI values (> 0.6), while proteins encoded by genes with low CAI values (≤ 0.2) are

generally inefficiently expressed. This suggested a reason for the poor production of IL-29 in *E. coli*. Additionally, the rare codons are clustered in the second half of the message leading to higher probability of translational stalling, premature termination of translation, and amino acid misincorporation (Kane JF. Curr. Opin. Biotechnol. 6(5):494-500, 1995)..

It has been shown that the expression level of proteins whose genes contain rare codons can be dramatically improved when the level of certain rare tRNAs is increased within the host (Zdanovsky et al., Applied Enviromental Microb. 66:3166-3173, 2000; You et al,. Biotechniques 27:950-954, 1999). The pRARE plasmid carries genes encoding the tRNAs for several codons that are rarely used *E. coli* (argU, argW, leuW , proL, ileX and glyT). The genes are under the control of their native promoters (Novy, *ibid.*) Co-expression with pRARE enhanced IL-29 production in *E. coli* and yield approximately 200 mg/L. These data suggest that re-resynthesizing the gene coding for IL-29 with more appropriate codon usage provides an improved vector for expression of large amounts of IL-29.

The codon optimized IL-29 coding sequence was constructed from sixteen overlaping oligonucleotides: zc44,566 (SEQ ID NO:48), zc44,565 (SEQ ID NO:49), zc44,564 (SEQ ID NO:50), zc44,563 (SEQ ID NO:51), zc44,562 (SEQ ID NO:52), zc44,561 (SEQ ID NO:53), zc44,560 (SEQ ID NO:54), zc244,559 (SEQ ID NO:55), zc44,558 (SEQ ID NO:56), zc44,557 (SEQ ID NO:57).Primer extension of these overlapping oligonucleotides followed by PCR amplication produced a full length IL-29 gene with codons optimized for expression in *E. col.*. The final PCR product was inserted into expression vector pTAP237 by yeast homologous recombination. The expression construct was extracted from yeast and transformed into competent *E. coli* MC1061. Clones resistance to kanamycin were identified by colony PCR. A positive clone was verified by sequencing and subsequently transformed into production host strain W3110. The expression vector with the optimized IL-29 sequence was named pSDH184. The resulting gene was expressed very well in *E. coli*. expression levels with the new construct increased to around 250 mg/L.

B. Generation of the codon optimized zcyto21 C172S Cysteine mutant expression construct

The strategy used to generate the zcyto21 C172S Cysteine mutant is based on the QuikChange Site-Directed Mutagenesis Kit (Stratagene). Primers were designed to introduce the C172S mutation based on manufacturer's suggestions. These primers were designated ZG44,340 (SEQ ID NO: 58) and ZG44,341 (SEQ ID NO: 59). PCR was performed to generate the zcyto21 C172S Cysteine mutant according to QuikChange Mutagenesis instructions. Five identical 50 µl reactions were set-up. 2.5 µl pSDH175 (missing yeast vector backbone sequence) DNA was used as template per reaction. A PCR cocktail was made up using the following amounts of reagents: 30 µl 10x PCR buffer, 125 ng (27.42 µl) ZG44,340, 125 ng (9.18 µl) ZG44,341, 6 µl dNTP, 6 µl Pfu Turbo polymerase (Stratagene, La Jolla, CA), and 206.4 µl water. 47.5 µl of the cocktail was aliquotted into each reaction. The PCR conditions were as follows: 1 cycle of 95°C for 30 seconds followed by 16 cycles of 95°C for 30 seconds, 55°C for 1 minute, 68°C for 7 minutes, followed by 1 cycle at 68°C for 7 minutes, and ending with a 4°C hold. All five PCR reactions were consolidated into one tube. As per manufacturer's instructions, 5 µl DpnI restriction enzyme was added to the PCR reaction and incubated at 37°C for 2 hours. DNA was precipitated my adding 10% 3 Molar Sodium Acetate and two volumes of 100% ethanol. Precipitation was carried-out at –20°C for 20 minutes. DNA was spun at 14,000 rpm for 5 minutes and pellet was speed-vac dried. DNA pellet was resuspended in 20 µl water. DNA resulting from PCR was transformed into *E.coli* strain DH10B. 5µl DNA was mixed with 40 µl ElectroMAX DH10B cells (Invitrogen). Cells and DNA mixture were then electroporated in a 0.1cm cuvette (Bio-Rad) using a Bio-Rad Gene Pulser II™ set to 1.75 kV, 100 Ω, and 25 µF. Electroporated cells were then outgrown at 37°C for 1 hour. Mixture was plated on an LB + 25 µg/ml kanamycin plate and incubated at 37°C overnight. Ten clones were screened for presence of zcyto21 C172S insert. DNA was isolated from all ten clones using the QIAprep™ Spin Miniprep Kit (Qiagen, Valencia, CA) and analyzed for presence of insert by cutting with XbaI and PstI restriction enzymes. Nine clones contained insert and were sequenced to insure the zcyto21 C172S mutation had been introduced. A clone was sequence verified and was subsequently labeled pSDH188.

Example 8

E. coli IL-29 expression construct

A DNA fragment of IL-29 containing the wildtype sequence was isolated using PCR. Primers zc41,212 (SEQ ID NO: 60) containing 41 base pair (bp) of vector flanking sequence and 24 bp corresponding to the amino terminus of IL-29, and primer zc41,041 (SEQ ID NO: 61) contained 38 bp corresponding to the 3' end of the vector which contained the zcyto21 insert were used in the reaction. The PCR conditions were as follows: 25 cycles of 94°C for 30 seconds, 50°C for 30 seconds, and 72°C for 1 minute; followed by a 4°C soak. A small sample (2-4 µL) of the PCR sample was run on a 1% agarose gel with 1X TBE buffer for analysis, and the expected band of approximately 500 bp fragment was seen. The remaining volume of the 100 µL reaction was precipitated with 200 µL absolute ethanol. The pellet was resuspended in 10 µL water to be used for recombining into recipient vector pTAP238 cut with SmaI to produce the construct encoding the zcyto21 as disclosed above. The clone with correct sequence was designated as pTAP377. Clone pTAP377 was digested with Not1/Nco1 (10µl DNA, 5µl buffer 3 New England BioLabs, 2 µL Not 1, 2 µL Nco1, 31 µL water for 1 hour at 37°C) and religated with T4 DNA ligase buffer (7 µL of the previous digest, 2 µL of 5X buffer, 1 µL of T4 DNA ligase). This step removed the yeast sequence, CEN-ARS, to streamline the vector. The pTAP337 DNA was diagnostically digested with Pvu2 and Pst1 to confirm the absence of the yeast sequence. P/taP377 DNA was transformed into *E. coli* strain W3110/pRARE, host strain carrying extra copies of rare *E. coli* tRNA genes.

Example 9

E. coli IL-28A expression construct

A DNA fragment containing the wildtype sequence of zcyto20 (as shown in SEQ ID NO: 1) was isolated using PCR. Primers zc43,431 (SEQ ID NO: 62) containing 41 bp of vector flanking sequence and 24 bp corresponding to the amino terminus of zcyto20, and primer zc43,437 (SEQ ID NO: 63) contained 38 bp corresponding to the 3' end of the vector which contained the zcyto20 insert. The PCR conditions were as follows: 25 cycles of 94°C for 30 seconds, 50°C for 30 seconds, and 72°C for 1 minute; followed by a 4°C soak. A small sample (2-4 µL) of the PCR

sample was run on a 1% agarose gel with 1X TBE buffer for analysis, and the expected band of approximately 500 bp fragment was seen. The remaining volume of the 100 µL reaction was precipitated with 200 µL absolute ethanol. . The pellet was resuspended in 10 µL water to be used for recombining into recipient vector pTAP238 cut with SmaI to produce the construct encoding the zcyto20 as disclosed above. The clone with correct sequence was designated as pYEL7. It was digested with Not1/Nco1 (10µl DNA, 5µl buffer 3 New England BioLabs, 2 µL Not1, 2 µL Nco1, 31 µL water for 1 hour at 37°C) and religated with T4 DNA ligase buffer (7 µL of the previous digest, 2 µL of 5X buffer, 1 µL of T4 DNA ligase). This step removed the yeast sequence, CEN-ARS, to streamline the vector. The relegated pYEL7 DNA was diagnostically digested with Pvu2 and Pst1 to confirm the absence of the yeast sequence. PYEL7 DNA was transformed into E. coli strain W3110/pRARE.

Example 10

zcyto21 C172S Cysteine mutant expression construct

The strategy used to generate the zcyto21 C172S Cysteine mutant (SEQ ID NO: 28) is based on the QuikChange® Site-Directed Mutagenesis Kit (Stratagene, La Jolla, CA). Primers were designed to introduce the C172S mutation based on manufacturer's suggestions. These primers were designated ZG44,327 and ZG44,328 (SEQ ID NOS: 64 and 65, respectively). PCR was performed to generate the zcyto21 C172S Cysteine mutant according to QuikChange Mutagenesis instructions. Five identical 50 µl reactions were set-up. 2.5 µl pTAP377 (missing yeast vector backbone sequence) DNA was used as template per reaction. A PCR cocktail was made up using the following amounts of reagents: 30 µl 10x PCR buffer, 125 ng (27.42 µl) ZG44,327 (SEQ ID NO: 64), 125 ng (9.18 µl) ZG44,328 (SEQ ID NO: 65), 6 µl dNTP, 6 µl Pfu Turbo polymerase (Strategene), and 206.4 µl water. 47.5 µl of the cocktail was aliquotted into each reaction. The PCR conditions were as follows: 1 cycle of 95°C for 30 seconds followed by 16 cycles of 95°C for 30 seconds, 55°C for 1 minute, 68°C for 7 minutes, followed by 1 cycle at 68°C for 7 minutes, and ending with a 4°C hold. All five PCR reactions were consolidated into one tube. As per manufacturer's instructions, 5 µl DpnI restriction enzyme was added to the PCR reaction and incubated at 37°C for 2 hours. DNA was precipitated my adding 10% 3 Molar Sodium Acetate

and two volumes of 100% ethanol (Aaper Alcohol, Shelbyville, KY). Precipitation was carried-out at –20°C for 20 minutes. DNA was spun at 14,000 rpm for 5 minutes and pellet was speed-vac dried. DNA pellet was resuspended in 20 µl water. DNA resulting from PCR was transformed into E.coli strain DH10B. 5 µl DNA was mixed with 40 µl ElectroMAX DH10B cells (Invitrogen, Carlsbad, CA). Cells and DNA mixture were then electroporated in a 0.1cm cuvette (Bio-Rad, Hercules, CA) using a Bio-Rad Gene Pulser II™ set to 1.75kV, 100Ω, and 25 µF. Electroporated cells were then outgrown at 37°C for 1 hour. Mixture was plated on an LB + 25 µg/ml kanamycin plate and incubated at 37°C overnight. Ten clones were screened for presence of IL-29 insert. DNA was isolated from all ten clones using the QIAprep™ Spin Miniprep Kit (Qiagen) and analyzed for presence of insert by cutting with XbaI (Roche) and PstI (New England Biolabs) restriction enzymes. Nine clones contained insert and were sequenced to insure the zcyto21 C172S mutation had been introduced. A clone (isolet #6) was sequence verified and was subsequently labeled pSDH171. A similar strategy can be implemented to generate a zcyto21 C15S mutant.

Example 11

zcyto20 C49S Cysteine mutant expression construct

The zcyto20 C49S Cysteine mutant coding sequence was generated by overlap PCR (SEQ ID NO: 20). The first 187 bases of the wildtype IL-28A sequence (SEQ ID NO:1) was generated by PCR amplification using pYEL7 (SEQ ID NO: 67) as template and oligonucleotide primers zc43,431 (SEQ ID NO: 62) and zc45,399 (SEQ ID NO: 66). The second DNA fragment from base 105 to 531 was generated by PCR amplification using pYEL7 (SEQ ID NO: 67) as template and oligonucleotide primers zc45,398 (SEQ ID NO: 68) and zc43,437 (SEQ ID NO: 63). Primers zc45,399 (SEQ ID NO: 66) and zc45,398 (SEQ ID NO: 68) contained the specific modified sequence which changed the cysteine 49 to a serine. These two PCR products were combined and PCR overlap amplified using oligonucleotide primers zc43,431 (SEQ ID NO: 62) and zc43,437 (SEQ ID NO: 63). The final PCR product was inserted into expression vector pTAP238 by yeast homologous recombination (Raymond et al. Biotechniques. Jan. 26(1):134-8, 140-1, 1999). The expression construct was extracted from yeast and transformed into competent *E. coli* DH10B. Kanamycin resistant clones

were screened by colony PCR. A positive clone was verified by sequencing and subsequently transformed into production host strain W3110/pRARE. The expression construct with the zcyto20 C49S Cysteine mutant coding sequence was named pCHAN9.

Example 12

zcyto20 C51S Cysteine mutant expression construct

The zcyto20 C51S Cysteine mutant coding sequence was generated by overlap PCR (SEQ ID NO: 24). The first 193 bases of the wildtype IL-28A sequence was generated by PCR amplification using pYEL7 (SEQ ID NO: 67) as template and oligonucleotide primers zc43,431 (SEQ ID NO: 62) and zc45,397 (SEQ ID NO: 63). The second DNA fragment from base 111 to 531 was generated by PCR amplification using pYEL7 (SEQ ID NO: 67) as template and oligonucleotide primers zc45,396 (SEQ ID NO:70) and zc43,437 (SEQ ID NO: 63). Primers zc45,397 (SEQ ID NO: 69) and zc45,396 (SEQ ID NO: 70) contained the specific modified sequence which changed the cysteine51 to a serine. These two PCR products were combined and PCR overlap amplified using oligonucleotide primers zc43,431 (SEQ ID NO: 62) and zc43,437 (SEQ ID NO: 63). The final PCR product was inserted into our in-house expression vector pTAP238 by yeast homologous recombination (Raymond et al. supra). The expression construct was extracted from yeast and transformed into competent *E. coli* DH10B. Kanamycin resistant clones were screened by colony PCR. A positive clone was verified by sequencing and subsequently transformed into production host strain W3110/pRARE. The expression construct with the zcyto20 C50S Cysteine mutant coding sequence was named pCHAN10.

Example 13

Expression of Il-28A, IL-29 and Cys to Ser Cysteine mutants in *E. coli*

In separate experiments, *E. coli* transformed with each of the expression vectors described in Examples 6-9 were inoculated into 100 mL Superbroth II medium (Becton Dickinson, San Diego, CA) with 0.01% Antifoam 289 (Sigma Aldrich, St. Louis, MO), 30 μg/ml kanamycin , 35 μg/ml chloramphenicol and cultured overnight at 37°C. A 5 mL inoculum was added to 500 mL of same medium in a 2 L culture flask

which was shaken at 250 rpm at 37°C until the culture attained an OD600 of 4. IPTG was then added to a final concentration of 1 mM and shaking was continued for another 2.5 hours. The cells were centrifuged at 4,000 x g for 10 min at 4 °C. The cell pellets were frozen at –80°C until use at a later time.

Example 14

Refolding and Purification of IL-28

A. Inclusion body preparation

Human wildtype IL-29 was expressed in *E. coli* strain W3110 as inclusion bodies as described above. A cell pellet from a fed-batch fermentation was resuspended in 50 mM Tris, pH 7.3. The suspension was passed through an APV-Gaulin homogenizer (Invensys APV, Tonawanda, New York) three times at 8000 psi. The insoluble material was recovered by centrifugation at 15,000 g for 30 minutes. The pellet was washed consecutively with 50 mM Tris, 1% (v/v) Triton X100, pH 7.3 and 4 M Urea. The inclusion body was then dispersed in 50 mM Tris, 6 M guanidine hydrochloride, 5 mM DTT at room temperature for 1 hour. The material was then centrifuged at 15,000 g for 1 hour. The supernatant from this step contains reduced soluble IL-29.

B. Refolding

The solubilized IL-29 was diluted slowly into 50 mM Tris, pH 8, 0.75 M Arginine, 0.05% PEG3350, 2 mM $MgCl_2$, 2 mM $CaCl_2$, 0.4 mM KCl, 10 mM NaCl, 4 mM reduced Glutathione, 0.8 mM oxidized Glutathione at room temperature while stirring. The final concentration of IL-29 in the refolding buffer was 0.1 mg/ml. The refolding mixture was left at room temperature overnight. Concentrated acetic acid was then used to adjust the pH of the suspension to 5. The suspension was then filtered through a 0.2 μm filter. RP-HPLC analysis of the refolding mixture showed two prominent peaks.

C. Purification

The refolding mixture was in-line diluted (1:2) with 50 mM NaOAc at pH 5 and loaded onto a Pharmacia SP Sepharose Fast Flow cation exchange column

(North Peapack, NJ). The column was washed with 3 column volumes of 50 mM NaOAc, 400 mM NaCl, pH 5. The bound IL-29 was eluted with 50 mM NaOAc, 1.4 M NaCl, pH 5. Solid $(NH_4)_2SO_4$ was added to the elute pool of the cation exchange step so that the final concentration of $(NH_4)_2SO_4$ was 0.5 M. The material was then loaded onto a ToyoPearl Phenyl 650S HIC column (Tosoh Biosep, Montgomery, PA). The column was then washed with 3 column volumes of 50 mM NaOAc, 1 M $(NH_4)_2SO_4$, pH 5. A linear gradient of 10 column volumes from 50 mM NaOAc, 1 M $(NH_4)_2SO_4$, pH 5 to 50 mM NaOAc, pH 5 was used to elute the bound zcyto21. Fractions were collected of the elute. Two prominent peaks were observed in this step. RP-HPLC analysis of the elute fractions was performed. Two products corresponding to two disulfide bond isomers were produced after final buffer exchange into PBS, pH 7.3.

Example 15

Refolding and Purification of IL-29 Cysteine mutant

As described in Example 3, purification of IL-29 produced two disulfide bond isomers. A HIC FPLC step was employed to separate the two forms. The separation was not baseline resolved. Severe "Peak Shaving" had to be used to obtain substantially pure isomers (>95%). The yield for this step and by extension for the whole process suffered. The final yields were 8% and 9% for the C15-C112 form and C112-C171 form respectively. Wildtype IL-29 produced in CHO and baculovirus (BV) systems also showed similar phenomena. It was established that the C15-C112 form of the isomer is homologous in disulfide bond patterns to type I INF's. The C15-C112 form also demonstrated 30-fold higher bioactivity than the C112-C171 form in an ISRE assay (see below).

Refolding and purification of zcyto21 Cys172Ser mutein

The inclusion body preparation, refolding and purification of zcyto21 C172S polypeptide (SEQ ID NO:29) is essentially the same as those of IL-29 wild-type (SEQ ID NO:4). RP-HPLC analysis of the refolding mixture of the mutein showed only one prominent peak corresponding to the C15-C112 form of the wild-type IL-29. Subsequent HIC chromatography show only a single peak. It was therefore unnecessary to employ severe "peak shaving". The final yield for the entire process is close to 50%.

The zcyto21 Cys172Ser polypeptide (SEQ ID NO:29) showed equivalent bioactivity to the C15-C112 form of wild-type IL-29 in ISRE assay shown in Example 16.

Example 16

IL-28RA mRNA expression in liver and lymphocyte subsets

In order to further examine the mRNA distribution for IL-28RA, semi-quantitative RT-PCR was performed using the SDS 7900HT system (Applied Biosystems, CA). One-step RT-PCR was performed using 100ng total RNA for each sample and gene-specific primers. A standard curve was generated for each primer set using Bjab RNA and all sample values were normalized to HPRT. The normalized values for IFNAR2 and CRF2-4 are also shown.

Table 7: B and T cells express significant levels of IL-28RA mRNA. Low levels are seen in dendritic cells and most monocytes.

Table 7

Cell/Tissue	IL-28RA	IFNAR2	CRF2-4
Dendritic Cells unstim	.04	5.9	9.8
Dendritic Cells +IFNg	.07	3.6	4.3
Dendritic Cells	.16	7.85	3.9
CD14+ stim'd with LPS/IFNg	.13	12	27
CD14+ monocytes resting	.12	11	15.4
Hu CD14+ Unact.	4.2	TBD	TBD
Hu CD14+ 1 ug/ml LPS act.	2.3	TBD	TBD
H. Inflamed tonsil	3	12.4	9.5
H. B-cells+PMA/Iono 4 & 24 hrs	3.6	1.3	1.4
Hu CD19+ resting	6.2	TBD	TBD
Hu CD19+ 4 hr. PMA/Iono	10.6	TBD	TBD
Hu CD19+ 24 hr Act. PMA/Iono	3.7	TBD	TBD
IgD+ B-cells	6.47	13.15	6.42
IgM+ B-cells	9.06	15.4	2.18
IgD- B-cells	5.66	2.86	6.76
NKCells + PMA/Iono	0	6.7	2.9
Hu CD3+ Unactivated	2.1	TBD	TBD
CD4+ resting	.9	8.5	29.1
CD4+ Unstim 18 hrs	1.6	8.4	13.2
CD4+ +Poly I/C	2.2	4.5	5.1
CD4+ + PMA/Iono	.3	1.8	.9
CD3 neg resting	1.6	7.3	46
CD3 neg unstim 18 hrs	2.4	13.2	16.8
CD3 neg+Poly I/C 18 hrs	5.7	7	30.2
CD3 neg+LPS 18 hrs	3.1	11.9	28.2
CD8+ unstim 18 hrs	1.8	4.9	13.1
CD8+ stim'd with PMA/Ion 18 hrs	.3	.6	1.1

As shown in Table 8, normal liver tissue and liver derived cell lines display substantial levels of IL-28RA and CRF2-4 mRNA.

Table 8

Cell/Tissue	IL-28RA	IFNAR2	CRF2-4
HepG2	1.6	3.56	2.1
HepG2 UGAR 5/10/02	1.1	1.2	2.7
HepG2, CGAT HKES081501C	4.3	2.1	6
HuH7 5/10/02	1.63	16	2
HuH7 hepatoma - CGAT	4.2	7.2	3.1
Liver, normal - CGAT #HXYZ020801K	11.7	3.2	8.4
Liver, NAT - Normal adjacent tissue	4.5	4.9	7.7
Liver, NAT - Normal adjacent tissue	2.2	6.3	10.4
Hep SMVC hep vein	0	1.4	6.5
Hep SMCA hep. Artery	0	2.1	7.5
Hep. Fibro	0	2.9	6.2
Hep. Ca.	3.8	2.9	5.8
Adenoca liver	8.3	4.2	10.5
SK-Hep-1 adenoca. Liver	.1	1.3	2.5
AsPC-1 Hu. Pancreatic adenocarc.	.7	.8	1.3
Hu. Hep. Stellate cells	.025	4.4	9.7

As shown in Table 9, primary airway epithelial cells contain abundant levels of IL-28RA and CRF2-4.

Table 9

Cell/Tissue	IL-28RA	IFNAR2	CRF2-4
U87MG - glioma	0	.66	.99
NHBE unstim	1.9	1.7	8.8
NHBE + TNF-alpha	2.2	5.7	4.6
NHBE + poly I/C	1.8	nd	nd
Small Airway Epithelial Cells	3.9	3.3	27.8
NHLF - Normal human lung fibroblasts	0	nd	nd

As shown in Table 10, IL-28RA is present in normal and diseased liver specimens, with increased expression in tissue from Hepatitis C and Hepatitis B infected specimens.

Table 10

Cell/Tissue	IL-28RA	CRF2-4	IFNAR2
Liver with Coagulation Necrosis	8.87	15.12	1.72
Liver with Autoimmune Hepatitis	6.46	8.90	3.07
Neonatal Hepatitis	6.29	12.46	6.16
Endstage Liver disease	4.79	17.05	10.58
Fulminant Liver Failure	1.90	14.20	7.69
Fulminant Liver failure	2.52	11.25	8.84
Cirrhosis, primary biliary	4.64	12.03	3.62
Cirrhosis Alcoholic (Laennec's)	4.17	8.30	4.14
Cirrhosis, Cryptogenic	4.84	7.13	5.06
Hepatitis C+, with cirrhosis	3.64	7.99	6.62
Hepatitis C+	6.32	11.29	7.43
Fulminant hepatitis secondary to Hep A	8.94	21.63	8.48
Hepatitis C+	7.69	15.88	8.05
Hepatitis B+	1.61	12.79	6.93
Normal Liver	8.76	5.42	3.78
Normal Liver	1.46	4.13	4.83
Liver NAT	3.61	5.43	6.42
Liver NAT	1.97	10.37	6.31
Hu Fetal Liver	1.07	4.87	3.98
Hepatocellular Carcinoma	3.58	3.80	3.22
Adenocarcinoma Liver	8.30	10.48	4.17
hep. SMVC, hep. Vein	0.00	6.46	1.45
Hep SMCA hep. Artery	0.00	7.55	2.10
Hep. Fibroblast	0.00	6.20	2.94
HuH7 hepatoma	4.20	3.05	7.24
HepG2 Hepatocellular carcinoma	3.40	5.98	2.11
SK-Hep-1 adenocar. Liver	0.03	2.53	1.30
HepG2 Unstim	2.06	2.98	2.28
HepG2+zcyto21	2.28	3.01	2.53
HepG2+IFNα	2.61	3.05	3.00
Normal Female Liver - degraded	1.38	6.45	4.57
Normal Liver - degraded	1.93	4.99	6.25
Normal Liver - degraded	2.41	2.32	2.75
Disease Liver - degraded	2.33	3.00	6.04
Primary Hepatocytes from Clonetics	9.13	7.97	13.30

As shown in Tables 11-15, IL-28RA is detectable in normal B cells, B lymphoma cell lines, T cells, T lymphoma cell lines (Jurkat), normal and transformed lymphocytes (B cells and T cells) and normal human monocytes.

Table 11

	HPRT Mean	IL-28RA Mean	IL-28RA norm	IFNAR2	IFNR2 norm	CRF2-4	CRF2-4 Norm
CD14+ 24hr unstim #A38	13.1	68.9	5.2	92.3	7.0	199.8	15.2
CD14+ 24 hr stim #A38	6.9	7.6	1.1	219.5	31.8	276.6	40.1
CD14+ 24 hr unstim #A112	17.5	40.6	2.3	163.8	9.4	239.7	13.7
CD14+ 24 hr stim #A112	11.8	6.4	0.5	264.6	22.4	266.9	22.6
CD14+ rest #X	32.0	164.2	5.1	1279.7	39.9	699.9	21.8
CD14+ +LPS #X	21.4	40.8	1.9	338.2	15.8	518.0	24.2
CD14+ 24 hr unstim #A39	26.3	86.8	3.3	297.4	11.3	480.6	18.3
CD14+ 24 hr stim #A39	16.6	12.5	0.8	210.0	12.7	406.4	24.5
HL60 Resting	161.2	0.2	0.0	214.2	1.3	264.0	1.6
HL60+PMA	23.6	2.8	0.1	372.5	15.8	397.5	16.8
U937 Resting	246.7	0.0	0.0	449.4	1.8	362.5	1.5
U937+PMA	222.7	0.0	0.0	379.2	1.7	475.9	2.1
Jurkat Resting	241.7	103.0	0.4	327.7	1.4	36.1	0.1
Jurkat Activated	130.7	143.2	1.1				
Colo205	88.8	43.5	0.5				
HT-29	26.5	30.5	1.2				

Table 12

	HPRT SD	IL-28RA SD
Mono 24hr unstim #A38	0.6	2.4
Mono 24 hr stim #A38	0.7	0.2
Mono 24 hr unstim #A112	2.0	0.7
Mono 24 hr stim #A112	0.3	0.1
Mono rest #X	5.7	2.2
Mono+LPS #X	0.5	1.0
Mono 24 hr unstim #A39	0.7	0.8
Mono 24 hr stim #A39	0.1	0.7
HL60 Resting	19.7	0.1
HL60+PMA	0.7	0.4
U937 Resting	7.4	0.0
U937+PMA	7.1	0.0
Jurkat Resting	3.7	1.1
Jurkat Activated	2.4	1.8
Colo205	1.9	0.7
HT-29	2.3	1.7

Table 13

	Mean Hprt	Mean IFNAR2	Mean IL-28RA	Mean CRF
CD3+/CD4+ 0	10.1	85.9	9.0	294.6
CD4/CD3+ Unstim 18 hrs	12.9	108.7	20.3	170.4
CD4+/CD3+ +Poly I/C 18 hrs	24.1	108.5	52.1	121.8
CD4+/CD3+ + PMA/Iono 18 hrs	47.8	83.7	16.5	40.8
CD3 neg 0	15.4	111.7	24.8	706.1
CD3 neg unstim 18 hrs	15.7	206.6	37.5	263.0
CD3 neg +Poly I/C 18 hrs	9.6	67.0	54.7	289.5
CD3 neg +LPS 18 hrs	14.5	173.2	44.6	409.3
CD8+ Unstim. 18 hrs	6.1	29.7	11.1	79.9
CD8+ + PMA/Iono 18 hrs	78.4	47.6	26.1	85.5
12.8.1 - NHBE Unstim	47.4	81.1	76.5	415.6
12.8.2 - NHBE+TNF-alpha	42.3	238.8	127.7	193.9
SAEC	15.3	49.9	63.6	426.0

Table 14

	IL-28RA Norm	CRF Norm	IFNAR2 Norm	IL-28RA SD	CRF SD	IFNAR2 SD
CD3+/CD4+ 0	0.9	29.1	8.5	0.1	1.6	0.4
CD4/CD3+ Unstim 18 hrs	1.6	13.2	8.4	0.2	1.6	1.4
CD4+/CD3+ +Poly I/C 18 hrs	2.2	5.1	4.5	0.1	0.3	0.5
CD4+/CD3+ + PMA/Iono 18 hrs	0.3	0.9	1.8	0.0	0.1	0.3
CD3 neg 0	1.6	46.0	7.3	0.2	4.7	1.3
CD3 neg unstim 18 hrs	2.4	16.8	13.2	0.4	2.7	2.3
CD3 neg +Poly I/C 18 hrs	5.7	30.2	7.0	0.3	1.7	0.8
CD3 neg +LPS 18 hrs	3.1	28.2	11.9	0.4	5.4	2.9
CD8+ Unstim. 18 hrs	1.8	13.1	4.9	0.1	1.1	0.3
CD8+ + PMA/Iono 18 hrs	0.3	1.1	0.6	0.0	0.1	0.0
12.8.1 - NHBE Unstim	1.6	8.8	1.7	0.1	0.4	0.1
12.8.2 - NHBE+TNF-alpha	3.0	4.6	5.7	0.1	0.1	0.1
SAEC	4.1	27.8	3.3	0.2	1.1	0.3

Table 15

	SD Hprt	SD IFNAR2	SD IL-28RA	SD CRF
CD3+/CD4+ 0	0.3	3.5	0.6	12.8
CD4/CD3+ Unstim 18 hrs	1.4	13.7	1.1	8.5
CD4+/CD3+ +Poly I/C 18 hrs	1.3	9.8	1.6	3.4
CD4+/CD3+ + PMA/Iono 18 hrs	4.0	10.3	0.7	3.7
CD3 neg 0	1.4	16.6	1.6	28.6
CD3 neg unstim 18 hrs	2.4	16.2	2.7	12.6
CD3 neg +Poly I/C 18 hrs	0.5	7.0	1.0	8.3
CD3 neg +LPS 18 hrs	1.0	39.8	5.6	73.6
CD8+ Unstim. 18 hrs	0.2	1.6	0.5	6.1
CD8+ + PMA/Iono 18 hrs	1.3	1.7	0.2	8.1
12.8.1 - NHBE Unstim	2.4	5.6	2.7	2.8
12.8.2 - NHBE+TNF-alpha	0.5	3.4	3.5	3.4
SAEC	0.5	4.8	1.8	9.9

Example 17

Mouse IL-28 Does Not Have Antiproliferative Effect on Mouse B cells

Mouse B cells were isolated from 2 Balb/C spleens (7 months old) by depleting CD43+ cells using MACS magnetic beads. Purified B cells were cultured in vitro with LPS, anti-IgM or anti-CD40 monoclonal antibodies. Mouse IL-28 or mouse IFNα was added to the cultures and ^{3}H-thymidine was added at 48 hrs. and ^{3}H-thymidine incorporation was measured after 72 hrs. culture.

IFNα at 10 ng/ml inhibited ^{3}H-thymidine incorporation by mouse B cells stimulated with either LPS or anti-IgM. However mouse IL-28 did not inhibit ^{3}H-thymidine incorporation at any concentration tested including 1000 ng/ml. In contrast, both mIFNα and mouse IL-28 increased ^{3}H thymidine incorporation by mouse B cells stimulated with anti-CD40 MAb.

These data demonstrate that mouse IL-28 unlike IFNa displays no antiproliferative activity even at high concentrations. In addition, zcyto24 enhances proliferation in the presence of anti-CD40 MAbs. The results illustrate that mouse IL-28 differs from IFNα in that mouse IL-28 does not display antiproliferative activity on mouse B cells, even at high concentrations. In addition, mouse IL-28 enhances proliferation in the presence of anti-CD40 monoclonal antibodies.

Example 18

Bone marrow expansion assay

Fresh human marrow mononuclear cells (Poietic Technologies, Gaithersburg, Md.) were adhered to plastic for 2 hrs in αMEM, 10% FBS, 50 micromolar β–mercaptoethanol, 2 ng/ml FLT3L at 37°C. Non adherent cells were then plated at 25,000 to 45,000 cells/well (96 well tissue culture plates) in αMEM, 10% FBS, 50 micromolar β–mercaptoethanol, 2 ng/ml FLT3L in the presence or absence of 1000 ng/ml IL-29-CEE, 100 ng/ml IL-29-CEE, 10 ng/ml IL-29-CEE, 100 ng/ml IFN-α2a, 10 ng/ml IFN- α2a or 1 ng/ml IFN- α2a. These cells were incubated with a variety of cytokines to test for expansion or differentiation of hematopoietic cells from the marrow (20 ng/ml IL-2, 2 ng/ml IL-3, 20 ng/ml IL-4, 20 ng/ml IL-5, 20 ng/ml IL-7, 20 ng/ml IL-10, 20 ng/ml IL-12, 20 ng/ml IL-15, 10 ng/ml IL-21 or no added cytokine). After 8 to 12 days Alamar Blue (Accumed, Chicago, Ill.) was added at 20 microliters/well. Plates were further incubated at 37 °C, 5% CO, for 24 hours. Plates were read on the Fmax™ plate reader (Molecular Devices Sunnyvale, Calif.) using the SoftMax™ Pro program, at wavelengths 544 (Excitation) and 590 (Emission). Alamar Blue gives a fluourometric readout based on the metabolic activity of cells, and is thus a direct measurement of cell proliferation in comparison to a negative control.

IFN- α2a caused a significant inhibition of bone marrow expansion under all conditions tested. In contrast, IL-29 had no significant effect on expansion of

bone marrow cells in the presence of IL-3, IL-4, IL-5, IL-7, IL-10, IL-12, IL-21 or no added cytokine. A small inhibition of bone marrow cell expansion was seen in the presence of IL-2 or IL-15.

Example 19

Inhibition of IL-28 and IL-29 signaling with soluble receptor (zcytoR19/CRF2-4)

A. Signal Transduction Reporter Assay

A signal transduction reporter assay can be used to show the inhibitor properties of zcytor19-Fc4 homodimeric and zcytor19-Fc/CRF2-4-Fc heterodimeric soluble receptors on zcyto20, zcyto21 and zcyto24 signaling. Human embryonal kidney (HEK) cells overexpressing the zcytor19 receptor are transfected with a reporter plasmid containing an interferon-stimulated response element (ISRE) driving transcription of a luciferase reporter gene. Luciferase activity following stimulation of transfected cells with ligands (including zcyto20 (SEQ ID NO:2), zcyto21 (SEQ ID NO:15), zcyto24 (SEQ ID NO:8)) reflects the interaction of the ligand with soluble receptor.

B. Cell Transfections

293 HEK cells overexpressing zcytor19 were transfected as follows: 700,000 293 cells/well (6 well plates) were plated approximately 18h prior to transfection in 2 milliliters DMEM + 10% fetal bovine serum. Per well, 1 microgram pISRE-Luciferase DNA (Stratagene) and 1 microgram pIRES2-EGFP DNA (Clontech,) were added to 6 microliters Fugene 6 reagent (Roche Biochemicals) in a total of 100 microliters DMEM. This transfection mix was added 30 minutes later to the pre-plated 293 cells. Twenty-four hours later the transfected cells were removed from the plate using trypsin-EDTA and replated at approximately 25,000 cells/well in 96 well microtiter plates. Approximately 18 h prior to ligand stimulation, media was changed to DMEM + 0.5%FBS.

C. Signal Transduction Reporter Assays

The signal transduction reporter assays were done as follows: Following an 18h incubation at 37°C in DMEM + 0.5%FBS, transfected cells were stimulated with 10 ng/ml zcyto20, zcyto21 or zcyto24 and 10 micrograms/ml of the following soluble receptors; human zcytor19-Fc homodimer, human zcytor19-Fc/human CRF2-4-Fc heterodimer, human CRF2-4-Fc homodimer, murine zcytor19-Ig homodimer. Following a 4-hour incubation at 37°C, the cells were lysed, and the relative light units (RLU) were measured on a luminometer after addition of a luciferase substrate. The results obtained are shown as the percent inhibition of ligand-induced signaling in the presence of soluble receptor relative to the signaling in the presence of PBS alone. Table 16 shows that the human zcytor19-Fc/human CRF2-4 heterodimeric soluble receptor is able to inhibit zcyto20, zcyto21 and zcyto24-induced signaling between 16 and 45% of control. The human zcytor19-Fc homodimeric soluble receptor is also able to inhibit zcyto21-induced signaling by 45%. No significant effects were seen with huCRF2-4-Fc or muzcytor19-Ig homodimeric soluble receptors.

Table 16: Percent Inhibition of Ligand-induced Interferon Stimulated Response Element (ISRE) Signaling by Soluble Receptors

Ligand	Huzcytor19-Fc/huCRF2-4-Fc	Huzcytor19-Fc	HuCRF2-4-Fc	Muzcytor19-Ig
Zcyto20	16%	92%	80%	91%
Zcyto21	16%	45%	79%	103%
Zcyto24	47%	90%	82%	89%

Example 20

Induction of Interferon Stimulated Genes by IL-28 and IL-29

A. Human Peripheral Blood Mononuclear Cells

Freshly isolated human peripheral blood mononuclear cells were grown in the presence of IL-29 (20 ng/mL), IFNα2a (2 ng/ml) (PBL Biomedical Labs, Piscataway, NJ), or in medium alone. Cells were incubated for 6, 24, 48, or 72 hours, and then total RNA was isolated and treated with RNase-free DNase. 100 ng total RNA was used as a template for One-Step Semi-Quantitative RT-PCR® using Taqman One-Step RT-PCR Master Mix® Reagents and gene specific primers as suggested by the manufacturer. (Applied Biosystems, Branchburg, NJ) Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each

time-point. Table 17 shows that IL-29 induces Interferon Stimulated Gene Expression in human peripheral blood mononuclear cells at all time-points tested.

Table 17

	MxA Fold induction	Pkr Fold Induction	OAS Fold Induction
6 hr IL29	3.1	2.1	2.5
6 hr IFNα2a	17.2	9.6	16.2
24 hr IL29	19.2	5.0	8.8
24 hr IFNα2a	57.2	9.4	22.3
48 hr IL29	7.9	3.5	3.3
48hr IFNα2a	18.1	5.0	17.3
72 hr IL29	9.4	3.7	9.6
72 hr IFNα2a	29.9	6.4	47.3

B. Activated Human T Cells

Human T cells were isolated by negative selection from freshly harvested peripheral blood mononuclear cells using the Pan T-cell Isolation® kit according to manufacturer's instructions (Miltenyi, Auburn, CA). T cells were then activated and expanded for 5 days with plate-bound anti-CD3, soluble anti-CD28 (0.5ug/ml), (Pharmingen, San Diego, CA) and Interleukin 2 (IL-2; 100 U/ml) (R&D Systems, Minneapolis, MN), washed and then expanded for a further 5 days with IL-2. Following activation and expansion, cells were stimulated with IL-28A (20 ng/ml), IL-29 (20 ng/ml), or medium alone for 3, 6, or 18 hours. Total RNA was isolated and treated with RNase-Free DNase. One-Step Semi-Quantitative RT-PCR® was performed as described in the example above. Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each time-point. Table 18 shows that IL-28 and IL-29 induce Interferon Stimulated Gene expression in activated human T cells at all time-points tested.

Table 18

	MxA Fold Induction	Pkr Fold Induction	OAS Fold Induction
Donor #1 3 hr IL28	5.2	2.8	4.8
Donor #1 3 hr IL29	5.0	3.5	6.0
Donor #1 6 hr IL28	5.5	2.2	3.0
Donor #1 6 hr IL29	6.4	2.2	3.7
Donor #1 18 hr IL28	4.6	4.8	4.0
Donor #1 18 hr IL29	5.0	3.8	4.1
Donor #2 3 hr IL28	5.7	2.2	3.5
Donor #2 3 hr IL29	6.2	2.8	4.7
Donor #2 6 hr IL28	7.3	1.9	4.4
Donor #2 6 hr IL29	8.7	2.6	4.9
Donor #2 18 hr IL28	4.7	2.3	3.6
Donor #2 18 hr IL29	4.9	2.1	3.8

C. Primary Human Hepatocytes

Freshly isolated human hepatocytes from two separate donors (Cambrex, Baltimore, MD and CellzDirect, Tucson, AZ) were stimulated with IL-28A (50 ng/ml), IL-29 (50 ng/ml), IFNα2a (50 ng/ml), or medium alone for 24 hours. Following stimulation, total RNA was isolated and treated with RNase-Free DNase. One-step semi-quantitative RT-PCR was performed as described previously in the example above. Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each time-point. Table 19 shows that IL-28 and IL-29 induce Interferon Stimulated Gene expression in primary human hepatocytes following 24-hour stimulation.

Table 19

	MxA Fold Induction	Pkr Fold Induction	OAS Fold Induction
Donor #1 IL28	31.4	6.4	30.4
Donor #1 IL29	31.8	5.2	27.8
Donor #1 IFN-α2a	63.4	8.2	66.7
Donor #2 IL28	41.7	4.2	24.3
Donor #2 IL29	44.8	5.2	25.2
Donor #2 IFN-α2a	53.2	4.8	38.3

D. HepG2 and HuH7: Human Liver Hepatoma Cell Lines

HepG2 and HuH7 cells (ATCC NOS. 8065, Manassas, VA) were stimulated with IL-28A (10 ng/ml), IL-29 (10 ng/ml), IFNα2a (10 ng/ml), IFNB (1 ng/ml) (PBL Biomedical, Piscataway, NJ), or medium alone for 24 or 48 hours. In a separate culture, HepG2 cells were stimulated as described above with 20 ng/ml of MetIL-29C172S-PEG or MetIL-29-PEG. Total RNA was isolated and treated with RNase-Free DNase. 100 ng Total RNA was used as a template for one-step semi-quantitative RT-PCR as described previously. Results were normalized to HPRT and are shown as the fold induction over the medium alone control for each time-point. Table 20 shows that IL-28 and IL-29 induce ISG expression in HepG2 and HuH7 liver hepatoma cell lines after 24 and 48 hours.

Table 20

	MxA Fold Induction	Pkr Fold Induction	OAS Fold Induction
HepG2 24 hr IL28	12.4	0.7	3.3
HepG2 24 hr IL29	36.6	2.2	6.4
HepG2 24 hr IFNα2a	12.2	1.9	3.2
HepG2 24 hr IFNβ	93.6	3.9	19.0
HepG2 48hr IL28	2.7	0.9	1.1
HepG2 48hr IL29	27.2	2.1	5.3
HepG2 48 hr IFNα2a	2.5	0.9	1.2
HepG2 48hr IFNβ	15.9	1.8	3.3
HuH7 24 hr IL28	132.5	5.4	52.6
HuH7 24 hr IL29	220.2	7.0	116.6
HuH7 24 hr IFNα2a	157.0	5.7	67.0
HuH7 24 hr IFNβ	279.8	5.6	151.8
HuH7 48hr IL28	25.6	3.4	10.3
HuH7 48hr IL29	143.5	7.4	60.3
HuH7 48 hr IFNα2a	91.3	5.8	32.3
HuH7 48hr IFNβ	65.0	4.2	35.7

Table 21

	MxA Fold Induction	OAS Fold Induction	Pkr Fold Induction
MetIL-29-PEG	36.7	6.9	2.2
MetIL-29C172S-PEG	46.1	8.9	2.8

Data shown is for 20 ng/ml metIL-29-PEG and metIL-29C172S-PEG versions of IL-29 after culture for 24 hours.

Data shown is normalized to HPRT and shown as fold induction over unstimulated cells.

Example 21

IL-28, IL-29, metIL-29-PEG and metIL-29C172S-PEG Stimulate ISG induction in the Mouse Liver Cell line AML-12

Interferon stimulated genes (ISGs) are genes that are induced by type I interferons (IFNs) and also by the IL-28 and IL-29 family molecules, suggesting that IFN and IL-28 and IL-29 induce similar pathways leading to antiviral activity. Human type I IFNs (IFNα1-4 and IFNβ) have little or no activity on mouse cells, which is thought to be caused by lack of species cross-reactivity. To test if human IL-28 and IL-29 have effects on mouse cells, ISG induction by human IL-28 and IL-29 was evaluated by real-time PCR on the mouse liver derived cell line AML-12.

AML-12 cells were plated in 6-well plates in complete DMEM media at a concentration of 2 x 10^6 cells/well. Twenty-four hours after plating cells, human IL-28 and IL-29 were added to the culture at a concentration of 20 ng/ml. As a control, cells were either stimulated with mouse IFNα (positive control) or unstimulated (negative). Cells were harvested at 8, 24, 48 and 72 hours after addition of CHO-derived human IL-28A (SEQ ID NO:2) or IL-29 (SEQ ID NO:15) . RNA was isolated from cell pellets using RNAEasy-kit® (Qiagen, Valencia, CA). RNA was treated with DNase (Millipore, Billerica, MA) to clean RNA of any contaminating DNA. cDNA was generated using Perkin-Elmer RT mix. ISG gene induction was evaluated by real-time PCR using primers and probes specific for mouse OAS, Pkr and Mx1. To obtain quantitative data, HPRT real-time PCR was duplexed with ISG PCR. A standard curve was obtained using known amounts of RNA from IFN-stimulated mouse PBLs. All data are shown as expression relative to internal HPRT expression.

Human IL-28A and IL-29 stimulated ISG induction in the mouse hepatocyte cell line AML-12 and demonstrated that unlike type I IFNs, the IL-28/29 family proteins showed cross-species reactivity.

Table 22

Stimulation	**OAS**	**PkR**	**Mx1**
None	0.001	0.001	0.001
Human IL-28	0.04	0.02	0.06
Human IL-29	0.04	0.02	0.07
Mouse IL-28	0.04	0.02	0.08
Mouse IFNα	0.02	0.02	0.01

All data shown were expressed as fold relative to HPRT gene expression

ng of OAS mRNA = normalized value of OAS mRNA amount relative to internal

ng of HPRT mRNA housekeeping gene, HPRT

As an example, the data for the 48 hour time point is shown.

Table 23

AML12's

	Mx1 Fold Induction	OAS Fold Induction	Pkr Fold Induction
MetIL-29-PEG	728	614	8
MetIL-29C172S-PEG	761	657	8

Cells were stimulated with 20 ng/ml metIL-29-PEG or metIL-29C172S-PEG for 24 hours.

Data shown is normalized to HPRT and shown as fold induction over unstimulated cells.

Example 22

ISGs are Efficiently Induced in Spleens of Transgenic Mice Expressing Human IL-29

Transgenic (Tg) mice were generated expressing human IL-29 under the control of the Eu-lck promoter. To study if human IL-29 has biological activity *in vivo* in mice, expression of ISGs was analyzed by real-time PCR in the spleens of Eu-lck IL-29 transgenic mice.

Transgenic mice (C3H/C57BL/6) were generated using a construct that expressed the human IL-29 gene under the control of the Eu-lck promoter. This promoter is active in T cells and B cells. Transgenic mice and their non-transgenic littermates (n=2/gp) were sacrificed at about 10 weeks of age. Spleens of mice were isolated. RNA was isolated from cell pellets using RNAEasy-kit® (Qiagen). RNA was treated with DNase to clean RNA of any contaminating DNA. cDNA was generated using Perkin-Elmer RT® mix. ISG gene induction was evaluated by real-time PCR using primers and probes (5' FAM, 3' NFQ) specific for mouse OAS, Pkr and Mx1. To obtain quantitative data, HPRT real-time PCR was duplexed with ISG PCR. Furthermore, a standard curve was obtained using known amounts of IFN stimulated mouse PBLs. All data are shown as expression relative to internal HPRT expression.

Spleens isolated from IL-29 Tg mice showed high induction of ISGs OAS, Pkr and Mx1 compared to their non-Tg littermate controls suggesting that human IL-29 is biologically active *in vivo* in mice.

Table 24

Mice	**OAS**	**PkR**	**Mx1**
Non-Tg	4.5	4.5	3.5
IL-29 Tg	12	8	21

All data shown are fold expression relative to HPRT gene expresssion. The average expression in two mice is shown

Example 23

Human IL-28 and IL-29 Protein Induce ISG Gene Expression In Liver, Spleen and Blood of Mice

To determine whether human IL-28 and IL-29 induce interferon stimulated genes *in vivo*, CHO-derived human IL-28A and IL-29 protein were injected into mice. In addition, *E. coli* derived IL-29 was also tested in *in vivo* assays as described above using MetIL-29C172S-PEG and MetIL-29-PEG. At various time points and at different doses, ISG gene induction was measured in the blood, spleen and livers of the mice.

C57BL/6 mice were injected i.p or i.v with a range of doses (10 μg – 250 μg) of CHO-derived human IL-28A and IL-29 or MetIL-29C172S-PEG and MetIL-29C16-C113-PEG. Mice were sacrificed at various time points (1hr – 48hr). Spleens and livers were isolated from mice, and RNA was isolated. RNA was also isolated from the blood cells. The cells were pelleted and RNA isolated from pellets using RNAEasy®-kit (Qiagen). RNA was treated with DNase (Amicon) to rid RNA of any contaminating DNA. cDNA was generated using Perkin-Elmer RT mix (Perkin-Elmer). ISG gene induction was measured by real-time PCR using primers and probes specific for mouse OAS, Pkr and Mx1. To obtain quantitative data, HPRT real-time PCR was duplexed with ISG PCR. A standard curve was calculated using known amounts of IFN-stimulated mouse PBLs. All data are shown as expression relative to internal HPRT expression.

Human IL-29 induced ISG gene expression (OAS, Pkr, Mx1) in the livers, spleen and blood of mice in a dose dependent manner. Expression of ISGs peaked between 1-6 hours after injection and showed sustained expression above

control mice upto 48 hours. In this experiment, human IL-28A did not induce ISG gene expression.

Table 25

Injection	OAS- 1hr	OAS-6hr	OAS-24hr	OAS-48hr
None - liver	1.6	1.6	1.6	1.6
IL-29 liver	2.5	4	2.5	2.8
None - spleen	1.8	1.8	1.8	1.8
IL-29 - spleen	4	6	3.2	3.2
None - blood	5	5	5	5
IL-29 blood	12	18	11	10

Results shown are fold expression relative to HPRT gene expression. A sample data set for IL-29 induced OAS in liver at a single injection of 250 μg i.v. is shown. The data shown is the average expression from 5 different animals/group.

Table 26

Injection	OAS (24hr)
None	1.8
IL-29 10 μg	3.7
IL-29 50 μg	4.2
IL-29 250 μg	6

Table 27

	MetIL-29-PEG				MetIL-29C172S-PEG				Naive
	3hr	6hr	12hr	24hr	3hr	6hr	12hr	24hr	24hr
PKR	18.24	13.93	4.99	3.77	5.29	5.65	3.79	3.55	3.70
OAS	91.29	65.93	54.04	20.81	13.42	13.02	10.54	8.72	6.60
Mx1	537.51	124.99	33.58	35.82	27.89	29.34	16.61	0.00	10.98

Mice were injected with 100 μg of proteins i.v. Data shown is fold expression over HPRT expression from livers of mice. Similar data was obtained from blood and spleens of mice.

Example 24

IL-28 and IL-29 Induce ISG Protein In Mice

To analyze of the effect of human IL-28 and IL-29 on induction of ISG protein (OAS), serum and plasma from IL-28 and IL-29 treated mice were tested for OAS activity.

C57BL/6 mice were injected i.v with PBS or a range of concentrations (10 μg-250 μg) of human IL-28 or IL-29. Serum and plasma were isolated from mice at varying time points, and OAS activity was measured using the OAS radioimmunoassay (RIA) kit from Eiken Chemicals (Tokyo, Japan).

IL-28 and IL-29 induced OAS activity in the serum and plasma of mice showing that these proteins are biologically active *in vivo*.

Table 28

Injection	OAS-1hr	OAS-6hr	OAS-24hr	OAS-48hr
None	80	80	80	80
IL-29	80	80	180	200

OAS activity is shown at pmol/dL of plasma for a single concentration (250 μg) of human IL-29.

Example 25

Signal Transduction Reporter Assay

A signal transduction reporter assay can be used to determine the functional interaction of human and mouse IL-28 and IL-29 with the IL-28 receptor. Human embryonal kidney (HEK) cells are transfected with a reporter plasmid containing an interferon-stimulated response element (ISRE) driving transcription of a luciferase reporter gene in the presence or absence of pZP7 expression vectors containing cDNAs for class II cytokine receptors (including human DIRS1, IFNαR1, IFNαR2 and IL-28 receptor). Luciferase activity following stimulation of transfected cells with class II ligands (including IL-28A (SEQ ID NO: 2), IL-29 (SEQ ID NO: 4), IL-28B (SEQ ID NO: 6), zcyto10, huIL10 and huIFNa-2a) reflects the interaction of the ligand with transfected and native cytokine receptors on the cell surface. The results and methods are described below.

Cell Transfections

293 HEK cells were transfected as follows: 700,000 293 cells/well (6 well plates) were plated approximately 18h prior to transfection in 2 milliliters DMEM + 10% fetal bovine serum. Per well, 1 microgram pISRE-Luciferase DNA (Stratagene), 1 microgram cytokine receptor DNA and 1 microgram pIRES2-EGFP DNA (Clontech,) were added to 9 microliters Fugene 6 reagent (Roche Biochemicals) in a total of 100 microliters DMEM. Two micrograms pIRES2-EGFP DNA was used when cytokine receptor DNA was not included. This transfection mix was added 30 minutes later to the pre-plated 293 cells. Twenty-four hours later the transfected cells were removed from the plate using trypsin-EDTA and replated at approximately 25,000 cells/well in 96 well microtiter plates. Approximately 18 h prior to ligand stimulation, media was changed to DMEM + 0.5%FBS.

Signal Transduction Reporter Assays

The signal transduction reporter assays were done as follows: Following an 18h incubation at 37°C in DMEM + 0.5%FBS, transfected cells were stimulated with dilutions (in DMEM + 0.5%FBS) of the following class II ligands; IL-28A, IL-29, IL-28B, zcyto10, huIL10 and huIFNa-2a. Following a 4-hour incubation at 37°C, the cells were lysed, and the relative light units (RLU) were measured on a luminometer after addition of a luciferase substrate. The results obtained are shown as the fold induction of the RLU of the experimental samples over the medium alone control (RLU of experimental samples/RLU of medium alone = fold induction). Table 29 shows that IL-28A, IL-29, and IL-28B induce ISRE signaling in 293 cells transfected with ISRE-luciferase giving a 15 to 17-fold induction in luciferase activity over medium alone. The addition of IL-28 receptor alpha subunit DNA (SEQ ID NO:11), using the endogenous CRF2-4 (SEQ ID NO:71) to the transfection mix results in a 6 to 8-fold further induction in ISRE signaling by IL-28A, IL-29, and IL-28B giving a 104 to 125-fold total induction. None of the other transfected class II cytokine receptor DNAs resulted in increased ISRE signaling. These results indicate that IL-28A, IL-29, and IL-28B functionally interact with the IL-28 cytokine receptor. Table 29 also shows that huIFNa-2a can induce ISRE signaling in ISRE-luciferase transfected 293 cells giving a 205-fold induction of luciferase activity compared to medium alone. However, the addition of IL-28 receptor DNA to the transfection leads to an 11-fold reduction in

ISRE-signaling (compared to ISRE-luciferase DNA alone), suggesting that IL-28 receptor over-expression negatively effects interferon signaling, in contrast to the positive effects of IL-28 receptor over-expression on IL-28A, IL-29, and IL-28B signaling.

Table 29

Interferon Stimulated Response Element (ISRE) Signaling of Transfected 293 Cells Following Class II Cytokine Stimulation (Fold Induction)

Ligand	ISRE-Luc.	ISRE-Luc./IL-28R
IL-28A (125ng/ml)	15	125
IL-29 (125ng/ml)	17	108
IL-28B (125ng/ml)	17	104
HuIFNa-2a (100ng/ml)	205	18
Zcyto10 (125ng/ml)	1.3	1
HuIL10 (100ng/ml)	1	0.5

Example 26

Signal Transduction Assays with IL-29 Cysteine mutants

Cell Transfections

To produce 293 HEK cells stably overexpressing human IL-28 receptor, 293 cells were transfected as follows: 300,000 293 cells/well (6 well plates) were plated approximately 6h prior to transfection in 2 milliliters DMEM + 10% fetal bovine serum. Per well, 2 micrograms of a pZP7 expression vector containing the cDNA of human IL-28 receptor alpha subunit (SEQ ID NO: 11) was added to 6 microliters Fugene 6 reagent (Roche Biochemicals) in a total of 100 microliters DMEM. This transfection mix was added 30 minutes later to the pre-plated 293 cells. Forty-eight hours later the transfected cells were placed under 2 microgram/milliliter puromicin selection. Puromicin resistant cells were carried as a population of cells.

The 293 HEK cells overexpressing human IL-28 receptor were transfected as follows: 700,000 293 cells/well (6 well plates) were plated approximately 18h prior to transfection in 2 milliliters DMEM + 10% fetal bovine serum. Per well, 1 microgram KZ157 containing an interferon-stimulated response element (ISRE) driving transcription of a luciferase reporter gene were added to 3 microliters Fugene 6 reagent (Roche Biochemicals) in a total of 100 microliters DMEM. This transfection mix was added 30 minutes later to the pre-plated 293HEK cells. Forty-eight hours later the transfected cells were removed from the plate using trypsin-EDTA and replated in 500 micrograms/ml G418 (Geneticin, Life Technologies). Puromycin and G418 resistant cells were carried as a population of cells.

Signal Transduction Reporter Assays

The signal transduction reporter assays were done as follows: 293HEK cells overexpressing human IL-28 receptor and containing KZ157 were treated with trypsin-EDTA and replated at approximately 25,000 cells/well in 96 well microtiter plates. Approximately 18 h prior to ligand stimulation, media was changed to DMEM + 0.5%FBS.

Following an 18h incubation at 37°C in DMEM + 0.5%FBS, transfected cells were stimulated with dilutions (in DMEM + 0.5%FBS) of the different forms of E.coli-derived zcyto21 containing different cysteine binding patterns. Following a 4-hour incubation at 37°C, the cells were lysed, and the relative light units (RLU) were measured on a luminometer after addition of a luciferase substrate. The results obtained are shown as the fold induction of the RLU of the experimental samples over the medium alone control (RLU of experimental samples/RLU of medium alone = fold induction).

Table 30 shows that C1-C3 form (C16-C113) of wild-type *E. coli*-derived IL-29 is better able to induce ISRE signaling than wild-type C3-C5 form (C113-C172) or a mixture of wild-type C1-C3 form and C3-C5 form (C16-C113, C113-C172), all referring to SEQ ID NO:15.

Table 31 shows that C1-C3 (C16-C113) of wild-type *E. coli*-derived IL-29 and C1-C3 (C16-C113; SEQ ID NO:15) of Cysteine mutant (C172S) *E. coli*-derived IL-29 (SEQ ID NO:29) are equally able to induce ISRE signaling in 293HEK cells overexpressing human IL-28 receptor.

Table 30

ISRE Signaling by different forms of E.coli-derived IL-29 (Fold Induction)

Cytokine Concentration (ng/ml)	C1-C3 form (C16-C113)	C3-C5 form (C113-C172)	Mixture of C1-C3 and C3-C5
100	36	29	34
10	38	25	35
1	32	12	24
0.1	10	2	5
0.01	3	1	1
0.001	1	1	1

Table 31

ISRE Signaling by different forms of E.coli-derived IL-29 (Fold Induction)

Cytokine Concentration (ng/ml)	Wild-type C1-C3	Cysteine mutant C172S C1-C3
1000	9.9	8.9
100	9.3	8.7
10	9.3	8.1
1	7.8	7
0.1	4.6	3.3
0.01	1.9	1.5
0.001	1.3	0.9

Example 27

Human IL-29 Effect on B-cells and IL-29 Toxic Saporin Fusion

The effects of human IL-29 are tested on the following human B-cell lines: and human Burkitt's lymphoma cell lines Raji (ATCC No.CCL-86), and Ramos (ATCC No. CRL-1596); human EBV B-cell lymphoma cell line RPMI 1788 (ATCC No. CRL-156); human myeloma/plasmacytoma cell line IM-9 (ATCC No. CRL159); and human EBV transformed B-cell line DAKIKI (ATCC No. TIB-206), and HS Sultan cells (ATCC No. CRL-1484). Following about 2-5 days treatment with IL-29, changes in surface marker expression on the cells shows that these cells can respond to IL-29. Human B-cell lines treated with IL-29 grow much more slowly than untreated cells when replated in cell culture dishes. These cells also have an increased expression of FAS ligand, as assessed by flow cytometry (Example 27D and Example 27E), and moderately increased sensitivity to an activating FAS antibody (Example 27A). These results indicate that IL-29 could control some types of B-cell neoplasms by inducing them to differentiate to a less proliferative and or more FAS ligand sensitive state. Furthermore, IL-28 receptor is expressed on the surface of several B and T cell lines (Example 16). Thus, IL-29 and the human IL-29-saporin immunotoxin conjugate (Example 27B, below), or other IL-29-toxin fusion could be therapeutically used in B-cell leukemias and lymphomas.

A. The effect of human IL-29 on B-cell lines

IM-9 cells are seeded at about 50,000 cells per ml +/- 50 μg/ml purified human IL-29. After 3 days growth the cells are harvested, washed and counted then re-plated at about 2500 cells/ml in 96 well plates in to wells with 0, 0.033, 0.1 or 0.33 μg/ml anti-FAS antibody (R&D Systems, Minneapolis). After 2 days an Alamar blue fluorescence assay is performed (See U.S. Patent No. 6,307,024) to assess proliferation of the cells.

The growth of IL-29 treated IM-9 cells is inhibited relative to the growth of untreated cells in the absence of anti-FAS antibody. In the presence of 0.33 μg/ml anti-FAS antibody, the IL-29-treated cells are even further inhibited.

B. The effect of human IL-29-saporin immunotoxin on B-cell lines

The human IL-29-saporin immunotoxin conjugate (IL-29-sap) construction and purification is described in Example 28. The human IL-29-sap was far more potent than the saporin alone in inhibiting cell growth. When the treated cell are re-plated after a three or four day treatment the human IL-29-sap treated cells grow very poorly.

IM-9, Ramos and K562 (ATCC No. CCL-243) cells are seeded at about 2500 cells/well in 96 well plates with zero to 250 ng/ml human zalpha11L-sap conjugate or 0-250 ng/ml saporin (Stirpe et al., Biotechnology 10:405-412, 1992) only as a control. The plates are incubated 4 days then an Alamar Blue proliferation assay is performed (U.S. Patent No. 6,307,024). At the maximal concentration of human IL-29-sap conjugate, the growth of cells is inhibited. Cells lines low/negative by flow for expression of the IL-28 receptor are not affected by the IL-29-sap, thus showing the specificity of the conjugate's effect.

IM-9 cells are seeded a 50,000 cells/ml into 6 well plates at zero and 50 ng/ml human zalpha11L-sap conjugate. After 3 days the cells are harvested and counted then re-plated from 100 to 0.8 cells per well in 2 fold serial dilutions, and 12 wells per cell dilution without the human IL-29-saporin immunotoxin. After 6 days the number of wells with growth at each cell dilution is scored according to the results of an Alamar blue proliferation assay.

When cell number is assessed by Alamar blue assay the growth of the surviving treated IM-9 cells is markedly impaired even after the removal, by re-plating, of the IL-29-sap immunotoxin.

The limited tissue distribution of the human IL-28 receptor, and the specificity of action of the IL-29-sap to receptor-expressing cell lines suggest that this conjugate may be tolerated *in vivo*.

C. The effect of human IL-29-saporin immunotoxin on B-cell line viability

HS Sultan cells (ATCC No. CRL-1484) are seeded at about 40,000 cells per ml into 12 well plates and grown for five days with either no added cytokines or 40 ng/ml purified human IL-29 or 25 ng/ml human IL-29-sap conjugate (Example 28, below) or with 20 ng/ml IFN-alpha (RDI) or IL-29 and IFN-alpha. IL-29 and IFN-alpha inhibit the outgrowth of the cells indicating that the growth inhibitory effects of human IL-29 and IFN-alpha may be additive.

The results above support the possible use of IL-29 or human IL-29-sap in the treatment of malignancies or other diseases that express the IL-28 receptor, particularly those of B-cell origin. The combination of IL-29 with IFN-alpha is specifically suggested by their additive effect in the inhibition of HS Sultan cells. Some other types of lymphoid malignancies and diseases may also express the IL-28 receptor, as activated T-cells also express the receptor mRNA and some of these diseases may also be responsive to IL-29 of IL-29-toxic fusion therapy.

D. FAS (CD95) Expression on Human B-cell Lines is Increased by human IL-29 Stimulation

Human B-cell lines HS Sultan (ATCC No. CRL-1484), IM-9 (ATCC No. CRL159), RPMI 8226 (ATCC No. CCL-155), RAMOS (ATCC No. CRL-1596), DAKIKI (ATCC No. TIB-206), and RPMI 1788 (ATCC No. CRL-156), are all treated with or without purified 10 to 50 ng/ml human IL-29 for 2 to 8 days. The cells are then stained with anti-CD95 PE-conjugated antibody (PharMingen, San Diego, CA), per manufacturer's protocol, and analyzed on a FACScalibur (Becton Dickinson, San Jose, CA). In all cell lines, anti-CD95 (FAS or APO-1) staining is increased upon treatment with human IL-29.

E. FAS (CD95) Expression on Primary Mouse Spleen B-cells is Increased by Human IL-29 Stimulation

Primary mouse splenocytes are obtained by chopping up spleens from 8 to 12 week old C57/BL6 mice. Erythrocytes are lysed by treating the preparation for 5 seconds with water then put through a 70 micron sieve. The remaining splenocytes are washed and plated in RPMI (JRH Bioscience) plus 10% HIA-FBS (Hyclone, Logan, UT). IL-2 (R & D Systems) with or without human IL-29, as described above. They were then incubated at 37°C, in 5% CO_2 for 5 days. The splenocytes were harvested and stained with anti-CD95 PE conjugated antibody (PharMingen) and anti-CD19 FITC conjugated antibody (PharMingen) per manufacturer's protocol. The cells are analyzed by flow cytometry on a FACScalibur (Becton Dickinson).

Example 28

Construction and Purification of IL-29 Toxic Fusion

Ten mg human IL-29 is conjugated to the plant toxin saporin (Stirpe et al., Biotechnology 10,:405-412, 1992). The resulting 1.3 mg of a protein conjugate is comprised of 1.1 molecules saporin per molecule of human IL-29, formulated at a concentration of 1.14 mg/ml in 20 nM Sodium phosphate, 300 nM sodium cloride, pH 7.2.

Example 29

IL-29 Toxic Fusion *in vivo*

A. Testing IL-29-saporin conjugate in mice

IL-29-saporin conjugate (Example 27) is administered to C57BL6 mice (female, 12 weeks of age, purchased from Taconic) at two different dosages: 0.5 and 0.05 mg/kg. Injections are given i.v. in vehicle consisting of 0.1% BSA (ICN, Costa Mesa, CA). Three injections are given over a period of one week (day 0, 2, and 7). Blood samples are taken from the mice on day 0 (pre-injection) and on days 2 and 8 (post-injection). Blood is collected into heparinized tubes (Bectin Dickenson, Franklin Lakes, NJ), and cell counts are determined using an automated hematology analyzer (Abbot Cell-Dyn model No. CD-3500CS, Abbot Park, IL). Animals are euthanized and

necropsied on day 8 following blood collection. Spleen, thymus, liver, kidney and bone marrow are collected for histopathology. Spleen and thymus are weighed, and additional blood sample is collected in serum separator tubes. Serum is tested in a standard chemistry panel. Samples are also collected for flow cytometric analysis as described herein.

B. Testing IL-29 toxic saporin fusion on B-cell derived tumors in vivo

The effects of human IL-29 and the human IL-29 toxic saporin fusion (Example 28) on human tumor cells are tested *in vivo* using a mouse tumor xenograft model described herein. The xenograft models are initially tested using cell lines selected on the basis of *in vitro* experiments, such as those described in Example 27. These cell lines include, but are not limited to: human Burkitt's lymphoma cell lines Raji (ATCC No.CCL-86), and Ramos (ATCC No. CRL-1596); human cell line RPMI 1788 (ATCC No. CRL-156); human myeloma/plasmacytoma cell line IM-9 (ATCC No. CRL159); human cell line DAKIKI (ATCC No. TIB-206), and HS Sultan cells (ATCC No. CRL-1484). Cells derived directly from human tumors can also be used in this type of model. In this way, screening of patient samples for sensitivity to treatment with IL-29 or with a IL-29 toxic saporin fusion can be used to select optimal indications for use of zalpha11 in anti-cancer therapy.

After selection of the appropriate zenograft *in vivo* model, described above, IL-29-induced activity of natural killer cells and/or IL-29 effects on B-cell derived tumors is assessed *in vivo*. Human IL-29 is tested for its ability to generate cytotoxic effector cells (e.g., NK cells) with activity against B-cell derived tumors using mouse tumor xenograft models described herein. Moreover, direct affects of human IL-29 on tumors can be assessed. The xenograft models to be carried out are selected as described above. A protocol using IL-29 stimulated human cells is developed and tested for efficacy in depleting tumor cells and promoting survival in mice innoculated with cell lines or primary tumors.

Example 30

IL-29 Effect on B-cell Derived Tumors *in vivo*

A. Infusion of IL-29 using mini-osmotic pumps

Administration of IL-29 by constant infusion via mini-osmotic pumps results in steady state serum concentrations proportional to the concentration of the IL-29 contained in the pump. 0.22 ml of human IL-29 contained in phosphate buffered saline (pH 6.0) at a concentration of 2 mg/ml or 0.2 mg/ml is loaded under sterile conditions into Alzet mini-osmotic pumps (model 2004; Alza corporation Palo Alto, CA). Pumps are implanted subcutaneously in mice through a 1 cm incision in the dorsal skin, and the skin is closed with sterile wound closures. These pumps are designed to deliver their contents at a rate of 0.25 μl per hour over a period of 28 days. This method of administration results in significant increase in survival in mice injected with tumor cells (below).

B. IL-29 effect on B-cell derived tumors in vivo

The effects of human IL-29 are tested *in vivo* using a mouse tumor xenograft model described herein. The xenograft model to be tested is human lymphoblastoid cell line IM-9 (ATCC No. CRL159). C.B-17 SCID mice (female C.B-17/IcrHsd-scid; Harlan, Indianapolis, Indiana) are divided into 4 groups. On day 0, IM-9 cells (ATCC No. CRL159) are harvested from culture and injected intravenously, via the tail vein, to all mice (about 1,000,000 cells per mouse). On day 1, mini-osmotic pumps containing test article or control article are implanted subcutaneously in the mice. Mice in groups 1-3 (n=9 per group) are treated with increasing concentrations of IL-29: group 1 contains 2.0 mg/mL of human IL-29 and is delivered 12 μg per day; group 2 contains 0.20 mg/mL of human IL-29 and is delivered 1.2 μg per day; group 3 contained 0.02 mg/mL of human IL-29 and is delivered 0.12 μg per day. Mice in group 4 (n = 9) are a control and are treated with vehicle (PBS pH 6.0).

Mice treated with either 12 μg/day or 1.2 μg/day IL-29 infusion have increased survival compared to vehicle treated mice ($p<.0001$ and $p<.005$ for 12 μg/day or 1.2 μg/day vs. vehicle, respectively, using log rank tests of the survival function). These results show that IL-29 significantly reduced the effects of the B-cell tumor cells *in vivo*, significantly resulting in increased survival.

Example 31

In vivo Anti-tumor Effects of IL-29 in B16-F10 Melanoma and EG.7 Thymoma Models

A. Murine IL-29 effect on B16-F10 melanoma metastasis growth in vivo

Mice (female, C57Bl6, 9 weeks old; Charles River Labs, Kingston, NY) are divided into three groups. On day 0, B16-F10 melanoma cells (ATCC No. CRL-6475) are harvested from culture and injected intravenously, via the tail vein, to all mice (about 100,000 cells per mouse). Mice are then treated with the test article or associated vehicle by intraperitoneal injection of 0.1 ml of the indicated solution. Mice in the first group (n = 24) are treated with vehicle (PBS pH 6.0), which is injected on day 0, 2, 4, 6, and 8. Mice in the second group (n = 24) are treated with zcyto24 or zcyto25, which is injected at a dose of 75 μg on day 0, 2, 4, 6, and 8. Mice in the third group (n = 12) are treated with zcyto24 or zcyto25, which is injected at a dose of 75 μg daily from day 0 through day 9. All of the mice are sacrificed on day 18, and lungs are collected for quantitation of tumor. Foci of tumor growth greater than 0.5 mm in diameter are counted on all surfaces of each lung lobe. In both groups of mice treated with zcyto24 or zcyto25, the average number of tumor foci present on lungs is significantly reduced, compared to mice treated with vehicle. Mice treated more frequently (i.e. daily) have fewer tumor foci than mice treated on alternate days.

These results indicated that treatment with zcyto24 or zcyto25 either slowed the growth of the B16 melanoma tumors or enhanced the ability of the immune system to destroy the tumor cells. The effects of the treatment on tumor cells are likely mediated through cells of the immune system which do possess receptors for IL-29.

B. Murine IL-29 effect on EG.7 thymoma growth in vivo

Mice (female, C57Bl6, 9 weeks old; Charles River Labs, Kingston, NY) are divided into three groups. On day 0, EG.7 cells (ATCC No. CRL-2113) are harvested from culture and 1, 000, 000 cells are injected intraperitoneal in all mice. Mice are then treated with the test article or associated vehicle by intraperitoneal injection of 0.1 mL of the indicated solution. Mice in the first group (n = 6) are treated with vehicle (PBS pH 6.0), which is injected on day 0, 2, 4, and 6. Mice in the second group (n = 6) are treated with zcyto24 or zcyto25, which is injected at a dose of 10 μg on day 0, 2, 4, and 6. Mice in the third group (n = 6) are treated with zcyto24 or zcyto25, which is injected at a dose of 75 μg on day 0, 2, 4, and 6. In both groups of

mice treated with zcyto24 or zcyto25, time of survival is significantly increased, compared to mice treated with vehicle. These results indicate that treatment with zcyto24 or zcyto25 either slowed the growth of the EG.7 tumors or enhanced the ability of the immune system to destroy the tumor cells.

Example 32

Flow Cytometric Analysis IL-28 Receptor Expression.

The expression of IL-28 receptors on neoplastic B cells derived from non-Hodgkin's lymphoma (NHL) specimens is assessed. Multiple MAbs are used to identify neoplastic B cells and to co-localize IL-28 receptors. The immunofluorescent staining by anti-IL-28 receptor MAb or by biotin-IL-29 is recorded as mean peak fluorescence. The qualitative scores are assessed based on the shift in mean peak fluorescence relative to an isotype matched control MAb.

Anti-IL-28 receptor MAb or biotin-IL-29 is used to detect IL-28 receptor on the neoplastic B cells by immunofluorescent staining. The intensity of the staining signal correlates to the levels of IL-28 receptor. These data suggests that IL-28 receptors represent a therapeutic target for non Hodgkin's lymphoma.

Example 33

In vivo Effects of IL-29 on B-cell lymphomas

Human B-lymphoma cell lines are maintained *in vitro* by passage in growth medium. The cells are washed thoroughly in PBS to remove culture components.

SCID Mice are injected with (typically) one million human lymphoma cells via the tail vein in a 100 microliter volume. The optimal number of cell injected is determined empirically in a pilot study to yield tumor take consistently with desired kinetics. IL-29 treatment is begun the next day by either subcutaneous implantation of an ALZET® osmotic mini-pump (ALZET, Cupertino, CA) or by daily i.p. injection of IL-29 or vehicle. Mice are monitored for survival and significant morbidity. Mice that lose greater than 20% of their initial body weight are sacrificed, as well as mice that exhibit substantial morbidity such as hind limb paralysis. Depending on the lymphoma cell line employed, the untreated mice typically die in 3 to 6 weeks. For B cell

lymphomas that secrete IgG or IgM, the disease progression can also be monitored by weekly blood sampling and measuring serum human Immunoglobulin levels by ELISA.

IL-29 Dose response/ IM-9 model

Mice are injected with 1 x 10^6 IM-9 cells, and 28 day osmotic mini pumps implanted the following day. The pumps are loaded with the following concentrations of IL-29 to deliver: 0, 0.12, 1.2 or 12 micrograms per day with 8 mice per dose group. IL-29 exhibits a clear dose dependent effect in protecting mice from the tumor cell line. The effects of IL-29 are dose dependent. Surviving mice at the end of the experiment have no signs of disease and no detectable human IgG in their serum.

These data demonstrate that the efficacy of IL-29 in SCID mouse lymphoma models correlates with the ability to inhibit the growth of the lymphoma cell lines *in vivo*.

Example 34

The Effects of IL-29 in a Mouse Syngeneic Ovarian Carcinoma Model

The effect of IL-29 is tested for efficacy in ovarian carcinoma using a mouse syngeneic model as described in Zhang et al., Am. J. of Pathol. 161:2295-2309, 2002. Briefly, using retroviral transfection and fluorescence-activated cell sorting a C57BL6 murine ID8 ovarian carcinoma cell line is generated that stably overexpresses the murine VEGF164 isoform and the enhanced green fluorescence protein (GFP). The retroviral construct containing VEGF164 and GFP cDNAs was transfected into BOSC23 cells. The cells are analyzed by FACS cell sorting and GFP high positive cells are identified.

The ID8 VEGF164/GFP transfected cells are cultured to subconfluence and prepared in a single-cell suspension in phosphate buffer saline (PBS) and cold MATRIGEL (BD Biosciences, Bedford, MA). Six to eight week old femal C57BL6 mice are injected subcutaneously in the flank at 5 x 10^6 cells or untransfected control cells. Alternatively, the mice can be injected intraperitoneally at 7 x 10^6 cells or control cells. Animals are either followed for survival or sacrificed eight weeks after inoculation and evaluated for tumor growth. Mice are treated with recombinant

zcyto24 or zcyto25 beginning 3-14 days following tumor implantation, or when tumor engraftment and growth rate is established. Treatment levels of 0.5 - 5 mg/kg will be administered on a daily basis for 5-14 days, and may be continued thereafter if no evidence of neutralizing antibody formation is seen.

Example 35

The Effects of IL-29 in a Mouse RENCA Model

The efficacy of IL-29 in a renal cell carcinoma model is evaluated using BALB/c mice that have been injected with RENCA cells, a mouse renal adenocarcinoma of spontaneous origin, essentially as described in Wigginton et al., J. Nat. Cancer Instit. 88:38-43, 1996.

Briefly, BALB/c mice between eight and ten weeks are injected with RENCA cells R 1X 10^5 cells into the kidney capsule of the mice. Twelve days after tumor cell implantation, the mice are nepharectomized to remove primary tumors. The mice are allowed to recover from surgery, prior to administration of IL-29. Mice are treated with recombinant zcyto24 or zcyto25 beginning 3-14 days following tumor implantation, or when tumor engraftment and growth rate is established. Treatment levels of 0.5 - 5 mg/kg will be administered on a daily basis for 5-14 days, and may be continued thereafter if no evidence of neutralizing antibody formation is seen. Alternatively, RENCA cells may be introduced by subcutaneous (5 x 10e5 cells) or intravenous (1 x 10e5 cells) injection.

The mice are evaluated for tumor response as compared to untreated mice. Survival is compared using a Kaplan-Meier method, as well as tumor volume being evaluated.

Example 36

The Effects of IL-29 in a Mouse Colorectal Tumor Model

The effects of IL-29 in a colorectal mouse model are tested as described in Yao et al., Cancer Res. 63:586-592, 2003. In this model, MC-26 mouse colon tumor cells are implanted into the splenic subcapsul of BALB/c mice. After 14 days, the treated mice are administered IL-29. Mice are treated with recombinant zcyto24 or zcyto25 beginning 3-14 days following tumor implantation, or when tumor engraftment

and growth rate is established. Treatment levels of 0.5 - 5 mg/kg will be administered on a daily basis for 5-14 days, and may be continued thereafter if no evidence of neutralizing antibody formation is seen.

The efficacy of IL-29 in prolonging survival or promoting a tumor response is evaluated using standard techniques described herein.

Example 37

The Effect of IL-29 in a Mouse Pancreatic Cancer Model

The efficacy of IL-29 in a mouse pancreatic cancer model is evaluated using the protocol developed by Mukherjee et al., J. Immunol. 165:3451-3460, 2000. Briefly, MUC1 transgenic (MUC1.Tg) mice are bred with oncogene-expressing mice that spontaneously develop tumors of the pancreas (ET mice) designated as MET. MUC1.Tg mice. ET mice express the first 127 aa of SV40 large T Ag under the control of the rat elastase promoter. Fifty percent of the animals develop life-threatening pancreatic tumors by about 21 wk of age. Cells are routinely tested by flow cytometry for the presence of MUC1. All mice are on the C57BL/6 background. Animals are sacrificed and characterized at 3-wk intervals from 3 to 24 wk. Mice are carefully observed for signs of ill-health, including lethargy, abdominal distention, failure to eat or drink, marked weight loss, pale feces, and hunched posture.

The entire pancreas is dissected free of fat and lymph nodes, weighed, and spread on bibulus paper for photography. Nodules are counted, and the pancreas is fixed in methacarn, processed for microscopy by conventional methods, step sectioned at 5 μm (about 10 sections per mouse pancreas), stained with hematoxylin and eosin, and examined by light microscopy. Tumors are obtained from MET mice at various time points during tumor progression, fixed in methacarn (60% methanol, 30% chloroform, 10% glacial acetic acid), embedded in paraffin, and sectioned for immunohistochemical analysis. MUC1 antibodies used are CT1, a rabbit polyclonal Ab that recognizes mouse and human cytoplasmic tail region of MUC1, HMFG-2, BC2, and SM-3, which have epitopes in the TR domain of MUC1.

Determination of CTL activity is performed using a standard ^{51}Cr release method after a 6-day in vitro peptide stimulation without additional added cytokines.

Splenocytes from individual MET mice are harvested by passing through a nylon mesh followed by lysis of RBC.

Single cells from spleens of MET mice are analyzed by two-color immunofluorescence for alterations in lymphocyte subpopulations: CD3, CD4, CD8, Fas, FasL, CD11c, and MHC class I and II. Intracellular cytokine levels were determined after cells are stimulated with MUC1 peptide (10 μg/ml for 6 days) and treated with brefeldin-A (also called Golgi-Stop; PharMingen) as directed by the manufacturer's recommendation (4 μl/1.2 x 10^7 cells/6 ml for 3 h at 37°C before staining). Cells are permeabilized using the PharMingen permeabilization kit and stained for intracellular IFN-γ, IL-2, IL-4, and IL-5 as described by PharMingen. All fluorescently labeled Abs are purchased from PharMingen. Flow cytometric analysis is done on Becton Dickinson FACscan using the CellQuest program (Becton Dickinson, Mountain View, CA).

Mice are treated with recombinant zcyto24 or zcyto25 beginning 3-14 days following tumor implantation, or when tumor engraftment and growth rate is established. Treatment levels of 0.5 - 5 mg/kg will be administered on a daily basis for 5-14 days, and may be continued thereafter if no evidence of neutralizing antibody formation is seen.

Example 38

The Effects of IL-29 in a Murine Breast Cancer Model

The efficacy of IL-29 in a murine model for breast cancer is made using a syngeneic model as described in Colombo et al., Cancer Research 62:941-946, 2002. Briefly, TS/A cells which are a spontaneous mammary carcinoma for BALB/C mice. The cells are cultured for approximately one week to select for clones. The selected TS/A cells are grown and used to challenge CD-1 *nu/nu* BR mice (Charles River Laboratories) by injected 2 x 10^2 TS/A cells subcutaneously into the flank of the mouse.

Mice are treated with recombinant zcyto24 or zcyto25 beginning 3-14 days following tumor implantation, or when tumor engraftment and growth rate is established. Treatment levels of 0.5 - 5 mg/kg will be administered on a daily basis for 5-14 days, and may be continued thereafter if no evidence of neutralizing antibody

formation is seen. The tumors are excised after sacrificing the animals and analyzed for volume and using histochemistry and immunohistochemistry.

Example 39

The Effects of IL-29 in a Murine Prostate Cancer Model

The effects of IL-29 on tumor response are evaluated in murine prostate cancer model, using a model similar to that described in Kwon et al., PNAS 96:15074-15079, 1999. In this model, there is a metastatic outgrowth of transgenic adenocarcinoma of mouse prostate (TRAMP) derived prostate cancer cell line TRAMP-C2, which are implanted in C57BL/6 mice. Metastatic relapse is reliable, occurring primarily in the draining lymph nodes in close proximity to the primary tumor.

Briefly, the C2 cell line used is an early passage line derived from the TRAMP mouse that spontaneously develops autochthonous tumors attributable to prostate-restricted SV40 antigen expression. The cells are cultured and injected subcutaneously into the C57BL/6 mice at 2.5-5 x 10^6 cells/0.1 ml media. Mice are treated with recombinant zcyto24 or zcyto25 beginning 3-14 days following tumor implantation, or when tumor engraftment and growth rate is established. Treatment levels of 0.5 - 5 mg/kg will be administered on a daily basis for 5-14 days, and may be continued thereafter if no evidence of neutralizing antibody formation is seen. The tumors are excised after sacrificing the animals and analyzed for volume and using histochemistry and immunohistochemistry.

Example 40

The Effects of IL-28 and IL-29 in the Murine Experimental Allergic Encephalomyelitis (EAE) Model

Experimental allergic encephalomyelitis (EAE) is a mouse model for human Multiple Sclerosis (MS) (Gold et al., Mol. Med. Today, 6:88-91, 2000; Anderton et al., Immunol. Rev., 169:123-137, 1999). There are multiple ways of inducing disease in mice. One such method is to immunize mice with a peptide of the myelin protein myelin oligodendrocyte glycoprotein (MOG). This protein is present on the outside of the myelin sheath and acts as a protective layer for myelin. Mice were

immunized sub-cutaneously with MOG peptide (MOG35-55) emulsified in RIBI adjuvant on day 0. Mice were then injected intravenously with pertussis toxin (PT) on day 2. The mice started showing symptoms of paralysis starting with a limp tail, wobbly motion, followed by hind limb and forelimb paralysis, which were scored according to several different parameters that measured the timing, extent and severity of disease. Delay in onset of disease indicates that the drug is modifying the disease process in mice. Decrease in incidence indicates that the drug is having an effect on the number of mice that are getting sick. Decrease in clinical score indicates that the drug has an effect on the severity of disease. Groups of mice were given PBS or either mouse IL28 (SEQ ID NO:8) or human IL29C172S (SEQ ID NO:29)-PEG. The onset of symptoms, incidence of disease scores and severity of disease scores in IL-28/29 treated mice indicates the effect of IL-28/29 on these parameters in this model. Mice (n=13/gp) were immunized s.c with 100ug MOG35-55 in RIBI adjuvant on d0. All mice received 200ng pertussis toxin i.v on d2. Groups of mice were treated i.p with PBS, 25ug human IL29C172S every other day (EOD) on days 1-18 or with PBS, BSA or mouse IL28. As specified above, mice were scored for clinical signs and weight loss daily from d0-d30. IL29 C172S(SEQ ID NO:29)-PEG or mouse IL28 (SEQ ID NO:8) treated mice showed a delay in the onset of disease compared to PBS treated animals.

Table 32

Treatment groups D0-18 (EOD)	**Mean Day of Onset (MDO)**	**P value (vs PBS group) Mantel-Cox test**
PBS	21.1 ± 4.7	-
25ug human IL29 C172S-PEG	28.8 ± 4.5	0.0006

Table 33

Treatment groups Days 1-21 EOD	Mean Day of Onset (MDO)	P value (vs PBS group) Mantel-Cox test
PBS	8.6 ± 1.6	-
130ug BSA	8.6 ± 1.3	NS
130ug mIL28	12.2 ± 3.3	P=0.0009 (PBS) P=0.001 (BSA)

Table 34

Treatment groups Days 1-11 EOD	Mean Day of Onset (MDO)	P value (vs PBS group) Mantel-Cox test
PBS	9.5 ± 2.5	-
50ug mIL28	12.4 ± 3.8	P=0.0354
200ug mIL28	13.5 ± 3.2	P=0.0007

IL-29 delays onset of disease in a mouse model for multiple sclerosis

A. Summary

To test if human IL-29 had any effects on multiple sclerosis, the ablility of IL-29 to inhibit experimental autoimmune encephalomyelitis (EAE), a mouse model for MS was tested. The well characterized myelin oligodendrocyte glycoprotein (MOG) 35-55 peptide immunization model in C57BL/6 mice was used. The experiment was run to determine that IL-29 could delay and/or inhibit disease scores in EAE. IL-29 delayed onset of disease in the EAE model, suggesting that use of IL-29 may be beneficial in MS.

B. Study design

Experimental autoimmune encephalomyelitis (EAE) is a mouse model for MS. In one such model, C57BL/6 mice are immunized with 100 μg MOG pepetide (MOG35-55) emulsified in RIBI adjuvant. Two milliliters of a 0.5 mg/ml preparation of the MOG35-55 in PBS was added to a vial of RIBI and vortexed vigorously to emulsify the solution. The backs of mice were shaved and 100 μg MOG/RIBI was injected s.c in the backs of mice. Weights of mice were taken 2 days before and every

day after the immunization. Mice were then injected on day 2 i.v with 200 µl pertussis toxin (PT), a final concentration of 200 ng/mouse. Mice were monitored daily for clinical scores. Groups of mice were injected i.p. with 200 µl PBS, or 25ug IL-29 C172S(SEQ ID NO:29)-PEG in a 200 µl volume EOD from days 0-18. The weights of mice, clinical scores and incidence were evaluated and plotted for analysis.

C. Results and conclusion

Administration of IL-29 EOD from days 0-18 delayed onset of disease in this model. This delay was significant compared to PBS treated mice (p=0.0006, Mantel-Cox test).

IL-28 delays onset of disease in a mouse model for multiple sclerosis

A. Summary

To test if mouse IL-28 had any effects on multiple sclerosis, the ablility of IL-28 to inhibit experimental autoimmune encephalomyelitis (EAE), a mouse model for MS was tested. The well characterized myelin oligodendrocyte glycoprotein (MOG) 35-55 peptide immunization model in C57BL/6 mice was used. The experiment was run to determine that IL-28 could delay and/or inhibit disease scores in EAE. IL-28 delayed onset of disease in the EAE model, suggesting that use of IL-28 may be beneficial in treatment of MS.

B. Study design

Experimental autoimmune encephalomyelitis (EAE) is a mouse model for MS. In one such model, C57BL/6 mice are immunized with 100 µg MOG pepetide (MOG35-55) emulsified in RIBI adjuvant. Two milliliters of a 0.5 mg/ml preparation of the MOG35-55 in PBS was added to a vial of RIBI and vortexed vigorously to emulsify the solution. The backs of mice were shaved and 100 µg MOG/RIBI was injected s.c in the backs of mice. Weights of mice were taken 2 days before and every day after the immunization. Mice were then injected on day 2 i.v with 200 µl pertussis toxin (PT), a final concentration of 200 ng/mouse. Mice were monitored daily for clinical scores. In one experiment groups of mice were injected i.p. with 200 µl PBS,

50ug mIL28 or 200ug mIL28 (SEQ ID NO:8) in a 200 µl volume EOD from days 1-11. In a second experiment groups of mice were injected i.p. with 200 µl PBS, 130ug BSA or 130ug mIL28 (SEQ ID NO:8) in a 200 µl volume EOD from days 1-21. The weights of mice, clinical scores and incidence were evaluated and plotted for analysis.

C. Results and conclusion

Administration of IL-28 EOD delayed onset of disease in this model in a dose dependent manner. This delay was significant compared to PBS or BSA treated mice.

Example 41

IL-29 and IFNα2a MicroArray Comparison in Hepatoma Cell Line HepG2

A. Introduction

Type 1 interferons (IFNs) are induced following viral infection as part of the body's immune response to the virus. These proteins inhibit viral replication through the induction of interferon-stimulated genes (ISGs) that act to directly inhibit viral replication, increase the lytic potential of NK cells (Biron, C. A. 1998. Role of early cytokines, including alpha and beta interferons (IFN-alpha/beta), in innate and adaptive immune responses to viral infections. *Semin Immunol* 10:383-90) and modulate the adaptive immune response by increasing MHC class I expression to promote antigen presentation (Fellous, M., Nir, U., Wallach, D., Merlin, G., Rubinstein, M., and Revel, M. 1982. Interferon-dependent induction of mRNA for the major histocompatibility antigens in human fibroblasts and lymphoblastoid cells. *Proc Natl Acad Sci U S A* 79:3082-6), promoting T cell survival (Marrack, P., Kappler, J., and Mitchell, T. 1999. Type I interferons keep activated T cells alive. *J Exp Med* 189:521-30) and stimulating dendritic cell maturation (Buelens, C., Bartholome, E. J., Amraoui, Z., Boutriaux, M., Salmon, I., Thielemans, K., Willems, F., and Goldman, M. 2002. Interleukin-3 and interferon beta cooperate to induce differentiation of monocytes into dendritic cells with potent helper T-cell stimulatory properties. *Blood* 99:993-8). Because of this profound effect on the viral lifecycle, IFNα2a has proved to be a valuable therapeutic agent for the treatment of Hepatitis C.

In addition to the type I interferons, viral infection induces the production of IL-28 and IL-29 (IFNλ 1-3), a recently discovered family of novel class II cytokines distantly related to IFNα and IL-10. Like the Type 1 IFNs IL28/29 have antiviral activity against a number of viruses (Sheppard, P. et al., 2003. IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol* 4:63-8; Kotenko, S. V. et al., 2003. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol* 4:69-77; and Robek, M. D. et al., 2005. Lambda interferon inhibits hepatitis B and C virus replication. *J Virol* 79:3851-4). We and others have previously shown that IL-29 induces the ISGs Mx1, PRKR and OAS in primary human hepatocytes a well as human hepatoma cell lines such as HuH7 and HepG2. Therefore IL28/29 may regulate biology similar to IFNα2a and have therapeutic value against chronic viral hepatitis in human patients. However, IL-29 and IFNα utilize distinct receptors making it possible that these two cytokines could potentially regulate other cytokine-specific genes subsets and biological processes. It was therefore of interest to compare the gene regulation profiles of these two cytokines on a global scale. Accordingly, HepG2 cells were treated with IL-29 and IFNα2a for varying times prior to isolation of total RNA and analysis of gene regulation using DNA microarray analysis.

B. Study Design

To identify genes regulated by IL-29 and IFNα2a in hepatocytes, microarray experiments were performed on the hepatoma cell line HepG2. For these studies triplicate cultures of HepG2 cells were treated with media as a negative control, 50 μg/ml human IL-29 (SEQ ID NO:4) or 5 μg/ml human IFNα2a for one, six or twenty-four hours. Following stimulation, total RNA was extracted using the RNeasy Mini kit from QIAGEN and RNA quality and quantity were assessed on an Agilent 2100 Bioanalyzer using the RNA 6000 Nano Assay (Agilent) according to the manufacturers instructions. Briefly, biotin-labeled cRNAs were synthesized using the GeneChip® One-Cycle Target Labeling and Control Reagents from Affymetrix. Fragmented cRNA for each sample was hybridized to Affymetrix Human Genome Focus Arrays and stained according to the manufacturer's instructions. Arrays were then scanned on an Affymetrix GeneChip® Scanner 3000 and raw data generated using

Affymetrix GeneChip® Operating Software (GCOS) data mining software. Raw data was then loaded into the GeneSpring 7.0 microarray analysis program (Silicon Genetics) for data analysis purposes. Values of less than 0.01 were transformed to a value of 0.01. The intensity of each array was normalized to the 50th percentile for all arrays using all values not absent and having a raw value of 50 or greater. Values on a per gene basis were normalized to the median calculated for values with a raw value of 50 or greater on all arrays. Scatter plots were generated using unfiltered data. Genes regulated by IL-29 were identified as having a 1-way analysis of variance (ANOVA) *p*-value of less than or equal to 0.05, a raw intensity in IL-29-treated samples of 600 (three times the background) or greater and a fold change of 2 or greater as compared to the media-treated sample at the corresponding time point. The most profound induction of genes was observed at the six-hour time point.

C. Results and Discussion

Upon analyzing the microarray results it was apparent that gene regulation by both IL-29 and IFNα2a in HepG2 cells was transient, peaking at six hours followed by a gradual decline. After comparing the data from the IL-29-treated sample to the data from the IFNα2a-treated sample all genes were found to be regulated similarly by the two cytokines indicating that IL-29 and IFNα2a regulate identical gene subsets in hepatocytes. However, the degree of induction by IFNα2a in HepG2 cells was more profound than that elicited by IL-29. The list of all genes identified as upregulated by IL-29 as determined by the criteria listed in the Study Design is listed below in Table 35. These genes were found to consist exclusively of known interferon-stimulated genes (ISGs) coding for proteins involved in antiviral responses (OAS genes, MX genes and PRKR, ADAR), regulation of proliferation (IFITM1, IFITM3, CEB1), apoptosis (TNFSF10) and signal transduction (NMI, STAT1, IRF9). These data suggest that IL-29 mediates biology identical to that regulated by the type 1 interferons in cells such as hepatocytes that express the IL-28 receptor.

. Table 35

Gene Name	Description	Unigene ID	IFN Fold Change	IL-29 Fold Change
IFIT1	interferon-induced protein with tetratricopeptide repeats 1	Hs.20315	384.1	198.1
IFI27	interferon, alpha-inducible protein 27	Hs.532634	221.5	91.96
OAS2	2'-5' oligoadenylate synthetase 2	Hs.414332	92.73	40.91
MX1	myxovirus (influenza virus) resistance 1	Hs.517307	81.47	42.44
G1P3	interferon, alpha-inducible protein (clone IFI-6-16)	Hs.523847	38.48	32.87
CEB1	cyclin-E binding protein 1	Hs.26663	34.09	4.526
IFIT3	interferon-induced protein with tetratricopeptide repeats 3	Hs.47338	33.06	12.58
OAS1	2',5'-oligoadenylate synthetase 1	Hs.524760	26.78	13.1
OASL	2'-5'-oligoadenylate synthetase-like	Hs.118633	25.87	8.516
OAS3	2'-5'-oligoadenylate synthetase 3	Hs.528634	23.15	10.83
MDA5	melanoma differentiation associated protein-5	Hs.163173	22.7	7.423
G1P2	interferon, alpha-inducible protein (clone IFI-15K)	Hs.458485	22.49	13.6
DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	Hs.190622	21.63	8.265
APOL6	apolipoprotein L, 6	Hs.257352	18.16	7.865
HSXIAPAF1	XIAP associated factor-1	Hs.441975	15.2	7.96
NMI	N-myc (and STAT) interactor	Hs.54483	13.85	3.855
PLSCR1	phospholipid scramblase 1	Hs.130759	11.64	6.899
UBE2L6	ubiquitin-conjugating enzyme E2L 6	Hs.425777	11.21	4.463
SP110	SP110 nuclear body protein	Hs.145150	10.94	4.551
USP18	ubiquitin specific protease 18	Hs.38260	10.83	4.357
ISGF3G	interferon regulatory factor 9	Hs.1706	10.44	7.496
STAT1	signal transducer and activator of transcription 1, 91kDa	Hs.470943	9.701	5.565
SP100	Nuclear antigen Sp100	Hs.369056	9.328	3.567
PSMB9	proteasome (prosome, macropain) subunit, beta type, 9	Hs.381081	9.227	3.128
TNFSF10	tumor necrosis factor superfamily, member 10 (TRAIL)	Hs.478275	8.819	3.003
MX2	myxovirus (influenza virus) resistance 2	Hs.926	7.847	3.368
IFIT5	interferon-induced protein with tetratricopeptide repeats 5	Hs.252839	7.208	4.143
ISG20	interferon stimulated gene 20kDa	Hs.459265	7.188	2.489
PRKR	interferon-inducible double stranded RNA dependent protein kinase	Hs.131431	7.025	4.924
IFITM1	interferon induced transmembrane protein 1 (9-27)	Hs.458414	6.288	3.144
LY6E	lymphocyte antigen 6 complex, locus E (Sca-2)	Hs.521903	4.047	2.282
BST2	bone marrow stromal cell antigen 2	Hs.118110	3.737	2.127
IFITM3	interferon induced transmembrane protein 3 (1-8U)	Hs.374650	3.057	2.25

Example 42

Mouse IL28 plasmid inhibits growth of renal cell carcinoma RENCA tumors in mice

A. Summary

To determine whether IL28/IL29 has an effect on tumor growth in mice, groups of mice were injected s.c with the RENCA tumor on Day 0. Mice were then injected with 50ug control vector plasmid or mIL28 plasmid (SEQ ID NO:7) by hydrodynamic delivery (HDD) on Days 5 and 12. Tumor volume was monitored 3X/week for 5 weeks. Mouse IL28 protein level in serum was measured by ELISA. Mice injected with mIL28 plasmid showed significantly smaller tumors compared to control plasmid injected mice, suggesting that mouse IL28 has anti-tumor activity.

B. Study design

Ten-week old female BALB/c mice (Charles River Laboratories) were injected s.c. on the right flank with 0.1 x 10^6 RENCA cells on Day 0. On days 5 and 12, groups of mice (n=10/group) were injected i.v. with 50ug of either empty pZP-7 plasmid or pZP-7/mIL28 using the hydrodynamic push method (inject plasmid resuspended in 1.6ml of physiological saline via tail vein in 5-8 seconds). Mice were bled 24hrs after plasmid injections (Days 6 and 13) to assess serum mIL28 levels by ELISA. Tumor growth was monitored 3X/week for 5 weeks using caliper measurements. Tumor volume was calculated using the formula ½*$(B)^2$*L (mm^3).

C. Results and conclusion

Injection of mIL28 plasmid resulted in protein expression between 50-200ng/ml 24 hours after plasmid delivery. Injection of mIL-28 plasmid inhibited tumor growth in the RENCA model. The differences in tumor volume between control plasmid and IL28 plasmid injected mice was statistically significant ($p = 0.0125$ compared to controls on Day 36) (Figure 1). These data suggest that IL28 has anti-tumor activity and is a possible therapeutic for cancer.

Example 43

Mouse IL28 plasmid and human IL29 C172S-PEG protein inhibit growth of RENCA tumors in mice

A. Summary

To determine if IL28/IL29 has an effect on tumor growth in mice, groups of mice were injected s.c with the RENCA tumor on Day 0. Mice were then injected with 50ug control vector plasmid, mIL28 plasmid (SEQ ID NO:7) or mIFNα plasmid by hydrodynamic delivery (HDD) on Days 5 and 12. A separate group of tumor bearing mice received 25ug human IL29 C172S (SEQ ID NO:29)-PEG (20kD N-terminally conjugated methoxy-polyethylene glycol propionaldehyde) protein by i.p. injection every other day (EOD) from Days 5-21. Tumor volume was monitored 3X/week for 4 weeks. Mouse IL28 and IFNα protein levels in serum were measured by ELISA. Mice injected with mIL28 or mIFNα plasmid showed significantly smaller tumors compared to control plasmid injected mice, suggesting that mouse IL28 has anti-tumor activity. Furthermore, mice injected with IL29 C172S-PEG protein also showed decreased tumor volume compared to controls. These data suggest that both IL28 and IL29 have anti-tumor activity.

B. Study design

Ten-week old female BALB/c mice (Charles River Laboratories) were injected s.c. on the right flank with 0.1 x 10^6 RENCA cells on Day 0. On days 5 and 12, groups of mice (n=10/group) were injected i.v. with 50ug of either empty pZP-7 plasmid, pZP-7/mIL28 or pORF/mIFNa using the hydrodynamic push method (inject plasmid resuspended in 1.6ml of physiological saline via tail vein in 5-8 seconds). A separate group of mice (n=10) were injected i.p. with 25ug human IL29 C172S-PEG EOD from days 5-21. Intra-peritoneal injections were given in a total volume of 200ul. Mice were bled 24hrs after plasmid injections (Days 6 and 13) to assess serum mIL28 and mIFNα levels by ELISA. Tumor growth was monitored 3X/week for 4 weeks using caliper measurements. Tumor volume was calculated using the formula $½*(B)^2*L$ (mm^3).

C. Results and conclusion

Administration of mIL-28 or mIFNα plasmid significantly inhibited tumor growth in this RENCA model ($p< 0.001$ for all 3 groups compared to control group on Day 28) (Figure 2). Human IL-29 C172S-PEG protein injection also

significantly inhibited tumor growth compared to controls. These data suggest that mIL28 and human IL29 have anti-tumor activity and are possible therapeutics for cancer.

Example 44

Low doses of 2 different forms of human IL29 protein show anti-tumor activity in the RENCA model

A. Summary

To determine if anti-tumor activity of IL29 can be achieved at lower doses than described above, groups of mice were injected s.c with the RENCA tumor on Day 0. Groups (n=10/group) of tumor bearing mice received 1ug, 5ug, 25ug human IL29 C172S (SEQ ID NO:29)-PEG (20kD N-terminally conjugated methoxy-polyethylene glycol propionaldehyde) or human IL29 C172S d2-7 (SEQ ID NO:159)-PEG (20kD N-terminally conjugated methoxy-polyethylene glycol propionaldehyde) protein by i.p. injection every other day (EOD) from Days 5-23. Tumor volume was monitored 3X/week for 4 weeks. Mice injected with 1, 5 or 25ug IL29 C172S-PEG protein showed decreased tumor volume compared to controls. Furthermore, mice injected with 1, 5 or 25ug human IL29 C172S d2-7-PEG protein also showed significantly decreased tumor growth compared to controls. These data suggest that low doses of 2 different forms of human IL29 protein have anti-tumor activity in mice.

B. Study design

Ten-week old female BALB/c mice (Charles River Laboratories) were injected s.c. on the right flank with 0.1 x 10^6 RENCA cells on Day 0. Groups of mice (n=10/group) were injected i.p. with 1ug, 5ug, or 25ug human IL29 C172S-PEG or human IL29 C172S d2-7-PEG EOD from days 5-23. Intra-peritoneal injections were given in a total volume of 200ul. Tumor growth was monitored 3X/week for 4 weeks using caliper measurements. Tumor volume was calculated using the formula $½*(B)^2*L$ (mm^3).

C. Results and conclusion

Administration of 1ug, 5ug or 25ug human IL29 C172S-PEG protein significantly inhibited tumor growth. Furthermore, 1ug, 5ug or 25ug IL29 C172S d2-7-PEG protein injection also inhibited tumor growth compared to vehicle treated mice (Figure 3). These data provide evidence that human IL29 protein has anti-tumor activity and is a potential therapeutic for various tumors.

Example 45

Therapeutic treatment with Pegylated human IL29 shows potent anti-tumor activity in the RENCA model

A. Summary

To determine if therapeutic treatment with IL29 can induce anti-tumor activity groups of mice were injected s.c with the RENCA tumor on Day 0. When tumor volume of $100mm^3$ was reached, mice received vehicle, 5ug or 25ug human IL29 C172S d2-7 (SEQ ID NO:159)-PEG (20kD N-terminally conjugated methoxy-polyethylene glycol propionaldehyde) protein every other day (EOD) for 10 injections or 5ug human IL29 C172S d2-7 (SEQ ID NO:159)-PEG (20kD N-terminally conjugated methoxy-polyethylene glycol propionaldehyde) protein every day (ED) for 20 injections. As a control, one group of mice was treated prophylactically with 5ug human IL29 C172S d2-7-PEG EOD for 20 days starting on day 5 of tumor injection (Day 5-23). Each individual mouse received injections only after its tumor volume reached $100mm^3$. All injections of protein were by i.p. administration. Tumor volume was monitored 3X/week for 4 weeks. Mice injected with 5ug or 25ug EOD or 5ug ED showed significantly less tumor growth compared to controls. Consistent with previous results, mice given prophylactic treatment with 5ug IL29 also showed decreased tumor growth compared to controls. These data suggest that therapeutic treatment with human IL29 protein have anti-tumor activity in mice.

B. Study design

Ten-week old female BALB/c mice (Charles River Laboratories) were injected s.c. on the right flank with 0.1×10^6 RENCA cells on Day 0. Groups of mice (n=10/group) were injected i.p. with vehicle, 5ug or 25ug human IL29 C172S d2-7-PEG EOD for 20 days or 5ug human IL29 C172S d2-7-PEG ED for 20 days starting

with a tumor volume of approximately 100mm^3. A separate group of mice received 5ug human IL29 C172S d2-7-PEG EOD for 20 days starting d5 of experiment (prophylactic treatment). Intra-peritoneal injections were given in a total volume of 200ul. Tumor growth was monitored 3X/week for 4 weeks using caliper measurements. Tumor volume was calculated using the formula ½*(B)^2*L (mm^3).

C. Results and conclusion

Mice injected with 5ug or 25ug EOD or 5ug ED showed significantly less tumor growth compared to controls. Consistent with previous results, mice given prophylactic treatment with 5ug IL29 also showed decreased tumor growth compared to controls (Figure 4). These data provide evidence that human IL29 protein has anti-tumor activity and is a potential therapeutic for various tumors.

Example 46

Prophylactic treatment with Pegylated human IL29 inhibits tumor growth in the E.G7 thymoma model

A. Summary

To determine if IL29 can induce anti-tumor activity in other tumors, groups of mice were injected s.c with the E.G7 tumor on Day 0. Groups of mice received vehicle or 25ug human IL29 C172S d2-7 (SEQ ID NO:159)-PEG (20kD N-terminally conjugated methoxy-polyethylene glycol propionaldehyde) protein every other day (EOD) for 10 injections (days 0-18). All injections of protein were by i.p. administration. Tumor volume was monitored 3X/week for 4 weeks. Mice injected with 25ug EOD showed significantly less tumor growth compared to controls. These data suggest that treatment with human IL29 protein have anti-tumor activity in mice.

B. Study design

Ten-week old female C57BL/6 mice (Charles River Laboratories) were injected s.c. on the right flank with 0.4 x 10^6 E.G7 cells on Day 0. Groups of mice (n=10/group) were injected i.p. with vehicle or 25ug human IL29 C172S d2-7-PEG EOD for 20 days. Intra-peritoneal injections were given in a total volume of 200ul.

Tumor growth was monitored 3X/week for 4 weeks using caliper measurements. Tumor volume was calculated using the formula $\frac{1}{2}*(B)^2*L$ (mm^3).

C. Results and conclusion

Mice injected with 25ug EOD showed significantly less tumor growth compared to controls and also prolonged survival of mice compared to control animals (Figure 5A and 5B). These data provide evidence that human IL29 protein has anti-tumor activity and is a potential therapeutic for various tumors.

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.

The claims defining the invention are as follows:

1. A method of treating cancer and/or autoimmune disorder comprising the step of administering to a subject in need thereof a therapeutically-effective amount of a polypeptide comprising amino acid residues 1-182 of SEQ ID NO:29 or amino acid residues 1-176 of SEQ ID NO:159.

2. A method according to claim 1, wherein the cancer is selected from the group consisting of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, thymoma, malignant gliomas, breast cancer, colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer.

3. A method according to claim 2, wherein the cancer is selected from the group consisting of thymoma and renal cell carcinoma.

4. A method according to claim 1, wherein the autoimmune disorder is selected from the group consisting of multiple sclerosis, arthritis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and psoriasis.

5. A method according to claim 4, wherein the autoimmune disorder is multiple sclerosis.

6. A method according to any one of claims 1 to 5, wherein the polypeptide is conjugated to a polyethylene glycol moiety.

7. A method according to claim 6, wherein the

polyethylene glycol moiety is mPEG propionaldehyde.

8. A method according to claim 6 or claim 7, wherein the polyethylene glycol moiety has a molecular weight of about 20kD.

9. Use of a polypeptide comprising amino acid residues 1-182 of SEQ ID NO:29 or amino acid residues 1-176 of SEQ ID NO:159 in the manufacture of a medicament used in the treatment of cancer and/or autoimmune disorder.

10. Use according to claim 9, wherein the cancer is selected from the group consisting of B-cell lymphomas, chronic lymphocytic leukemia, acute lymphocytic leukemia, Non-Hodgkin's lymphomas, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, renal cell carcinoma, cervical cancer, melanoma, thyroid carcinoma, thymoma, malignant gliomas, breast cancer, colon cancer, lung cancer, pancreatic cancer, prostate cancer, stomach cancer, ovarian cancer, testicular cancer, Kaposi's sarcoma, and bone cancer.

11. Use according to claim 10, wherein the cancer is selected from the group consisting of thymoma and renal cell carcinoma.

12. Use according to claim 9, wherein the autoimmune disorder is selected from the group consisting of multiple sclerosis, arthritis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and psoriasis.

13. Use according to claim 12, wherein the autoimmune disorder is multiple sclerosis.

14. Use according to any one of claims 9 to 13, wherein the polypeptide is conjugated to a polyethylene glycol

moiety.

15. Use according to claim 14, wherein the polyethylene glycol moiety is mPEG propionaldehyde.

16. Use according to claim 14 or claim 15, wherein the polyethylene glycol moiety has a molecular weight of about 20kD.

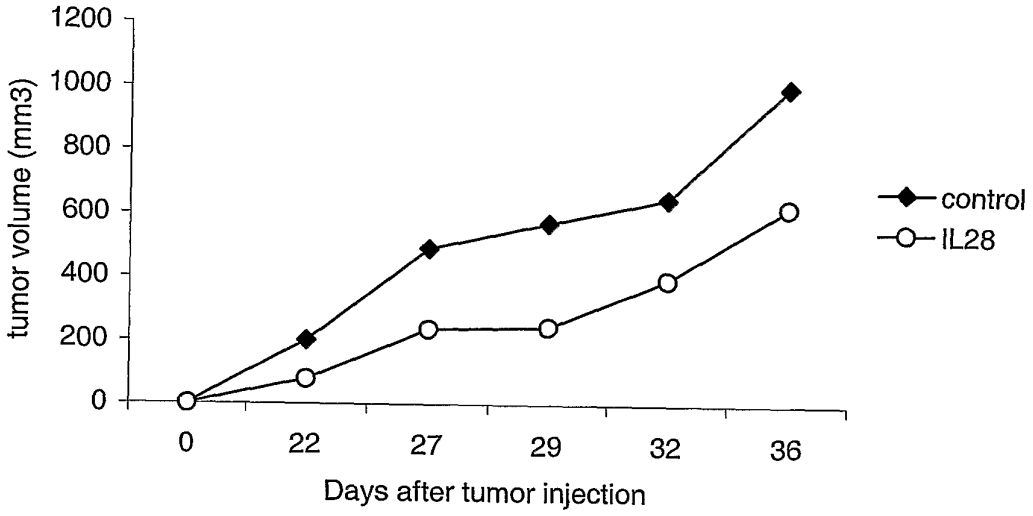
17. A method or a use according to any one of claims 1 to 16, further comprising a second polypeptide which encodes an Interferon.

18. A method or use according to claim 17, wherein the second polypeptide is Interferon alpha, Interferon beta or Interferon gamma.

19. A method or a use according to any one of claims 1 to 18, wherein the subject is a mammal.

20. A method or a use according to claim 19, wherein the mammal is a human.

21. A method according to claim 1 or a use according to claim 9 substantially as hereinbefore described with reference to any one of the Examples.



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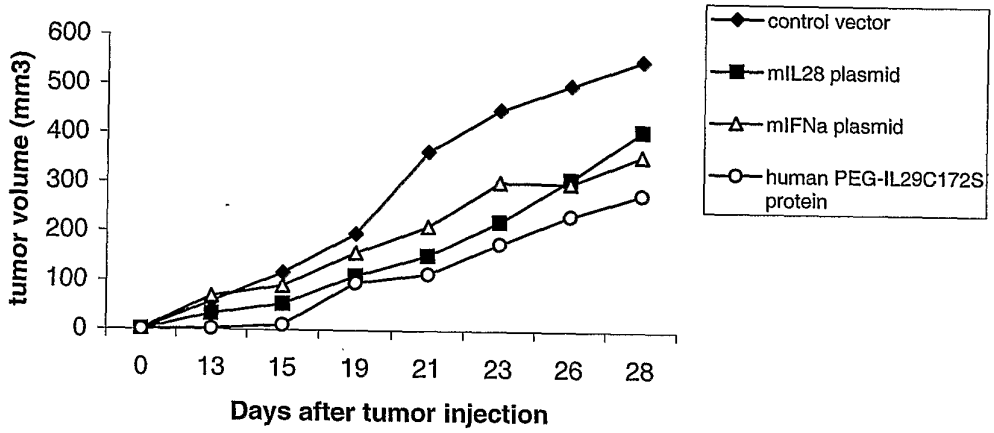
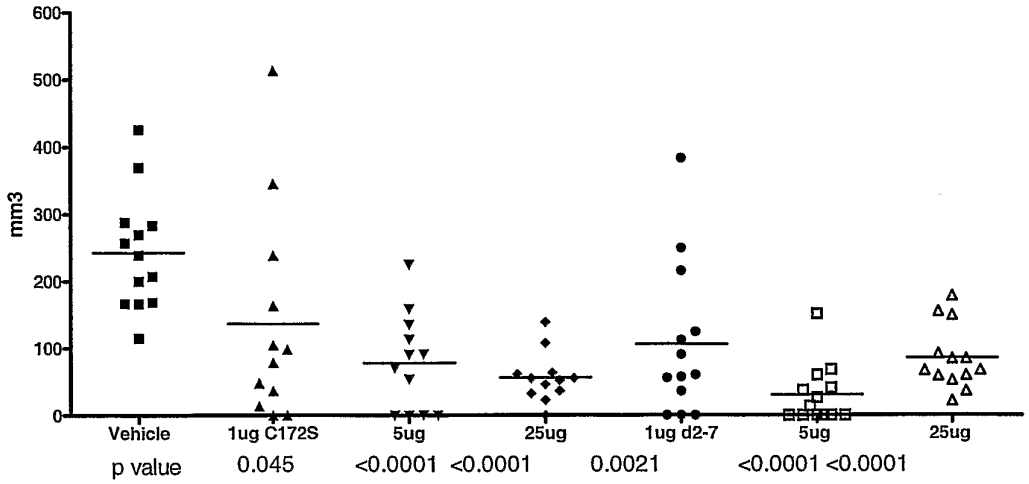


Figure 2

Sheet 2 of 3



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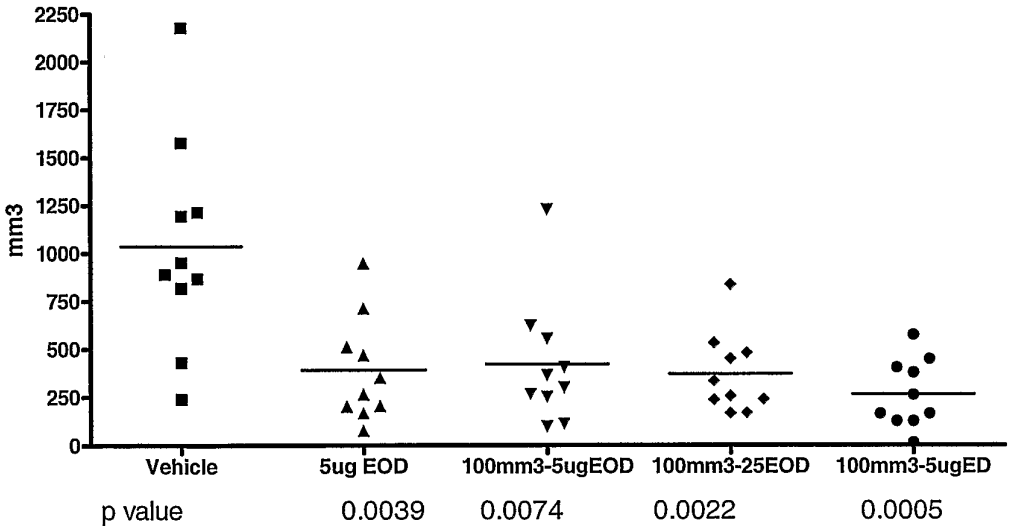

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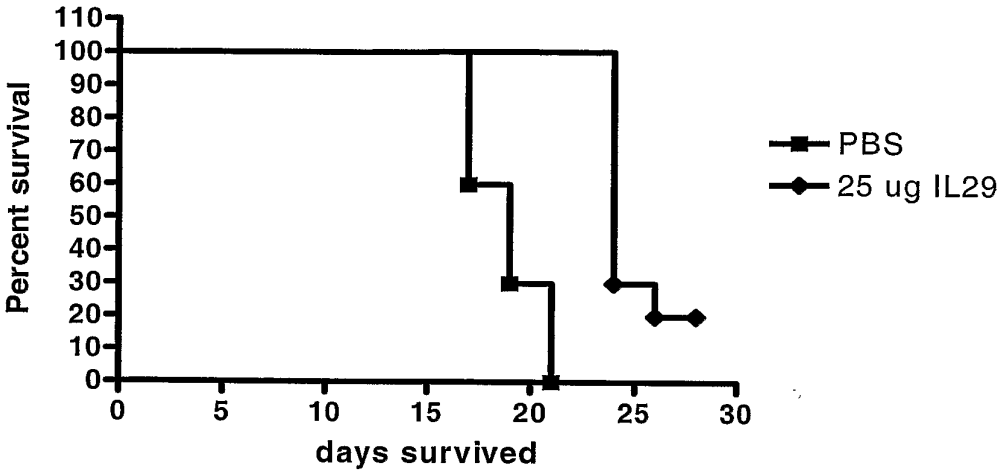

Figure 5A

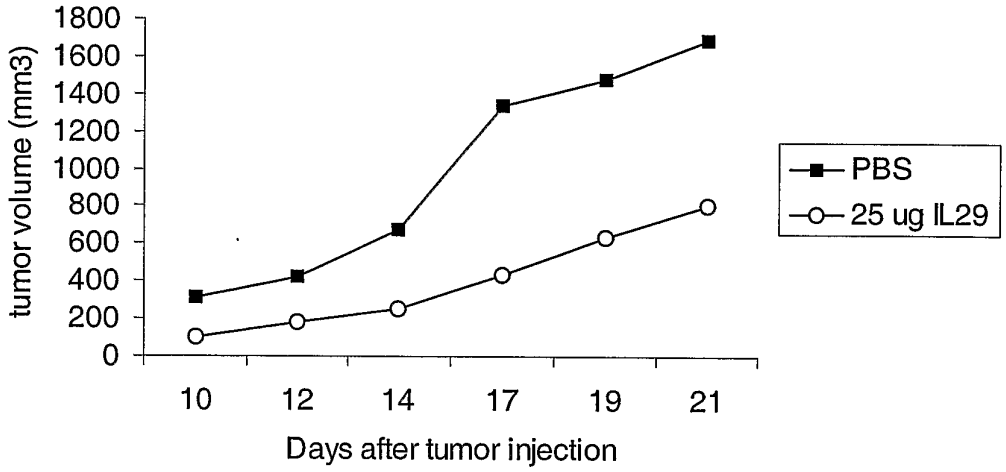

Figure 5B

SEQUENCE LISTING

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<120> USE OF IL-28 AND IL-29 TO TREAT CANCER
AND AUTOIMMUNE DISORDERS

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-5 1 5

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10 15 20 25

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acc tgg gac ctg agg cag ctg cag gtg agg gag cgc ccc atg gct ttg 346
Thr Trp Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Met Ala Leu
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Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr Ala Asp
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 90                  95                  100                 105

cac cat atc ctc tcc cag ttc cgg gcc tgt atc cag cct cag ccc acg   490
His His Ile Leu Ser Gln Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr
                110                 115                 120

gca ggg ccc agg acc cgg ggc cgc ctc cac cat tgg ctg tac cgg ctc   538
Ala Gly Pro Arg Thr Arg Gly Arg Leu His His Trp Leu Tyr Arg Leu
            125                 130                 135

cag gag gcc cca aaa aag gag tcc cct ggc tgc ctc gag gcc tct gtc   586
Gln Glu Ala Pro Lys Lys Glu Ser Pro Gly Cys Leu Glu Ala Ser Val
        140                 145                 150

acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctg aat tgt gtt gcc   634
Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Asn Cys Val Ala
    155                 160                 165

agt ggg gac ctg tgt gtc tga ccctcccacc agtcatgcaa cctgagattt      685
Ser Gly Asp Leu Cys Val  *
170                 175

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

gtg gtg ctg gtg act ttg gtg cta ggc ttg gcc gtg gca ggc cct gtc   163
Val Val Leu Val Thr Leu Val Leu Gly Leu Ala Val Ala Gly Pro Val
            -10                 -5                  1

ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac att ggc agg   211
Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg
     5                  10                  15

ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag aag gcc agg   259
Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg
 20                  25                  30                  35

gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc tct   307
Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser
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cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg gag   355
Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu
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cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc ctg   403
Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu
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gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac cag ccc ctt   451
Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu
     85                  90                  95

cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc cag cct   499
His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro
100                 105                 110                 115

cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg ctg   547
Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu
                120                 125                 130
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gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc aaa   643
Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys
        150                 155                 160

tat gtg gcc gat ggg aac ctg tgt ctg aga acg tca acc cac cct gag   691
Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser Thr His Pro Glu
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Ser Thr  *
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ttaatttatt tcctctcacc ctttatttat gaagctgcag ccctgactga gacatagggc 800
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Ser Phe Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys
30                  35                  40                  45
Asn Trp Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg
                50                  55                  60
Leu Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala
            65                  70                  75
Leu Thr Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp
        80                  85                  90
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
    95                  100                 105
Gln Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly
110                 115                 120                 125
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
                130                 135                 140
Ser Ala Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
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gtg ctg acc gtg act gga gca gtt cct gtc gcc agg ctc cgc ggg gct  154
Val Leu Thr Val Thr Gly Ala Val Pro Val Ala Arg Leu Arg Gly Ala
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tcg ctt ctg ctg aag gac tgc aag tgc cgc tcc cgc ctc ttc ccc agg  298
Ser Leu Leu Leu Lys Asp Cys Lys Cys Arg Ser Arg Leu Phe Pro Arg
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acc tgg gac ctg agg cag ctg cag gtg agg gag cgc ccc gtg gct ttg  346
Thr Trp Asp Leu Arg Gln Leu Gln Val Arg Glu Arg Pro Val Ala Leu
         60                  65                  70

gag gct gag ctg gcc ctg acg ctg aag gtt ctg gag gcc acc gct gac  394
Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Thr Ala Asp
     75                  80                  85

act gac cca gcc ctg ggg gat gtc ttg gac cag ccc ctt cac acc ctg  442
Thr Asp Pro Ala Leu Gly Asp Val Leu Asp Gln Pro Leu His Thr Leu
 90                  95                  100                 105

cac cat atc ctc tcc cag ctc cgg gcc tgt atc cag cct cag ccc acg  490
His His Ile Leu Ser Gln Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr
                110                 115                 120

gca ggg ccc agg acc cgg ggc cgc ctc cac cat tgg ctg cac cgg ctc  538
Ala Gly Pro Arg Thr Arg Gly Arg Leu His His Trp Leu His Arg Leu
            125                 130                 135

cag gag gcc cca aaa aag gag tcc cct ggc tgc ctc gag gcc tct gtc  586
Gln Glu Ala Pro Lys Lys Glu Ser Pro Gly Cys Leu Glu Ala Ser Val
        140                 145                 150

acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctg aat tgt gtt gcc  634
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Ser Gly Asp Leu Cys Val  *
170                 175

tatttataaa ttagccactt ggcttaattt attgccaccc agtcgctat             734

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

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 15                  20                  25                  30

gcc ttc aaa aag gcc aag gat gcc atc gag aag agg ctg ctt gag aag   243
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                35                  40                  45

gac ctg agg tgc agt tcc cac ctc ttc ccc agg gcc tgg gac ctg aag   291
Asp Leu Arg Cys Ser Ser His Leu Phe Pro Arg Ala Trp Asp Leu Lys
            50                  55                  60

cag ctg cag gtc caa gag cgc ccc aag gcc ttg cag gct gag gtg gcc   339
Gln Leu Gln Val Gln Glu Arg Pro Lys Ala Leu Gln Ala Glu Val Ala
        65                  70                  75

ctg acc ctg aag gtc tgg gag aac atg act gac tca gcc ctg gcc acc   387
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atc ctg ggc cag cct ctt cat aca ctg agc cac att cac tcc cag ctg   435
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 95                  100                 105                 110

cag acc tgt aca cag ctt cag gcc aca gca gag ccc agg tcc ccg agc   483
Gln Thr Cys Thr Gln Leu Gln Ala Thr Ala Glu Pro Arg Ser Pro Ser
                115                 120                 125

cgc cgc ctc tcc cgc tgg ctg cac agg ctc cag gag gcc cag agc aag   531
Arg Arg Leu Ser Arg Trp Leu His Arg Leu Gln Glu Ala Gln Ser Lys
            130                 135                 140

gag acc cct ggc tgc ctg gag gcc tct gtc acc tcc aac ctg ttt cgc   579
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Phe Lys Ser Leu Ser Pro Lys Glu Leu Gln Ala Phe Lys Lys Ala Lys
25 30 35
Asp Ala Ile Glu Lys Arg Leu Leu Glu Lys Asp Leu Arg Cys Ser Ser
40 45 50
His Leu Phe Pro Arg Ala Trp Asp Leu Lys Gln Leu Gln Val Gln Glu
55 60 65
Arg Pro Lys Ala Leu Gln Ala Glu Val Ala Leu Thr Leu Lys Val Trp
70 75 80
Glu Asn Met Thr Asp Ser Ala Leu Ala Thr Ile Leu Gly Gln Pro Leu
85 90 95 100
His Thr Leu Ser His Ile His Ser Gln Leu Gln Thr Cys Thr Gln Leu
105 110 115
Gln Ala Thr Ala Glu Pro Arg Ser Pro Ser Arg Arg Leu Ser Arg Trp
120 125 130
Leu His Arg Leu Gln Glu Ala Gln Ser Lys Glu Thr Pro Gly Cys Leu
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Gln Ala Asp Pro Val Pro Arg Ala Thr Arg Leu Pro Val Glu Ala Lys
        1               5                  10

gat tgc cac att gct cag ttc aag tct ctg tcc cca aaa gag ctg cag   195
Asp Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Lys Glu Leu Gln
 15                  20                  25                  30

gcc ttc aaa aag gcc aag ggt gcc atc gag aag agg ctg ctt gag aag   243
Ala Phe Lys Lys Ala Lys Gly Ala Ile Glu Lys Arg Leu Leu Glu Lys
                 35                  40                  45

gac atg agg tgc agt tcc cac ctc atc tcc agg gcc tgg gac ctg aag   291
Asp Met Arg Cys Ser Ser His Leu Ile Ser Arg Ala Trp Asp Leu Lys
             50                  55                  60

cag ctg cag gtc caa gag cgc ccc aag gcc ttg cag gct gag gtg gcc   339
Gln Leu Gln Val Gln Glu Arg Pro Lys Ala Leu Gln Ala Glu Val Ala
         65                  70                  75

ctg acc ctg aag gtc tgg gag aac ata aat gac tca gcc ctg acc acc   387
Leu Thr Leu Lys Val Trp Glu Asn Ile Asn Asp Ser Ala Leu Thr Thr
     80                  85                  90

atc ctg ggc cag cct ctt cat aca ctg agc cac att cac tcc cag ctg   435
Ile Leu Gly Gln Pro Leu His Thr Leu Ser His Ile His Ser Gln Leu
 95                 100                 105                 110

cag acc tgt aca cag ctt cag gcc aca gca gag ccc aag ccc ccg agt   483
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cgc cgc ctc tcc cgc tgg ctg cac agg ctc cag gag gcc cag agc aag   531
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            130                 135                 140

gag act cct ggc tgc ctg gag gac tct gtc acc tcc aac ctg ttt caa   579
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        145                 150                 155

ctg ctc ctc cgg gac ctc aag tgt gtg gcc agt gga gac cag tgt gtc   627
Leu Leu Leu Arg Asp Leu Lys Cys Val Ala Ser Gly Asp Gln Cys Val
    160                 165                 170

tga cc                                                           632
 *
```

<210> 10
<211> 202
<212> PRT
<213> Mus musculus

<220>
<221> SIGNAL
<222> (1)...(28)

<400> 10

```
Met Lys Pro Glu Thr Ala Gly Gly His Met Leu Leu Leu Leu Leu Pro
            -25                 -20                 -15
Leu Leu Leu Ala Ala Val Leu Thr Arg Thr Gln Ala Asp Pro Val Pro
```

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

<210> 11
<211> 520
<212> PRT
<213> Homo sapiens

<400> 11

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

```
Val Ile Ala Ala Gly Gly Val Ile Trp Lys Thr Leu Met Gly Asn Pro
                245                 250                 255
Trp Phe Gln Arg Ala Lys Met Pro Arg Ala Leu Asp Phe Ser Gly His
            260                 265                 270
Thr His Pro Val Ala Thr Phe Gln Pro Ser Arg Pro Glu Ser Val Asn
        275                 280                 285
Asp Leu Phe Leu Cys Pro Gln Lys Glu Leu Thr Arg Gly Val Arg Pro
    290                 295                 300
Thr Pro Arg Val Arg Ala Pro Ala Thr Gln Gln Thr Arg Trp Lys Lys
305                 310                 315                 320
Asp Leu Ala Glu Asp Glu Glu Glu Glu Asp Glu Glu Asp Thr Glu Asp
                325                 330                 335
Gly Val Ser Phe Gln Pro Tyr Ile Glu Pro Pro Ser Phe Leu Gly Gln
            340                 345                 350
Glu His Gln Ala Pro Gly His Ser Glu Ala Gly Gly Val Asp Ser Gly
        355                 360                 365
Arg Pro Arg Ala Pro Leu Val Pro Ser Glu Gly Ser Ser Ala Trp Asp
    370                 375                 380
Ser Ser Asp Arg Ser Trp Ala Ser Thr Val Asp Ser Ser Trp Asp Arg
385                 390                 395                 400
Ala Gly Ser Ser Gly Tyr Leu Ala Glu Lys Gly Pro Gly Gln Gly Pro
                405                 410                 415
Gly Gly Asp Gly His Gln Glu Ser Leu Pro Pro Pro Glu Phe Ser Lys
            420                 425                 430
Asp Ser Gly Phe Leu Glu Glu Leu Pro Glu Asp Asn Leu Ser Ser Trp
        435                 440                 445
Ala Thr Trp Gly Thr Leu Pro Pro Glu Pro Asn Leu Val Pro Gly Gly
    450                 455                 460
Pro Pro Val Ser Leu Gln Thr Leu Thr Phe Cys Trp Glu Ser Ser Pro
465                 470                 475                 480
Glu Glu Glu Glu Glu Ala Arg Glu Ser Glu Ile Glu Asp Ser Asp Ala
                485                 490                 495
Gly Ser Trp Gly Ala Glu Ser Thr Gln Arg Thr Glu Asp Arg Gly Arg
            500                 505                 510
Thr Leu Gly His Tyr Met Ala Arg
        515                 520
```

<210> 12
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> mature protein of SEQ ID NO: 1, with 3' Met added

<221> CDS
<222> (1)...(531)

<400> 12

```
atg gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc   48
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
 1               5                  10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc   96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
             20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
         35                  40                  45
```

```
tgc agg tgc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Cys Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
     50                  55                  60

ctg cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
 65                  70                  75                  80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
                 85                  90                  95

gac gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ttc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125

ggc cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
```

<210> 13
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> mature protein of SEQ ID NO: 1, with 3' Met added

<400> 13

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

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


<210> 14
<211> 621
<212> DNA
<213> Artificial Sequence

<220>
<223> mature protein of SEQ ID NO: 3, with 3' Met added

<221> CDS
<222> (1)...(549)

<400> 14
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160
```

```
cga gac ctc aaa tat gtg gcc gat ggg aac ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga caccccacac cttatttatg cgctgagccc      579
Thr His Pro Glu Ser Thr  *
            180

tactccttcc ttaatttatt tcctctcacc ctttatttat ga                    621

<210> 15
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> mature protein of SEQ ID NO: 3, with 3' Met added

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


<210> 16
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> mature protein of SEQ ID NO: 5, with 3' Met added

<221> CDS
<222> (1)...(531)

<400> 16
atg gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc   48
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
 1               5                  10                  15
```

```
tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc   96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
             20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
         35                  40                  45

tgc aag tgc cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Cys Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
     50                  55                  60

ctg cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
 65                  70                  75                  80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg ggg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly
                 85                  90                  95

gat gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ctc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125

ggc cgc ctc cac cat tgg ctg cac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
```

<210> 17
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> mature protein of SEQ ID NO: 5, with 3' Met added

<400> 17

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

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

<210> 18
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28A mutant C48S

<221> CDS
<222> (1)...(528)

<400> 18

```
gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc tgc   48
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys
 1               5                  10                  15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt   96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
            20                  25                  30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac tcc   144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Ser
        35                  40                  45

agg tgc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg   192
Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
    50                  55                  60

cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg gac   288
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val Asp
                85                  90                  95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ttc   336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Phe
            100                 105                 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc   384
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
        115                 120                 125
```

```
cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag gag   432
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc   480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160

ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc tga   528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val  *
                165                 170                 175
```

<210> 19
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-28A mutant C48S

<400> 19

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

<210> 20
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C49S

<221> CDS
<222> (1)...(531)

<400> 20

```
atg gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc   48
```

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

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc   96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
             20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
         35                  40                  45

tcc agg tgc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Ser Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
     50                  55                  60

ctg cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
 65                  70                  75                  80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
                 85                  90                  95

gac gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ttc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125

ggc cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
```

<210> 21
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C49S

<400> 21

```
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
 1               5                  10                  15
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20                  25                  30
```

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


<210> 22
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28A mutant C50S

<221> CDS
<222> (1)...(528)

<400> 22
gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc tgc   48
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys
 1               5                  10                  15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt   96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
             20                  25                  30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac tgc   144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Cys
         35                  40                  45

agg tcc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg   192
Arg Ser His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
     50                  55                  60

cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu Thr
 65                  70                  75                  80

ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg gac   288
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val Asp
                 85                  90                  95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ttc   336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Phe
            100                 105                 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc   384
```

```
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
        115                 120                 125

cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag gag   432
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc   480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160

ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc tga   528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val  *
                165                 170                 175
```

<210> 23
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-28A mutant C50S

<400> 23

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

<210> 24
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C51S

<221> CDS
<222> (1)...(531)

<400> 24
atg gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc 48
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1 5 10 15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc 96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
20 25 30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac 144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
35 40 45

tgc agg tcc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag 192
Cys Arg Ser His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
50 55 60

ctg cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg 240
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65 70 75 80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg 288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
85 90 95

gac gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag 336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
100 105 110

ttc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg 384
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
115 120 125

ggc cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag 432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
130 135 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc 480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145 150 155 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc 528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
165 170 175

tga 531
*

<210> 25
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C51S

<400> 25
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1 5 10 15

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

<210> 26
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 mutant C171S

<221> CDS
<222> (1)...(546)

<400> 26

```
ggt ccg gtt ccg acc tct aaa cca acc acc act ggt aaa ggt tgc cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His
 1               5                  10                  15

atc ggt cgt ttc aaa tct ctg tct ccg cag gaa ctg gct tct ttc aaa   96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aaa gct cgt gac gct ctg gaa gaa tct ctg aaa ctg aaa aac tgg tct  144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc tct tct ccg gtt ttc ccg ggt aac tgg gat ctg cgt ctg ctg cag  192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtt cgt gaa cgt ccg gtt gct ctg gaa gct gaa ctg gct ctg acc ctg  240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aaa gtt ctg gaa gct gct gca ggt cct gct ctg gaa gat gtt ctg gat  288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccg ctg cac act ctg cac cac atc ctg tct cag ctg cag gct tgc  336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110
```

```
att caa ccg caa ccg acc gct ggt ccg cgt ccg cgt ggt cgt ctg cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cat cgt ctg cag gaa gct ccg aaa aaa gaa tct gct ggt   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gaa gct tct gtt acc ttc aac ctg ttc cgt ctg ctg acc cgt   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gat ctg aaa tac gtt gct gat ggt aac ctg tct ctg cgt acc tct acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Ser Leu Arg Thr Ser Thr
                165                 170                 175

cat ccg gaa tct acc taa                                         546
His Pro Glu Ser Thr  *
            180
```

<210> 27
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 mutant C171S

<400> 27

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

<210> 28
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> met IL-29 mutant C172S

<221> CDS
<222> (1)...(549)

<400> 28

```
atg ggt ccg gtt ccg acc tct aaa cca acc acc act ggt aaa ggt tgc   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15

cac atc ggt cgt ttc aaa tct ctg tct ccg cag gaa ctg gct tct ttc   96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aaa aaa gct cgt gac gct ctg gaa gaa tct ctg aaa ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

tct tgc tct tct ccg gtt ttc ccg ggt aac tgg gat ctg cgt ctg ctg   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtt cgt gaa cgt ccg gtt gct ctg gaa gct gaa ctg gct ctg acc   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aaa gtt ctg gaa gct gct gca ggt cct gct ctg gaa gat gtt ctg   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gat cag ccg ctg cac act ctg cac cac atc ctg tct cag ctg cag gct   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgc att caa ccg caa ccg acc gct ggt ccg cgt ccg cgt ggt cgt ctg   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cat cgt ctg cag gaa gct ccg aaa aaa gaa tct gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggt tgc ctg gaa gct tct gtt acc ttc aac ctg ttc cgt ctg ctg acc   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cgt gat ctg aaa tac gtt gct gat ggt aac ctg tct ctg cgt acc tct   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Ser Leu Arg Thr Ser
                165                 170                 175

acc cat ccg gaa tct acc taa                                     549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 29
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-29 mutant C172S

<400> 29
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
1 5 10 15
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
50 55 60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
85 90 95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
100 105 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
115 120 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
130 135 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145 150 155 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Ser Leu Arg Thr Ser
165 170 175
Thr His Pro Glu Ser Thr
180

<210> 30
<211> 525
<212> DNA
<213> Artificial Sequence

<220>
<223> degenerate sequence of SEQ ID NO: 18

<221> misc_feature
<222> (1)...(525)
<223> n = A,T,C or G

<400> 30
gtnccngtng cnmgnytnca yggngcnytn ccngaygcnm gnggntgyca yathgcncar 60
ttyaarwsny tnwsnccnca rgarytncar gcnttyaarm gngcnaarga ygcnytngar 120
garwsnytny tnytnaarga ywsnmgntgy caywsnmgny tnttyccnmg nacntgggay 180
ytnmgncary tncargtnmg ngarmgnccn atggcnytng argcngaryt ngcnytnacn 240
ytnaargtny tngargcnac ngcngayacn gayccngcny tngtngaygt nytngaycar 300
ccnytncaya cnytncayca yathytnwsn carttymgng cntgyathca rccncarccn 360
acngcnggnc cnmgnacnmg nggnmgnytn caycaytggy tntaymgnyt ncargargcn 420
ccnaaraarg arwsnccngg ntgyytngar gcnwsngtna cnttyaayyt nttymgnytn 480
ytnacnmgng ayytnaaytg ygtngcnwsn ggngayytnt gygtn 525

<210> 31
<211> 525
<212> DNA
<213> Artificial Sequence

<220>
<223> degenerate sequence of SEQ ID NO: 20

<221> misc_feature
<222> (1)...(525)
<223> n = A,T,C or G

<400> 31
gtnccngtng cnmgnytnca yggngcnytn ccngaygcnm gnggntgyca yathgcncar 60
ttyaarwsny tnwsnccnca rgarytncar gcnttyaarm gngcnaarga ygcnytngar 120
garwsnytny tnytnaarga ywsnmgntgy caywsnmgny tnttyccnmg nacntgggay 180
ytnmgncary tncargtnmg ngarmgnccn atggcnytng argcngaryt ngcnytnacn 240
ytnaargtny tngargcnac ngcngayacn gayccngcny tngtngaygt nytngaycar 300
ccnytncaya cnytncayca yathytnwsn carttymgng cntgyathca rccncarccn 360
acngcnggnc cnmgnacnmg nggnmgnytn caycaytggy tntaymgnyt ncargargcn 420
ccnaaraarg arwsnccngg ntgyytngar gcnwsngtna cnttyaayyt nttymgnytn 480
ytnacnmgng ayytnaaytg ygtngcnwsn ggngayytnt gygtn 525

<210> 32
<211> 525
<212> DNA
<213> Artificial Sequence

<220>
<223> degenerate sequence of SEQ ID NO: 22

<221> misc_feature
<222> (1)...(525)
<223> n = A,T,C or G

<400> 32
gtnccngtng cnmgnytnca yggngcnytn ccngaygcnm gnggntgyca yathgcncar 60
ttyaarwsny tnwsnccnca rgarytncar gcnttyaarm gngcnaarga ygcnytngar 120
garwsnytny tnytnaarga ywsnmgntgy caywsnmgny tnttyccnmg nacntgggay 180
ytnmgncary tncargtnmg ngarmgnccn atggcnytng argcngaryt ngcnytnacn 240
ytnaargtny tngargcnac ngcngayacn gayccngcny tngtngaygt nytngaycar 300
ccnytncaya cnytncayca yathytnwsn carttymgng cntgyathca rccncarccn 360
acngcnggnc cnmgnacnmg nggnmgnytn caycaytggy tntaymgnyt ncargargcn 420
ccnaaraarg arwsnccngg ntgyytngar gcnwsngtna cnttyaayyt nttymgnytn 480
ytnacnmgng ayytnaaytg ygtngcnwsn ggngayytnt gygtn 525

<210> 33
<211> 525
<212> DNA
<213> Artificial Sequence

<220>
<223> degenerate sequence of SEQ ID NO: 24

<221> misc_feature
<222> (1)...(525)
<223> n = A,T,C or G

<400> 33
gtnccngtng cnmgnytnca yggngcnytn ccngaygcnm gnggntgyca yathgcncar 60
ttyaarwsny tnwsnccnca rgarytncar gcnttyaarm gngcnaarga ygcnytngar 120
garwsnytny tnytnaarga ywsnmgntgy caywsnmgny tnttyccnmg nacntgggay 180
ytnmgncary tncargtnmg ngarmgnccn atggcnytng argcngaryt ngcnytnacn 240
ytnaargtny tngargcnac ngcngayacn gayccngcny tngtngaygt nytngaycar 300
ccnytncaya cnytncayca yathytnwsn carttymgng cntgyathca rccncarccn 360
acngcnggnc cnmgnacnmg nggnmgnytn caycaytggy tntaymgnyt ncargargcn 420
ccnaaraarg arwsnccngg ntgyytngar gcnwsngtna cnttyaayyt nttymgnytn 480
ytnacnmgng ayytnaaytg ygtngcnwsn ggngayytnt gygtn 525

<210> 34
<211> 525
<212> DNA
<213> Artificial Sequence

<220>
<223> degenerate sequence of SEQ ID NO: 26

<221> misc_feature
<222> (1)...(525)
<223> n = A,T,C or G

<400> 34
gtnccngtng cnmgnytnca yggngcnytn ccngaygcnm gnggntgyca yathgcncar 60
ttyaarwsny tnwsnccnca rgarytncar gcnttyaarm gngcnaarga ygcnytngar 120
garwsnytny tnytnaarga ywsnmgntgy caywsnmgny tnttyccnmg nacntgggay 180
ytnmgncary tncargtnmg ngarmgnccn atggcnytng argcngaryt ngcnytnacn 240
ytnaargtny tngargcnac ngcngayacn gayccngcny tngtngaygt nytngaycar 300
ccnytncaya cnytncayca yathytnwsn carttymgng cntgyathca rccncarccn 360
acngcnggnc cnmgnacnmg nggnmgnytn caycaytggy tntaymgnyt ncargargcn 420
ccnaaraarg arwsnccngg ntgyytngar gcnwsngtna cnttyaayyt nttymgnytn 480
ytnacnmgng ayytnaaytg ygtngcnwsn ggngayytnt gygtn 525

<210> 35
<211> 525
<212> DNA
<213> Artificial Sequence

<220>
<223> degenerate sequence of SEQ ID NO: 28

<221> misc_feature
<222> (1)...(525)
<223> n = A,T,C or G

<400> 35
gtnccngtng cnmgnytnca yggngcnytn ccngaygcnm gnggntgyca yathgcncar 60
ttyaarwsny tnwsnccnca rgarytncar gcnttyaarm gngcnaarga ygcnytngar 120
garwsnytny tnytnaarga ywsnmgntgy caywsnmgny tnttyccnmg nacntgggay 180
ytnmgncary tncargtnmg ngarmgnccn atggcnytng argcngaryt ngcnytnacn 240
ytnaargtny tngargcnac ngcngayacn gayccngcny tngtngaygt nytngaycar 300
ccnytncaya cnytncayca yathytnwsn carttymgng cntgyathca rccncarccn 360
acngcnggnc cnmgnacnmg nggnmgnytn caycaytggy tntaymgnyt ncargargcn 420
ccnaaraarg arwsnccngg ntgyytngar gcnwsngtna cnttyaayyt nttymgnytn 480
ytnacnmgng ayytnaaytg ygtngcnwsn ggngayytnt gygtn 525

<210> 36
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-28A mutant C48X

<221> VARIANT
<222> (48)...(48)
<223> Xaa = Ser, Ala, Thr, Val or Asn

<400> 36
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys

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

<210> 37
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C49X

<221> VARIANT
<222> (49)...(49)
<223> Xaa = Ser, Ala, Thr, Val or Asn

<400> 37

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

<210> 38

<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-28A mutant C50X

<221> VARIANT
<222> (50)...(50)
<223> Xaa = Ser, Ala, Thr, Val or Asn

<400> 38
Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly Cys
1 5 10 15
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
20 25 30
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Cys
35 40 45
Arg Xaa His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
50 55 60
Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val Asp
85 90 95
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Phe
100 105 110
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
115 120 125
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
130 135 140
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145 150 155 160
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
165 170 175

<210> 39
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-28A mutant C51X

<221> VARIANT
<222> (51)...(51)
<223> Xaa = Ser, Ala, Thr, Val or Asn

<400> 39
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1 5 10 15
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
20 25 30
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
35 40 45
Cys Arg Xaa His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
50 55 60
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65 70 75 80
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
85 90 95

```
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175


<210> 40
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 mutant C171X

<221> VARIANT
<222> (171)...(171)
<223> Xaa = Ser, Ala, Thr, Val or Asn

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


<210> 41
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> met IL-29 mutant C172X

<221> VARIANT
<222> (172)...(172)
```

<223> Xaa = Ser, Ala, Thr, Val or Asn

<400> 41

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

<210> 42
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC40923

<400> 42
tccagggaat tcatataggc cggccaccat gaaactagac atgactggg 49

<210> 43
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC43152

<400> 43
ggggtgggta caaccccaga gctgttttaa ggcgcgcctc tagactattt ttagacacac 60
aggtccccac tggc 74

<210> 44
<211> 50
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC29740

<400> 44

ttgacaatta atcatcggct cgtataatgt gtggaattgt gagcggataa 50

<210> 45
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC29741

<400> 45
tctgatttaa tctgtatcag gctgaaaatc ttatctcatc cg 42

<210> 46
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC29736

<400> 46
gtggaattgt gagcggataa caatttcaca cagaattcat taaagaggag aaattaactc 60
cc 62

<210> 47
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC29738

<400> 47
gctgaaaatc ttatctcatc cgccaaaaca cccgggagtt aatttctcct ctttaatgaa 60
ttc 63

<210> 48
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44566

<400> 48
tcttccagag cgtcacgagc ttttttgaaa gaagccagtt cctgcggaga cagagatttg 60
aaacgaccga tgtggcaa 78

<210> 49
<211> 84
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44565

<400> 49
tcgtgacgct ctggaagaat ctctgaaact gaaaaactgg tcttgctctt ctccggtttt 60
cccgggtaac tgggatctgc gtct 84

<210> 50
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44564

<400> 50
aacagaagct tccaggcaac cagcagattc ttttttcgga gcttcctgca gacgatgcag 60
ccagtggtgc a 71

<210> 51
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44563

<400> 51
aactggctct gaccctgaaa gttctggaag ctgctgcagg tcctgctctg gaagatgttc 60
tggatcagcc gct 73

<210> 52
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44562

<400> 52
tcagggtcag agccagttca gcttccagag caaccggacg ttcacgaacc tgcagcagac 60
gcagatccca gtta 74

<210> 53
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44561

<400> 53
tcagctgcag gcttgcattc aaccgcaacc gaccgctggt ccgcgtccgc gtggtcgtct 60
gcaccactgg ctgcat 76

<210> 54
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44560

<400> 54
atgcaagcct gcagctgaga caggatgtgg tgcagagtgt gcagcggctg atccagaaca 60

<210> 55

<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44559

<400> 55
atgggtccgg ttccgacctc taaaccaacc accactggta aaggttgcca catcggtcgt 60
tt 62

<210> 56
<211> 65
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44558

<400> 56
ttaggtagat tccggatggg tagaggtacg caggcacagg ttaccatcag caacgtattt 60
cagat 65

<210> 57
<211> 69
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44557

<400> 57
tgcctggaag cttctgttac cttcaacctg ttccgtctgc tgacccgtga tctgaaatac 60
gttgctgat 69

<210> 58
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44340

<400> 58
cgttgctgat ggtaacctgt ctctgcgtac ctctacccat c 41

<210> 59
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44341

<400> 59
gatgggtaga ggtacgcaga gacaggttac catcagcaac g 41

<210> 60
<211> 68
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC41212

<400> 60
ctagaaataa ttttgtttaa ctttaagaag gagatatata tatgggccct gtccccactt 60
ccaagccc 68

<210> 61
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC41041

<400> 61
tctgtatcag gctgaaaatc ttatctcatc cgccaaaaca ttaggtggac tcagggtggg 60
ttgacgt 67

<210> 62
<211> 65
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC43431

<400> 62
ctagaaataa ttttgtttaa ctttaagaag gagatatata tatggttcct gtcgccaggc 60
tccac 65

<210> 63
<211> 67
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC43437

<400> 63
taatctgtat caggctgaaa atcttatctc atccgccaaa acatcagaca cacaggtccc 60
cactggc 67

<210> 64
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC44327

<400> 64
gtggccgatg ggaacctgtc cctgagaacg tcaacccac 39

<210> 65
<211> 39
<212> DNA
<213> Artificial Sequence

<220>

<223> oligonucleotide primer ZC44328

<400> 65
gtgggttgac gttctcaggg acaggttccc atcggccac 39

<210> 66
<211> 83
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC45399

<400> 66
tcaggtccca ggtcctgggg aagaggcggg agtggcacct ggagtccttc agcagaagcg 60
actcttctaa ggcatctttg gcc 83

<210> 67
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> zcyto20 mature start from pYEL7b

<221> CDS
<222> (1)...(531)

<400> 67
atg gtt cct gtc gcc agg ctc cac ggg gct ctc ccg gat gca agg ggc 48
Met Val Pro Val Ala Arg Leu His Gly Ala Leu Pro Asp Ala Arg Gly
1 5 10 15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc 96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
20 25 30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac 144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
35 40 45

tgc agg tgc cac tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag 192
Cys Arg Cys His Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
50 55 60

ctg cag gtg agg gag cgc ccc atg gct ttg gag gct gag ctg gcc ctg 240
Leu Gln Val Arg Glu Arg Pro Met Ala Leu Glu Ala Glu Leu Ala Leu
65 70 75 80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg gtg 288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Val
85 90 95

gac gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag 336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
100 105 110

ttc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg 384
Phe Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
115 120 125

```
ggc cgc ctc cac cat tgg ctg tac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agt ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
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<210> 68
<211> 83
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC45398

<400> 68
ggccaaagat gccttagaag agtcgcttct gctgaaggac tccaggtgcc actcccgcct 60
cttccccagg acctgggacc tga 83

<210> 69
<211> 83
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC45397

<400> 69
gctgcctcag gtcccaggtc ctggggaaga ggcgggagtg ggacctgcag tccttcagca 60
gaagcgactc ttctaaggca tct 83

<210> 70
<211> 83
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC45396

<400> 70
agatgcctta gaagagtcgc ttctgctgaa ggactgcagg tcccactccc gcctcttccc 60
caggacctgg gacctgaggc agc 83

<210> 71
<211> 1013
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (14)...(991)

<400> 71

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ccagcgtccg tcc atg gcg tgg agc ctt ggg agc tgg ctg ggt ggc tgc    49
               Met Ala Trp Ser Leu Gly Ser Trp Leu Gly Gly Cys
                1               5                  10

ctg ctg gtg tca gca ttg gga atg gta cca cct ccc gaa aat gtc aga    97
Leu Leu Val Ser Ala Leu Gly Met Val Pro Pro Pro Glu Asn Val Arg
         15                  20                  25

atg aat tct gtt aat ttc aag aac att cta cag tgg gag tca cct gct   145
Met Asn Ser Val Asn Phe Lys Asn Ile Leu Gln Trp Glu Ser Pro Ala
     30                  35                  40

ttt gcc aaa ggg aac ctg act ttc aca gct cag tac cta agt tat agg   193
Phe Ala Lys Gly Asn Leu Thr Phe Thr Ala Gln Tyr Leu Ser Tyr Arg
 45                  50                  55                  60

ata ttc caa gat aaa tgc atg aat act acc ttg acg gaa tgt gat ttc   241
Ile Phe Gln Asp Lys Cys Met Asn Thr Thr Leu Thr Glu Cys Asp Phe
                 65                  70                  75

tca agt ctt tcc aag tat ggt gac cac acc ttg aga gtc agg gct gaa   289
Ser Ser Leu Ser Lys Tyr Gly Asp His Thr Leu Arg Val Arg Ala Glu
             80                  85                  90

ttt gca gat gag cat tca gac tgg gta aac atc acc ttc tgt cct gtg   337
Phe Ala Asp Glu His Ser Asp Trp Val Asn Ile Thr Phe Cys Pro Val
         95                  100                 105

gat gac acc att att gga ccc cct gga atg caa gta gaa gta ctt gct   385
Asp Asp Thr Ile Ile Gly Pro Pro Gly Met Gln Val Glu Val Leu Ala
    110                 115                 120

gat tct tta cat atg cgt ttc tta gcc cct aaa att gag aat gaa tac   433
Asp Ser Leu His Met Arg Phe Leu Ala Pro Lys Ile Glu Asn Glu Tyr
125                 130                 135                 140

gaa act tgg act atg aag aat gtg tat aac tca tgg act tat aat gtg   481
Glu Thr Trp Thr Met Lys Asn Val Tyr Asn Ser Trp Thr Tyr Asn Val
                145                 150                 155

caa tac tgg aaa aac ggt act gat gaa aag ttt caa att act ccc cag   529
Gln Tyr Trp Lys Asn Gly Thr Asp Glu Lys Phe Gln Ile Thr Pro Gln
            160                 165                 170

tat gac ttt gag gtc ctc aga aac ctg gag cca tgg aca act tat tgt   577
Tyr Asp Phe Glu Val Leu Arg Asn Leu Glu Pro Trp Thr Thr Tyr Cys
        175                 180                 185

gtt caa gtt cga ggg ttt ctt cct gat cgg aac aaa gct ggg gaa tgg   625
Val Gln Val Arg Gly Phe Leu Pro Asp Arg Asn Lys Ala Gly Glu Trp
    190                 195                 200

agt gag cct gtc tgt gag caa aca acc cat gac gaa acg gtc ccc tcc   673
Ser Glu Pro Val Cys Glu Gln Thr Thr His Asp Glu Thr Val Pro Ser
205                 210                 215                 220

tgg atg gtg gcc gtc atc ctc atg gcc tcg gtc ttc atg gtc tgc ctg   721
Trp Met Val Ala Val Ile Leu Met Ala Ser Val Phe Met Val Cys Leu
                225                 230                 235
```

```
gca ctc ctc ggc tgc ttc tcc ttg ctg tgg tgc gtt tac aag aag aca   769
Ala Leu Leu Gly Cys Phe Ser Leu Leu Trp Cys Val Tyr Lys Lys Thr
            240                 245                 250

aag tac gcc ttc tcc cct agg aat tct ctt cca cag cac ctg aaa gag   817
Lys Tyr Ala Phe Ser Pro Arg Asn Ser Leu Pro Gln His Leu Lys Glu
        255                 260                 265

ttt ttg ggc cat cct cat cat aac aca ctt ctg ttt ttc tcc ttt cca   865
Phe Leu Gly His Pro His His Asn Thr Leu Leu Phe Phe Ser Phe Pro
    270                 275                 280

ttg tcg gat gag aat gat gtt ttt gac aag cta agt gtc att gca gaa   913
Leu Ser Asp Glu Asn Asp Val Phe Asp Lys Leu Ser Val Ile Ala Glu
285                 290                 295                 300

gac tct gag agc ggc aag cag aat cct ggt gac agc tgc agc ctc ggg   961
Asp Ser Glu Ser Gly Lys Gln Asn Pro Gly Asp Ser Cys Ser Leu Gly
                305                 310                 315

acc ccg cct ggg cag ggg ccc caa agc tag gctctgagaa ggaaacacac     1011
Thr Pro Pro Gly Gln Gly Pro Gln Ser  *
            320                 325

tc                                                                1013
```

<210> 72
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC40922

<400> 72
tccagggaat tcatataggc cggccaccat ggctgcagct tggaccgtg 49

<210> 73
<211> 71
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide primer ZC43153

<400> 73
ggggtgggta caaccccaga gctgttttaa ggcgcgcctc tagactattt ttaggtggac 60
tcagggtggg t 71

<210> 74
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant C15X, Asn169

<221> CDS
<222> (1)...(546)

<221> variation
<222> (44)...(45)
<223> n = A, G, T; or C

<400> 74

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ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa His
 1               5                  10                  15

att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
             20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
         35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
     50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
 65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                 85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg aay ctg tgt ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                         546
His Pro Glu Ser Thr  *
            180
```

<210> 75
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT

<222> (15)...(15)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> IL29 mutant C15X, Asn169

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

<210> 76
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant C16X, Asn170

<221> CDS
<222> (1)...(549)

<221> variation
<222> (47)...(48)
<223> n = A, T, G, or C

<400> 76
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn 48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa
1 5 10 15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc 96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg 144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc 192

```
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
     50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
 65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                 85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg aay ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 77
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (16)...(16)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> Met IL29 mutant C16X, Asn170

<400> 77

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

```
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
                165                 170                 175
Thr His Pro Glu Ser Thr
            180
```

<210> 78
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant C15X, Asp169

<221> CDS
<222> (1)...(546)

<221> variation
<222> (44)...(45)
<223> n = A, T, G, or C

<400> 78

```
ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa His
 1               5                  10                  15

att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125
```

```
cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg gay ctg tgt ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                         546
His Pro Glu Ser Thr  *
            180
```

<210> 79
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant C15X, Asp169

<221> VARIANT
<222> (15)...(15)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 79

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

<210> 80
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant C16X, Asp170

<221> CDS
<222> (1)...(549)

<221> variation
<222> (47)...(48)
<223> n = A, T, G, or C

<400> 80

```
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa
 1               5                  10                  15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg gay ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                     549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 81
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant C16X, Asp170

<221> VARIANT
<222> (16)...(16)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 81
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa
1 5 10 15
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
50 55 60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
85 90 95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
100 105 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
115 120 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
130 135 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145 150 155 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser
165 170 175
Thr His Pro Glu Ser Thr
180

<210> 82
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant Asp169, C171X

<221> CDS
<222> (1)...(546)

<221> variation
<222> (512)...(513)
<223> n = A, T, G, or C

<400> 82
ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac 48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His
1 5 10 15

att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag 96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys

```
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
         35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
     50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
 65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg gay ctg dnn ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                          546
His Pro Glu Ser Thr  *
            180
```

<210> 83
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant Asp169, C171X

<221> VARIANT
<222> (171)...(171)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 83

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

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

<210> 84
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant Asp170, C172X

<221> CDS
<222> (1)...(549)

<221> variation
<222> (515)...(516)
<223> n = A, T, G, or C

<400> 84

```
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
             20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
         35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
     50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
 65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                 85                  90                  95
```

```
gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg gay ctg dnn ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 85
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant Asp170, C172X

<221> VARIANT
<222> (172)...(172)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 85

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

180

<210> 86
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, Asn169, C171X

<221> CDS
<222> (1)...(546)

<221> variation
<222> (512)...(513)
<223> n = A, T, G, or C

<400> 86

```
ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc tgc cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Cys His
 1               5                  10                  15

att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr
```

```
               165                 170                 175

cac cct gag tcc acc tga                                                546
His Pro Glu Ser Thr  *
            180


<210> 87
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, Asn169, C171X

<221> VARIANT
<222> (171)...(171)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 87
Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Cys His
 1               5                  10                  15
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr
                165                 170                 175
His Pro Glu Ser Thr
            180


<210> 88
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, Asn170, C172X

<221> CDS
<222> (1)...(549)

<221> variation
<222> (515)...(516)
<223> n = A, T, G, or C
```

<400> 88
atg ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc tgc 48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Cys
1 5 10 15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc 96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg 144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc 192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
50 55 60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg 240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta 288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
85 90 95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc 336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
100 105 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc 384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
115 120 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct 432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
130 135 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg 480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145 150 155 160

cga gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca 528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
165 170 175

acc cac cct gag tcc acc tga 549
Thr His Pro Glu Ser Thr *
180

<210> 89
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, Asn170, C172X

<221> VARIANT
<222> (172)...(172)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 89
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Cys
1 5 10 15
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
50 55 60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
85 90 95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
100 105 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
115 120 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
130 135 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145 150 155 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
165 170 175
Thr His Pro Glu Ser Thr
180

<210> 90
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, C15X, Asn169

<221> CDS
<222> (1)...(546)

<221> variation
<222> 30, 44, 45
<223> n = A, T, G, or C

<400> 90
ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc dnn cac 48
Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Xaa His
1 5 10 15

att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag 96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
20 25 30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt 144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
35 40 45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag 192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
50 55 60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg 240

```
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
 65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                 85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg aay ctg tgt ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                          546
His Pro Glu Ser Thr  *
            180
```

<210> 91
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, C15X, Asn169

<221> VARIANT
<222> (15)...(15)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 91

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

```
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser Thr
                165                 170                 175
His Pro Glu Ser Thr
            180
```

<210> 92
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, C16X, Asn170

<221> CDS
<222> (1)...(549)

<221> variation
<222> 33, 47, 48
<223> n = A, T, G, or C

<400> 92

```
atg ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc dnn   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Xaa
 1               5                  10                  15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140
```

```
ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg aay ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                     549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 93
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, C16X, Asn170

<221> VARIANT
<222> (16)...(16)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 93

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

<210> 94
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, Asp169, C171X

<221> CDS
<222> (1)...(546)

<221> variation
<222> 30, 512, 513
<223> n = A, T, G, or C

<400> 94

```
ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc tgc cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Cys His
 1               5                  10                  15

att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg gay ctg dnn ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                         546
His Pro Glu Ser Thr  *
            180
```

<210> 95
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, Asp169, C171X

<221> VARIANT
<222> (171)...(171)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

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

<210> 96
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, Asp170, C172X

<221> CDS
<222> (1)...(549)

<221> variation
<222> 33, 515, 516
<223> n = A, T, G, or C

<400> 96
atg ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc tgc 48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Cys
1 5 10 15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc 96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg 144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp

```
         35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
     50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
 65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                 85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg gay ctg dnn ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 97
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, Asp170, C172X

<221> VARIANT
<222> (172)...(172)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 97

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

```
65                  70                  75                  80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser
                165                 170                 175
Thr His Pro Glu Ser Thr
            180
```

<210> 98
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, C15X, Asp169

<221> CDS
<222> (1)...(546)

<221> variation
<222> 30, 44, 45
<223> n = A, T, G, or C

<400> 98

```
ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc dnn cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Xaa His
 1               5                  10                  15

att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110
```

```
atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg gay ctg tgt ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                         546
His Pro Glu Ser Thr  *
            180
```

<210> 99
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant T10P, C15X, Asp169

<221> VARIANT
<222> (15)...(15)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 99

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

<210> 100

<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, C16X, Asp170

<221> CDS
<222> (1)...(549)

<221> variation
<222> 33, 47, 48
<223> n = A, T, G, or C

<400> 100

```
atg ggc cct gtc ccc act tcc aag ccc acc ccn act ggg aag ggc dnn   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Xaa
 1               5                  10                  15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg gay ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                     549
Thr His Pro Glu Ser Thr  *
```

180

<210> 101
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant T11P, C16X, Asp170

<221> VARIANT
<222> (16)...(16)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 101
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Pro Thr Gly Lys Gly Xaa
1 5 10 15
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
50 55 60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
85 90 95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
100 105 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
115 120 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
130 135 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145 150 155 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser
165 170 175
Thr His Pro Glu Ser Thr
180

<210> 102
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant G18D, Asn169, C171X

<221> CDS
<222> (1)...(546)

<221> variation
<222> (512)...(513)
<223> n = A, T, G, or C

<400> 102
ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac 48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His
1 5 10 15

```
att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                         546
His Pro Glu Ser Thr  *
            180
```

<210> 103
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant G18D, Asn169, C171X

<221> VARIANT
<222> (171)...(171)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 103

```
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His
 1               5                  10                  15
```

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

<210> 104
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant G19D, Asn170, C172X

<221> CDS
<222> (1)...(549)

<221> variation
<222> (515)...(516)
<223> n = A, T, G, or C

<400> 104

```
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15

cac att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
```

```
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                 85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 105
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant G19D, Asn170, C172X

<221> VARIANT
<222> (172)...(172)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 105

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

```
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
                165                 170                 175
Thr His Pro Glu Ser Thr
            180


<210> 106
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant C15X, G18D, Asn169

<221> CDS
<222> (1)...(546)

<221> variation
<222> (44)...(45)
<223> n = A, T, G, or C

<400> 106
ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa His
 1               5                  10                  15

att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160
```

```
gac ctc aaa tat gtg gcc gat ggg aay ctg tgt ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                       546
His Pro Glu Ser Thr  *
            180
```

<210> 107
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant C15X, G18D, Asn169

<221> VARIANT
<222> (15)...(15)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 107

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

<210> 108
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant C16X, G19D, Asn170

<221> CDS
<222> (1)...(549)

<221> variation

<222> (47)...(48)
<223> n = A, T, G, or C

<400> 108

```
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa
 1               5                  10                  15

cac att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg aay ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 109
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant C16X, G19D, Asn170

<221> VARIANT
<222> (16)...(16)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 109
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa
1 5 10 15
His Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
50 55 60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
85 90 95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
100 105 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
115 120 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
130 135 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145 150 155 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Cys Leu Arg Thr Ser
165 170 175
Thr His Pro Glu Ser Thr
180

<210> 110
<211> 546
<212> DNA
<213> qArtificial Sequence

<220>
<223> IL29 mutant G18D, Asp169, C171X

<221> CDS
<222> (1)...(546)

<221> variation
<222> (512)...(513)
<223> n = A, T, G, or C

<400> 110
ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac 48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His
1 5 10 15

att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag 96
Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
20 25 30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt 144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
35 40 45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag 192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln

```
     50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
 65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                 85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg gay ctg dnn ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                          546
His Pro Glu Ser Thr  *
            180
```

<210> 111
<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant G18D, Asp169, C171X

<221> VARIANT
<222> (171)...(171)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 111

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

```
            100                 105                 110
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160
Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser Thr
                165                 170                 175
His Pro Glu Ser Thr
            180
```

<210> 112
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant G19D, Asp170, C172X

<221> CDS
<222> (1)...(549)

<221> variation
<222> (515)...(516)
<223> n = A, T, G, or C

<400> 112

```
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc   48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15

cac att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125
```

```
cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg gay ctg dnn ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Xaa Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 113
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant G19D, Asp170, C172X

<221> VARIANT
<222> (172)...(172)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 113

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

<210> 114
<211> 546
<212> DNA
<213> Artificial Sequence

<220>
<223> IL29 mutant C15X, G18D, Asp169

<221> CDS
<222> (1)...(546)

<221> variation
<222> (44)...(45)
<223> n = A, T, G, or C

<400> 114

```
ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn cac   48
Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa His
 1               5                  10                  15

att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag   96
Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys
            20                  25                  30

aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt   144
Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser
        35                  40                  45

tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag   192
Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln
    50                  55                  60

gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg   240
Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu
65                  70                  75                  80

aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac   288
Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp
                85                  90                  95

cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt   336
Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys
            100                 105                 110

atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac   384
Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His
        115                 120                 125

cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc   432
His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly
    130                 135                 140

tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga   480
Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg
145                 150                 155                 160

gac ctc aaa tat gtg gcc gat ggg gay ctg tgt ctg aga acg tca acc   528
Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser Thr
                165                 170                 175

cac cct gag tcc acc tga                                         546
His Pro Glu Ser Thr  *
            180
```

<210> 115

<211> 181
<212> PRT
<213> Artificial Sequence

<220>
<223> IL29 mutant C15X, G18D, Asp169

<221> VARIANT
<222> (15)...(15)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

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

<210> 116
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL29 mutant C16X, G19D, Asp170

<221> CDS
<222> (1)...(549)

<221> variation
<222> (47)...(48)
<223> n = A, T, G, or C

<400> 116
atg ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc dnn 48
Met Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Xaa
1 5 10 15

cac att gay agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc 96
His Ile Asp Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30

```
aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg   144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
         35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc   192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
     50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
 65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                 85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg gay ctg tgt ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asp Leu Cys Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
```

<210> 117
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> Met IL29 mutant C16X, G19D, Asp170

<221> VARIANT
<222> (16)...(16)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 117

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

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

<210> 118
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<223> Signal sequence

<221> CDS
<222> (1)...(57)

<400> 118

```
atg gct gca gct tgg acc gtg gtg ctg gtg act ttg gtg cta ggc ttg   48
Met Ala Ala Ala Trp Thr Val Val Leu Val Thr Leu Val Leu Gly Leu
 1               5                  10                  15

gcc gtg gca                                                      57
Ala Val Ala
```

<210> 119
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Signal sequence

<400> 119

```
Met Ala Ala Ala Trp Thr Val Val Leu Val Thr Leu Val Leu Gly Leu
 1               5                  10                  15
Ala Val Ala
```

<210> 120
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Signal sequence

<221> CDS
<222> (1)...(66)

<400> 120
atg gtg ccc acc aca ttg gct tgg acc gtg gtg ctg gtg act ttg gtg 48
Met Val Pro Thr Thr Leu Ala Trp Thr Val Val Leu Val Thr Leu Val
1 5 10 15

cta ggc ttg gcc gtg gca 66
Leu Gly Leu Ala Val Ala
20

<210> 121
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Signal sequence

<400> 121
Met Val Pro Thr Thr Leu Ala Trp Thr Val Val Leu Val Thr Leu Val
1 5 10 15
Leu Gly Leu Ala Val Ala
20

<210> 122
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28B C48S

<221> CDS
<222> (1)...(528)

<221> variation
<222> (143)...(144)
<223> n = A, T, G, or C

<400> 122
gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc tgc 48
Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly Cys
1 5 10 15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt 96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
20 25 30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac dnn 144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Xaa
35 40 45

aag tgc cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg 192
Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu

```
     50                  55                  60

cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
 65                  70                  75                  80

ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg ggg gat   288
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly Asp
                 85                  90                  95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ctc   336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
            100                 105                 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc   384
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
        115                 120                 125

cgc ctc cac cat tgg ctg cac cgg ctc cag gag gcc cca aaa aag gag   432
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc   480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160

ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc tga   528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val  *
                165                 170                 175
```

<210> 123
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (48)...(48)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> IL-28B C48S

<400> 123

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

```
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175


<210> 124
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL-28B C49S

<221> CDS
<222> (1)...(531)

<221> variation
<222> (146)...(147)
<223> n = A, T, G, or C

<400> 124
atg gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc   48
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
 1               5                  10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc   96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
        35                  40                  45

dnn aag tgc cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Xaa Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50                  55                  60

ctg cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80

acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg ggg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly
                85                  90                  95

gat gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ctc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125

ggc cgc ctc cac cat tgg ctg cac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
```

```
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
```

<210> 125
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (49)...(49)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> Met IL-28B C49S

<400> 125

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

<210> 126
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28B C50S

<221> CDS
<222> (1)...(528)

<221> variation

<222> (149)...(150)
<223> n = A, T, G, or C

<400> 126
gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc tgc 48
Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly Cys
1 5 10 15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt 96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
20 25 30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac tgc 144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Cys
35 40 45

aag dnn cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg 192
Lys Xaa Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
50 55 60

cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg acg 240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80

ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg ggg gat 288
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly Asp
85 90 95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ctc 336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
100 105 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc 384
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
115 120 125

cgc ctc cac cat tgg ctg cac cgg ctc cag gag gcc cca aaa aag gag 432
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
130 135 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc 480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145 150 155 160

ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc tga 528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val *
165 170 175

<210> 127
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (50)...(50)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> IL-28B C50S

<400> 127
Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly Cys
1 5 10 15
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
20 25 30
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Cys
35 40 45
Lys Xaa Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
50 55 60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65 70 75 80
Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly Asp
85 90 95
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
100 105 110
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
115 120 125
Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu
130 135 140
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145 150 155 160
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
165 170 175

<210> 128
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL-28B C51S

<221> CDS
<222> (1)...(531)

<221> variation
<222> (152)...(153)
<223> n = A, T, G, or C

<400> 128
atg gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc 48
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
1 5 10 15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc 96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
20 25 30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac 144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
35 40 45

tgc aag dnn cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag 192
Cys Lys Xaa Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
50 55 60

ctg cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg 240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65 70 75 80

```
acg ctg aag gtt ctg gag gcc acc gct gac act gac cca gcc ctg ggg   288
Thr Leu Lys Val Leu Glu Ala Thr Ala Asp Thr Asp Pro Ala Leu Gly
                 85                  90                  95

gat gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ctc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125

ggc cgc ctc cac cat tgg ctg cac cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
```

<210> 129
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (51)...(51)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> Met IL-28B C51S

<400> 129

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

```
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175


<210> 130
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28B C48S T87S H135Y

<221> CDS
<222> (1)...(528)

<221> variation
<222> 143, 144, 261
<223> n = A, T, G, or C

<400> 130
gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc tgc   48
Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly Cys
 1               5                  10                  15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt   96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
            20                  25                  30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac dnn   144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Xaa
        35                  40                  45

aag tgc cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg   192
Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
    50                  55                  60

cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtt ctg gag gcc wsn gct gac act gac cca gcc ctg ggg gat   288
Leu Lys Val Leu Glu Ala Xaa Ala Asp Thr Asp Pro Ala Leu Gly Asp
                85                  90                  95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ctc   336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
            100                 105                 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc   384
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
        115                 120                 125

cgc ctc cac cat tgg ctg tay cgg ctc cag gag gcc cca aaa aag gag   432
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc   480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160
```

```
ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc tga   528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val  *
                165                 170                 175
```

<210> 131
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (48)...(48)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<221> VARIANT
<222> (87)...(87)
<223> Xaa = Ser

<223> IL-28B C48S T87S H135Y

<400> 131

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

<210> 132
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL-28B C49S T88S H136Y

<221> CDS
<222> (1)...(531)

<221> variation
<222> 146, 147, 264

<223> n = A, T, G, or C

<400> 132

```
atg gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc   48
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
 1               5                  10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc   96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
        35                  40                  45

dnn aag tgc cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Xaa Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50                  55                  60

ctg cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80

acg ctg aag gtt ctg gag gcc wsn gct gac act gac cca gcc ctg ggg   288
Thr Leu Lys Val Leu Glu Ala Xaa Ala Asp Thr Asp Pro Ala Leu Gly
                85                  90                  95

gat gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ctc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125

ggc cgc ctc cac cat tgg ctg tay cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
```

<210> 133
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (49)...(49)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<221> VARIANT
<222> (88)...(88)
<223> Xaa = Ser

<223> Met IL-28B C49S T88S H136Y

<400> 133
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
 1   5   10   15
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20   25   30
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
        35   40   45
Xaa Lys Cys Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50   55   60
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65   70   75   80
Thr Leu Lys Val Leu Glu Ala Xaa Ala Asp Thr Asp Pro Ala Leu Gly
                85   90   95
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100   105   110
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115   120   125
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130   135   140
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145   150   155   160
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165   170   175

<210> 134
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-28B C50S T87S H135Y

<221> CDS
<222> (1)...(528)

<221> variation
<222> 149, 150, 261
<223> n = A, T, G, or C

<400> 134
gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc tgc 48
Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly Cys
 1   5   10   15

cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc ttt 96
His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala Phe
            20   25   30

aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac tgc 144
Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp Cys
        35   40   45

aag dnn cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag ctg 192

```
Lys Xaa Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln Leu
     50                  55                  60

cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg acg   240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
 65                  70                  75                  80

ctg aag gtt ctg gag gcc wsn gct gac act gac cca gcc ctg ggg gat   288
Leu Lys Val Leu Glu Ala Xaa Ala Asp Thr Asp Pro Ala Leu Gly Asp
                 85                  90                  95

gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag ctc   336
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
            100                 105                 110

cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg ggc   384
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
        115                 120                 125

cgc ctc cac cat tgg ctg tay cgg ctc cag gag gcc cca aaa aag gag   432
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140

tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc ctc   480
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160

ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc tga   528
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val  *
                165                 170                 175
```

<210> 135
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (50)...(50)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<221> VARIANT
<222> (87)...(87)
<223> Xaa = Ser

<223> IL-28B C50S T87S H135Y

<400> 135

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

```
                85                  90                  95
Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu
            100                 105                 110
Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg Gly
        115                 120                 125
Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys Glu
    130                 135                 140
Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu
145                 150                 155                 160
Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175


<210> 136
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> Met IL-28B C51S T88S H136Y

<221> CDS
<222> (1)...(531)

<221> variation
<222> 152, 153, 264
<223> n = A, T, G, or C

<400> 136
atg gtt cct gtc gcc agg ctc cgc ggg gct ctc ccg gat gca agg ggc   48
Met Val Pro Val Ala Arg Leu Arg Gly Ala Leu Pro Asp Ala Arg Gly
 1               5                  10                  15

tgc cac ata gcc cag ttc aag tcc ctg tct cca cag gag ctg cag gcc   96
Cys His Ile Ala Gln Phe Lys Ser Leu Ser Pro Gln Glu Leu Gln Ala
            20                  25                  30

ttt aag agg gcc aaa gat gcc tta gaa gag tcg ctt ctg ctg aag gac   144
Phe Lys Arg Ala Lys Asp Ala Leu Glu Glu Ser Leu Leu Leu Lys Asp
        35                  40                  45

tgc aag dnn cgc tcc cgc ctc ttc ccc agg acc tgg gac ctg agg cag   192
Cys Lys Xaa Arg Ser Arg Leu Phe Pro Arg Thr Trp Asp Leu Arg Gln
    50                  55                  60

ctg cag gtg agg gag cgc ccc gtg gct ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80

acg ctg aag gtt ctg gag gcc wsn gct gac act gac cca gcc ctg ggg   288
Thr Leu Lys Val Leu Glu Ala Xaa Ala Asp Thr Asp Pro Ala Leu Gly
                85                  90                  95

gat gtc ttg gac cag ccc ctt cac acc ctg cac cat atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ctc cgg gcc tgt atc cag cct cag ccc acg gca ggg ccc agg acc cgg   384
Leu Arg Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Thr Arg
        115                 120                 125
```

```
ggc cgc ctc cac cat tgg ctg tay cgg ctc cag gag gcc cca aaa aag   432
Gly Arg Leu His His Trp Leu Tyr Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc cct ggc tgc ctc gag gcc tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Pro Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctg aat tgt gtt gcc agc ggg gac ctg tgt gtc   528
Leu Leu Thr Arg Asp Leu Asn Cys Val Ala Ser Gly Asp Leu Cys Val
                165                 170                 175

tga                                                               531
 *
```

<210> 137
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (51)...(51)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<221> VARIANT
<222> (88)...(88)
<223> Xaa = Ser

<223> Met IL-28B C51S T88S H136Y

<400> 137

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

<210> 138
<211> 543
<212> DNA

<213> Artificial Sequence

<220>
<223> IL-29 C170X, truncated after N-terminal Methionine
and Glycine

<221> variation
<222> (509)...(510)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(543)

<400> 138

```
cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac att   48
Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile
 1               5                  10                  15

ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag aag   96
Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys
            20                  25                  30

gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc   144
Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys
        35                  40                  45

agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg   192
Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val
    50                  55                  60

agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag   240
Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys
65                  70                  75                  80

gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac cag   288
Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln
                85                  90                  95

ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc   336
Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile
            100                 105                 110

cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac   384
Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His
        115                 120                 125

tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc tgc   432
Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys
    130                 135                 140

ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac   480
Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp
145                 150                 155                 160

ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca acc cac   528
Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His
                165                 170                 175

cct gag tcc acc tga                                              543
Pro Glu Ser Thr  *
            180
```

<210> 139
<211> 180
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (170)...(170)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> IL-29 C170X, truncated after N-terminal Methionine and Glycine

<400> 139

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

<210> 140
<211> 540
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 C169X, truncated after N-terminal Methionine, Glycine, and Proline

<221> variation
<222> (506)...(507)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(540)

<400> 140
gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac att ggc 48
Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly

```
1               5                  10                  15

agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag aag gcc   96
Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala
            20                  25                  30

agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc   144
Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser
        35                  40                  45

tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg   192
Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg
    50                  55                  60

gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc   240
Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val
65                  70                  75                  80

ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac cag ccc   288
Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro
                85                  90                  95

ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc cag   336
Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln
            100                 105                 110

cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg   384
Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp
        115                 120                 125

ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc tgc ctg   432
Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu
    130                 135                 140

gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc   480
Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu
145                 150                 155                 160

aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca acc cac cct   528
Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro
                165                 170                 175

gag tcc acc tga                                                   540
Glu Ser Thr  *
```

<210> 141
<211> 179
<212> PRT
<213> Artificial Sequence

<220>
<221> VARIANT
<222> (169)...(169)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<223> L-29 C169X, truncated after N-terminal Methionine, Glycine, and Proline

<400> 141

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

<210> 142
<211> 537
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 C168X, truncated after N-terminal
Methionine, Glycine, Proline, and Valine

<221> variation
<222> (503)...(504)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(537)

<400> 142

```
ccc act tcc aag ccc acc aca act ggg aag ggc tgc cac att ggc agg   48
Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg
 1               5                  10                  15

ttc aaa tct ctg tca cca cag gag cta gcg agc ttc aag aag gcc agg   96
Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg
            20                  25                  30

gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc tct   144
Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser
        35                  40                  45

cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg gag   192
Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu
    50                  55                  60

cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc ctg   240
Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu
```

```
 65                  70                  75                  80

gag gcc gct gct ggc cca gcc ctg gag gac gtc cta gac cag ccc ctt   288
Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu
                85                  90                  95

cac acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc cag cct   336
His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro
            100                 105                 110

cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg ctg   384
Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu
        115                 120                 125

cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc tgc ctg gag   432
His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu
    130                 135                 140

gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc aaa   480
Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys
145                 150                 155                 160

tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca acc cac cct gag   528
Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro Glu
                165                 170                 175

tcc acc tga                                                       537
Ser Thr  *
```

<210> 143
<211> 178
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 C168X, truncated after N-terminal
Methionine, Glycine, Proline, and Valine

<221> VARIANT
<222> (168)...(168)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 143

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

```
His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu
    130                 135                 140
Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys
145                 150                 155                 160
Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro Glu
                165                 170                 175
Ser Thr
```

<210> 144
<211> 534
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 C167X, truncated after N-terminal
Methionine, Glycine, Proline, Valine, and Proline

<221> variation
<222> (500)...(501)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(534)

<400> 144

```
act tcc aag ccc acc aca act ggg aag ggc tgc cac att ggc agg ttc   48
Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg Phe
 1               5                  10                  15

aaa tct ctg tca cca cag gag cta gcg agc ttc aag aag gcc agg gac   96
Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg Asp
            20                  25                  30

gcc ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc tct cct  144
Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser Pro
        35                  40                  45

gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg gag cgc  192
Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu Arg
    50                  55                  60

cct gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc ctg gag  240
Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu
65                  70                  75                  80

gcc gct gct ggc cca gcc ctg gag gac gtc cta gac cag ccc ctt cac  288
Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu His
                85                  90                  95

acc ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc cag cct cag  336
Thr Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro Gln
            100                 105                 110

ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg ctg cac  384
Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu His
        115                 120                 125

cgg ctc cag gag gcc ccc aaa aag gag tcc gct ggc tgc ctg gag gca  432
Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu Ala
```

```
    130                 135                 140

tct gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc aaa tat   480
Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys Tyr
145                 150                 155                 160

gtg gcc gat ggg aac ctg dnn ctg aga acg tca acc cac cct gag tcc   528
Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro Glu Ser
                165                 170                 175

acc tga                                                           534
Thr  *
```

<210> 145
<211> 177
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 C167X, truncated after N-terminal
Methionine, Glycine, Proline, Valine, and Proline

<221> VARIANT
<222> (167)...(167)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 145

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

<210> 146
<211> 531
<212> DNA
<213> Artificial Sequence

<220>

<223> IL-29 C166X, truncated after N-terminal
Methionine, Glycine, Proline, Valine, Proline, and
Threonine

<221> variation
<222> (497)...(498)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(531)

<400> 146

```
tcc aag ccc acc aca act ggg aag ggc tgc cac att ggc agg ttc aaa   48
Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg Phe Lys
 1               5                  10                  15

tct ctg tca cca cag gag cta gcg agc ttc aag aag gcc agg gac gcc   96
Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg Asp Ala
             20                  25                  30

ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc tct cct gtc   144
Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser Pro Val
         35                  40                  45

ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg gag cgc cct   192
Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu Arg Pro
     50                  55                  60

gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc ctg gag gcc   240
Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala
 65                  70                  75                  80

gct gct ggc cca gcc ctg gag gac gtc cta gac cag ccc ctt cac acc   288
Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu His Thr
                 85                  90                  95

ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc cag cct cag ccc   336
Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro Gln Pro
            100                 105                 110

aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg ctg cac cgg   384
Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu His Arg
        115                 120                 125

ctc cag gag gcc ccc aaa aag gag tcc gct ggc tgc ctg gag gca tct   432
Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu Ala Ser
    130                 135                 140

gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc aaa tat gtg   480
Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys Tyr Val
145                 150                 155                 160

gcc gat ggg aac ctg dnn ctg aga acg tca acc cac cct gag tcc acc   528
Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro Glu Ser Thr
                165                 170                 175

tga                                                               531
 *
```

<210> 147
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 C166X, truncated after N-terminal Methionine, Glycine, Proline, Valine, Proline, and Threonine

<221> VARIANT
<222> (166)...(166)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 147
Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg Phe Lys
1 5 10 15
Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg Asp Ala
20 25 30
Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser Pro Val
35 40 45
Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu Arg Pro
50 55 60
Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala
65 70 75 80
Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu His Thr
85 90 95
Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro Gln Pro
100 105 110
Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu His Arg
115 120 125
Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu Ala Ser
130 135 140
Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys Tyr Val
145 150 155 160
Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro Glu Ser Thr
165 170 175

<210> 148
<211> 528
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 C165X, truncated after N-terminal Methionine, Glycine, Proline, Valine, Proline, Threonine, and Serine

<221> variation
<222> (494)...(495)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(528)

<400> 148
aag ccc acc aca act ggg aag ggc tgc cac att ggc agg ttc aaa tct 48
Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg Phe Lys Ser
1 5 10 15

```
ctg tca cca cag gag cta gcg agc ttc aag aag gcc agg gac gcc ttg   96
Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg Asp Ala Leu
             20                  25                  30

gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc tct cct gtc ttc   144
Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser Pro Val Phe
         35                  40                  45

ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg gag cgc cct gtg   192
Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu Arg Pro Val
     50                  55                  60

gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc ctg gag gcc gct   240
Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala Ala
 65                  70                  75                  80

gct ggc cca gcc ctg gag gac gtc cta gac cag ccc ctt cac acc ctg   288
Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu His Thr Leu
                 85                  90                  95

cac cac atc ctc tcc cag ctc cag gcc tgt atc cag cct cag ccc aca   336
His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro Gln Pro Thr
            100                 105                 110

gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg ctg cac cgg ctc   384
Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu His Arg Leu
        115                 120                 125

cag gag gcc ccc aaa aag gag tcc gct ggc tgc ctg gag gca tct gtc   432
Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu Ala Ser Val
    130                 135                 140

acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc aaa tat gtg gcc   480
Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys Tyr Val Ala
145                 150                 155                 160

gat ggg aac ctg dnn ctg aga acg tca acc cac cct gag tcc acc tga   528
Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro Glu Ser Thr  *
                165                 170                 175
```

<210> 149
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 C165X, truncated after N-terminal
Methionine, Glycine, Proline, Valine, Proline,
Threonine, and Serine

<221> VARIANT
<222> (165)...(165)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 149

```
Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg Phe Lys Ser
 1               5                  10                  15
Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg Asp Ala Leu
            20                  25                  30
```

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


<210> 150
<211> 552
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 Leu insert after N-terminal Met, C173X

<221> variation
<222> (518)...(519)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(552)

<400> 150
atg ytn ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc   48
Met Leu Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly
 1               5                  10                  15

tgc cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc   96
Cys His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser
            20                  25                  30

ttc aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac   144
Phe Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn
        35                  40                  45

tgg agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt   192
Trp Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu
    50                  55                  60

ctc cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg   240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80

acg ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc   288
Thr Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val
                85                  90                  95

cta gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag   336
```

```
Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln
            100                 105                 110

gcc tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc   384
Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg
        115                 120                 125

ctc cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc   432
Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser
    130                 135                 140

gct ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc   480
Ala Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu
145                 150                 155                 160

acg cga gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg   528
Thr Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr
                165                 170                 175

tca acc cac cct gag tcc acc tga                                  552
Ser Thr His Pro Glu Ser Thr  *
            180
```

<210> 151
<211> 183
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 Leu insert after N-terminal Met, C173X

<221> VARIANT
<222> (173)...(173)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 151

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

<210> 152
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 G2L C172X

<221> variation
<222> (515)...(516)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(549)

<400> 152

```
atg ytn cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc   48
Met Leu Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc   96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg  144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc  192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg  240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta  288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc  336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc  384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct  432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg  480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca  528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
                165                 170                 175
```

```
acc cac cct gag tcc acc tga                                          549
Thr His Pro Glu Ser Thr  *
            180


<210> 153
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 G2L C172X

<221> VARIANT
<222> (172)...(172)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 153
Met Leu Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
 1               5                  10                  15
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
            20                  25                  30
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
        35                  40                  45
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
    50                  55                  60
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr
65                  70                  75                  80
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                85                  90                  95
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
                165                 170                 175
Thr His Pro Glu Ser Thr
            180


<210> 154
<211> 552
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 Ile insert after N-terminal Met, C173X

<221> variation
<222> (518)...(519)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(552)

<400> 154
```

```
atg ath ggc cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc   48
Met Ile Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly
 1               5                  10                  15

tgc cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc   96
Cys His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser
            20                  25                  30

ttc aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac  144
Phe Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn
        35                  40                  45

tgg agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt  192
Trp Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu
    50                  55                  60

ctc cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg  240
Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu
65                  70                  75                  80

acg ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc  288
Thr Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val
                85                  90                  95

cta gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag  336
Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln
            100                 105                 110

gcc tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc  384
Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg
        115                 120                 125

ctc cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc  432
Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser
    130                 135                 140

gct ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc  480
Ala Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu
145                 150                 155                 160

acg cga gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg  528
Thr Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr
                165                 170                 175

tca acc cac cct gag tcc acc tga                                 552
Ser Thr His Pro Glu Ser Thr  *
            180
```

<210> 155
<211> 183
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 Ile insert after N-terminal Met, C173X

<221> VARIANT
<222> (173)...(173)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

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

<210> 156
<211> 549
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 G2I C172X

<221> variation
<222> (515)...(516)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(549)

<400> 156
atg ath cct gtc ccc act tcc aag ccc acc aca act ggg aag ggc tgc 48
Met Ile Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly Lys Gly Cys
1 5 10 15

cac att ggc agg ttc aaa tct ctg tca cca cag gag cta gcg agc ttc 96
His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe
20 25 30

aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg aaa aac tgg 144
Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp
35 40 45

agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg agg ctt ctc 192
Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu
50 55 60

cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg gcc ctg acg 240
Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu Ala Leu Thr

```
65                  70                  75                  80

ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag gac gtc cta   288
Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu Asp Val Leu
                 85                  90                  95

gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag ctc cag gcc   336
Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln Leu Gln Ala
            100                 105                 110

tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg ggc cgc ctc   384
Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu
        115                 120                 125

cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag gag tcc gct   432
His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala
    130                 135                 140

ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc ctc ctc acg   480
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160

cga gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg aga acg tca   528
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
                165                 170                 175

acc cac cct gag tcc acc tga                                      549
Thr His Pro Glu Ser Thr  *
            180
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<210> 157
<211> 182
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 G2I C172X

<221> VARIANT
<222> (172)...(172)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 157

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

```
    130                 135                 140
Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg Leu Leu Thr
145                 150                 155                 160
Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser
                165                 170                 175
Thr His Pro Glu Ser Thr
            180


<210> 158
<211> 531
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 after N-terminal Met amino acid residues 2-7
      deleted, C166X

<221> variation
<222> (497)...(498)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(531)

<400> 158
atg aag ccc acc aca act ggg aag ggc tgc cac att ggc agg ttc aaa   48
Met Lys Pro Thr Thr Thr Gly Lys Gly Cys His Ile Gly Arg Phe Lys
 1               5                  10                  15

tct ctg tca cca cag gag cta gcg agc ttc aag aag gcc agg gac gcc   96
Ser Leu Ser Pro Gln Glu Leu Ala Ser Phe Lys Lys Ala Arg Asp Ala
            20                  25                  30

ttg gaa gag tca ctc aag ctg aaa aac tgg agt tgc agc tct cct gtc   144
Leu Glu Glu Ser Leu Lys Leu Lys Asn Trp Ser Cys Ser Ser Pro Val
        35                  40                  45

ttc ccc ggg aat tgg gac ctg agg ctt ctc cag gtg agg gag cgc cct   192
Phe Pro Gly Asn Trp Asp Leu Arg Leu Leu Gln Val Arg Glu Arg Pro
    50                  55                  60

gtg gcc ttg gag gct gag ctg gcc ctg acg ctg aag gtc ctg gag gcc   240
Val Ala Leu Glu Ala Glu Leu Ala Leu Thr Leu Lys Val Leu Glu Ala
65                  70                  75                  80

gct gct ggc cca gcc ctg gag gac gtc cta gac cag ccc ctt cac acc   288
Ala Ala Gly Pro Ala Leu Glu Asp Val Leu Asp Gln Pro Leu His Thr
                85                  90                  95

ctg cac cac atc ctc tcc cag ctc cag gcc tgt atc cag cct cag ccc   336
Leu His His Ile Leu Ser Gln Leu Gln Ala Cys Ile Gln Pro Gln Pro
            100                 105                 110

aca gca ggg ccc agg ccc cgg ggc cgc ctc cac cac tgg ctg cac cgg   384
Thr Ala Gly Pro Arg Pro Arg Gly Arg Leu His His Trp Leu His Arg
        115                 120                 125

ctc cag gag gcc ccc aaa aag gag tcc gct ggc tgc ctg gag gca tct   432
Leu Gln Glu Ala Pro Lys Lys Glu Ser Ala Gly Cys Leu Glu Ala Ser
    130                 135                 140
```

```
gtc acc ttc aac ctc ttc cgc ctc ctc acg cga gac ctc aaa tat gtg   480
Val Thr Phe Asn Leu Phe Arg Leu Leu Thr Arg Asp Leu Lys Tyr Val
145                 150                 155                 160

gcc gat ggg aac ctg dnn ctg aga acg tca acc cac cct gag tcc acc   528
Ala Asp Gly Asn Leu Xaa Leu Arg Thr Ser Thr His Pro Glu Ser Thr
                165                 170                 175

tga                                                               531
 *
```

<210> 159
<211> 176
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 after N-terminal Met amino acid residues 2-7 deleted, C166X

<221> VARIANT
<222> (166)...(166)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 159

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

<210> 160
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-29 Glu, Ala, and Glu inserted after N-terminal Met, C175X

<221> variation
<222> (524)...(525)
<223> n = A, T, G, or C

<221> CDS
<222> (1)...(558)

<400> 160

```
atg gar gcn gar ggc cct gtc ccc act tcc aag ccc acc aca act ggg   48
Met Glu Ala Glu Gly Pro Val Pro Thr Ser Lys Pro Thr Thr Thr Gly
 1               5                  10                  15

aag ggc tgc cac att ggc agg ttc aaa tct ctg tca cca cag gag cta   96
Lys Gly Cys His Ile Gly Arg Phe Lys Ser Leu Ser Pro Gln Glu Leu
             20                  25                  30

gcg agc ttc aag aag gcc agg gac gcc ttg gaa gag tca ctc aag ctg   144
Ala Ser Phe Lys Lys Ala Arg Asp Ala Leu Glu Glu Ser Leu Lys Leu
         35                  40                  45

aaa aac tgg agt tgc agc tct cct gtc ttc ccc ggg aat tgg gac ctg   192
Lys Asn Trp Ser Cys Ser Ser Pro Val Phe Pro Gly Asn Trp Asp Leu
     50                  55                  60

agg ctt ctc cag gtg agg gag cgc cct gtg gcc ttg gag gct gag ctg   240
Arg Leu Leu Gln Val Arg Glu Arg Pro Val Ala Leu Glu Ala Glu Leu
 65                  70                  75                  80

gcc ctg acg ctg aag gtc ctg gag gcc gct gct ggc cca gcc ctg gag   288
Ala Leu Thr Leu Lys Val Leu Glu Ala Ala Ala Gly Pro Ala Leu Glu
                 85                  90                  95

gac gtc cta gac cag ccc ctt cac acc ctg cac cac atc ctc tcc cag   336
Asp Val Leu Asp Gln Pro Leu His Thr Leu His His Ile Leu Ser Gln
            100                 105                 110

ctc cag gcc tgt atc cag cct cag ccc aca gca ggg ccc agg ccc cgg   384
Leu Gln Ala Cys Ile Gln Pro Gln Pro Thr Ala Gly Pro Arg Pro Arg
        115                 120                 125

ggc cgc ctc cac cac tgg ctg cac cgg ctc cag gag gcc ccc aaa aag   432
Gly Arg Leu His His Trp Leu His Arg Leu Gln Glu Ala Pro Lys Lys
    130                 135                 140

gag tcc gct ggc tgc ctg gag gca tct gtc acc ttc aac ctc ttc cgc   480
Glu Ser Ala Gly Cys Leu Glu Ala Ser Val Thr Phe Asn Leu Phe Arg
145                 150                 155                 160

ctc ctc acg cga gac ctc aaa tat gtg gcc gat ggg aac ctg dnn ctg   528
Leu Leu Thr Arg Asp Leu Lys Tyr Val Ala Asp Gly Asn Leu Xaa Leu
                165                 170                 175

aga acg tca acc cac cct gag tcc acc tga                           558
Arg Thr Ser Thr His Pro Glu Ser Thr  *
            180                 185
```

<210> 161
<211> 185
<212> PRT
<213> Artificial Sequence

<220>
<223> IL-29 Glu, Ala, and Glu inserted after N-terminal Met, C175X

<221> VARIANT
<222> (175)...(175)
<223> Xaa = Ser, Ala, Thr, Val, or Asn

<400> 161

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