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(54) **MODULATING CYTOKINE OR HORMONE SIGNALLING IN AN ANIMAL COMPRISING UP-REGULATING THE EXPRESSION OF SOCS SEQUENCE IN THE ANIMAL**

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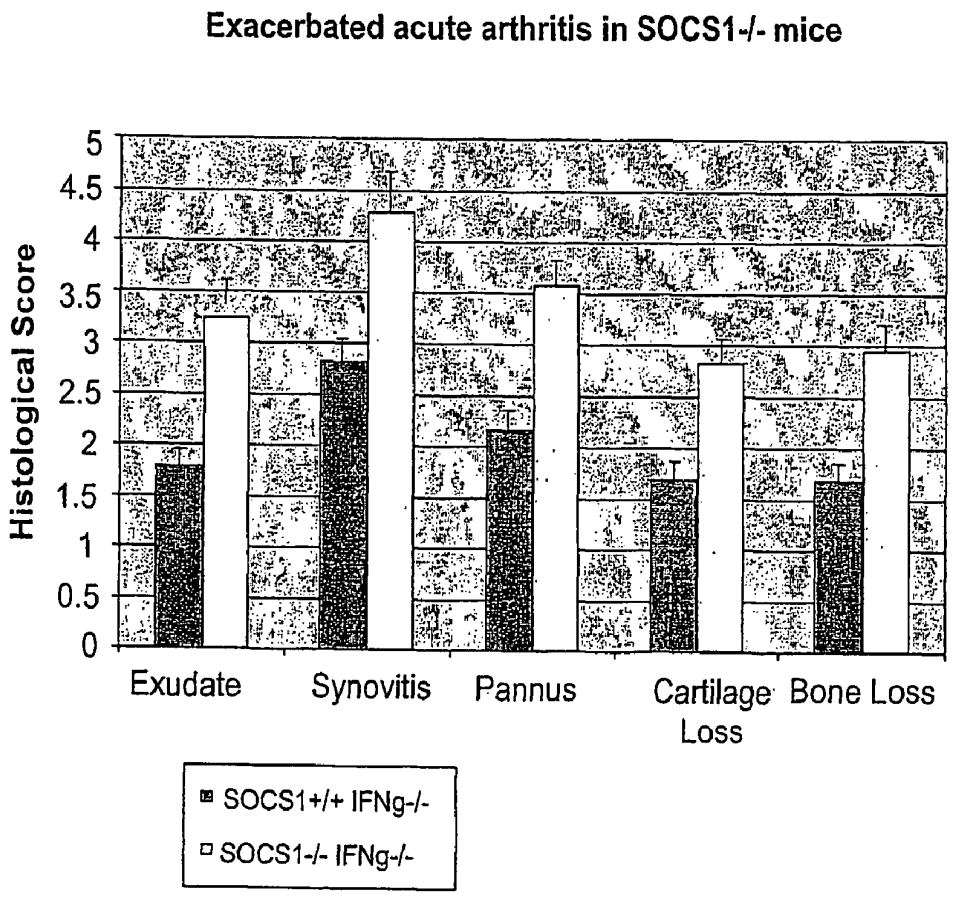
(57) **ABSTRACT**

The present invention relates generally to a method for the treatment and/or prophylaxis of conditions arising from or otherwise associated with aberrations in hormone signaling. More particularly, the present invention contemplates a method for the treatment and/or prophylaxis of conditions, the amelioration of symptoms of which, are facilitated by an over-expression of a gene encoding a suppressor of cytokine signaling molecule. The present invention further contemplates agents useful for the prophylaxis and/or treatment of such conditions in mammals including humans.



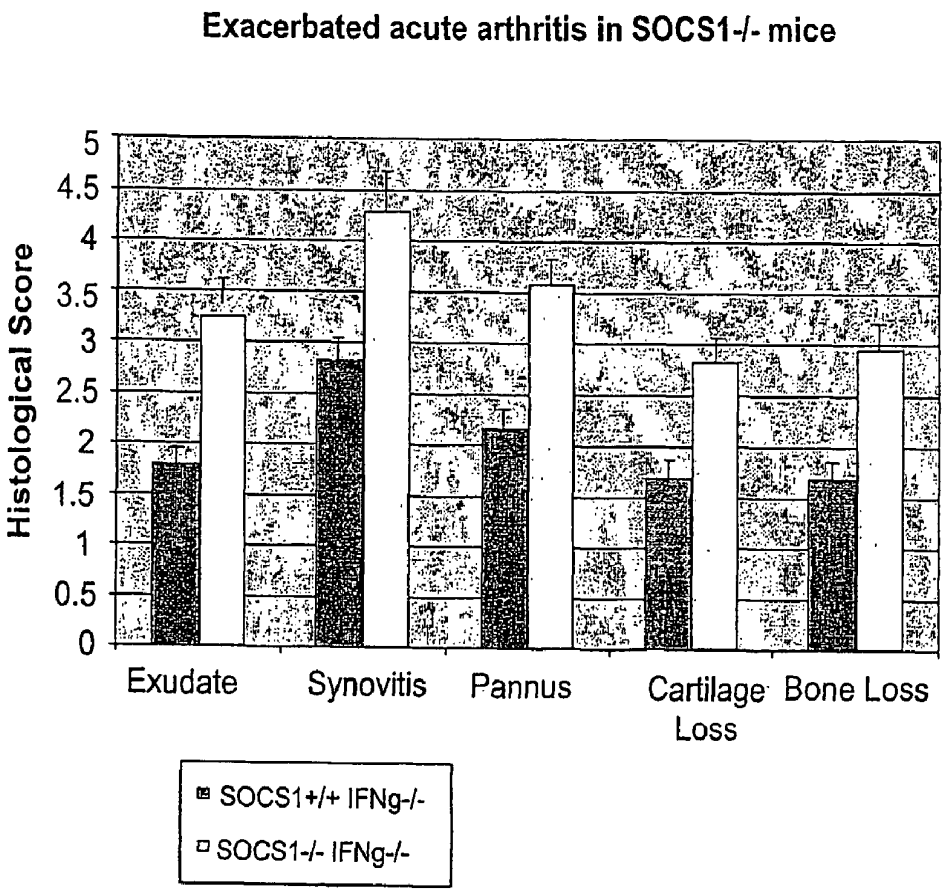

Exacerbated acute arthritis in SOCS1-/- mice
Histological Score
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Exudate
Synovitis
Pannus
Cartilage Loss
Bone Loss
SOCS1+/+ IFNg-/-
SOCS1-/- IFNg-/-

Figure 1

MODULATING CYTOKINE OR HORMONE SIGNALLING IN AN ANIMAL COMPRISING UP-REGULATING THE EXPRESSION OF SOCS SEQUENCE IN THE ANIMAL

FIELD OF THE INVENTION

[0001] The present invention relates generally to a method for the treatment and/or prophylaxis of conditions arising from or otherwise associated with aberrations in hormone signalling. More particularly, the present invention contemplates a method for the treatment and/or prophylaxis of conditions, the amelioration of symptoms of which are facilitated by an over-expression of a gene encoding a suppressor of cytokine signalling molecule. The present invention further contemplates agents useful for the prophylaxis and/or treatment of such conditions in mammals including humans.

BACKGROUND OF THE INVENTION

[0002] Bibliographic details of the publications numerically referred to in this specification are collected at the end of the description

[0003] Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in Australia or any other country.

[0004] The gene encoding Suppressor of Cytokine Signaling-1 (SOCS-1), the SOCS protein family prototype, was discovered in a functional genetic screen designed to identify inhibitors of cytokine signalling. Comparison to existing sequences on genetic databases identified a number of additional proteins that could be grouped into a "SOCS protein family" on the basis of homology within a novel COOH-terminal 'SOCS-box' sequence motif. Proteins containing the SOCS-box could be further divided into subfamilies on the basis of additional protein sequence motifs including, for example, SH2 domains (SOCS1-7), WD40 repeats (WSB1,2), ankyrin repeats (ASB1-3) and a SPRY domain (SSB1-3).

[0005] Subsequent analysis has revealed that SOCS-1 and other SOCS family members, most notably those which incorporate an SH2 domain, represent the key components of a classic negative feedback loop that regulates cytokine signalling. SOCS protein expression is induced by cytokine signalling and SOCS proteins interact with components of that process to turn signalling off.

[0006] SOCS-1, which inhibits the in vitro activity of a variety of cytokines including IL-6, LIF, and type DU interferons, binds directly to, and inhibits the action of, Janus kinases (JAKs). Published analysis indicates that this activity against JAKs may be mediated by three distinct functional domains within SOCS-1: the SH2 domain and preceding 12 amino acids (extended SH2 subdomain) of SOCS-1 are required for binding to the phosphorylated (Y1007) activation loop of JAK2; an additional 12 N-terminal amino acids (kinase inhibitory region) of SOCS-1 contribute to high affinity binding to the JAK2 tyrosine kinase domain and are required for the inhibition of JAK2 activity; and the SOCS-box has been found to mediate the interaction of SOCS proteins with elongin B and elongin C, intracellular proteins responsible for targeting proteins for degradation within the cell.

[0007] In addition to inhibiting the activity of cytokines that signal through the JAK/STAT pathway, SOCS-1 has also been reported to inhibit TNFα activities such as induction of cell death (1). Although the mechanism for this activity remains unclear, there is some evidence to suggest that SOCS-1 regulates the activity of p38 MAP kinase which in turn may act as a survival factor in TNF treated cells.

[0008] SOCS-3 has also been demonstrated to inhibit the in vitro activity of LIF and IL-6, however, in contrast to SOCS-1, it does not appear to bind directly to JAKs. Structure-function studies have identified an interaction between SOCS-3 and the cytoplasmic domain of shared receptor component gp130. In particular a single peptide representing the amino acid stretch 750-764 of gp130 and centred around the phosphorylated tyrosine residue 757 (pY757) is able to bind to the SOCS-3 protein with high affinity Kd=42 nM).

[0009] Thus, SOCS proteins appear to inhibit cytokine signalling by at least two mechanisms: they are able to bind to, and inhibit the activity of; signalling intermediates activated following receptor oligermerization (e.g. JAKs) or they interact with receptor components (e.g. gp130) to inhibit the phosphorlyation and activation of downstream substrates.

[0010] Cytokines are key mediators of a number of severe and debilitating diseases. For example, a number of cytokines including IL-1, IL-6, TNFα, GM-CSF and type I/II interferons are central to the pathophysiology of both acute and chronic inflammatory disease. This is reflected in the development and marketing of new therapeutic strategies which focus on inhibition of cytokine action. For example, specific antagonists of TNFα (monoclonal antibodies, soluble receptors) are now used successfully in the treatment of rheumatoid arthritis and Chrones disease.

[0011] As potent negative regulators of cytokine signalling SOCS proteins provide for a new approach to the treatment of cytokine mediated disease such as rheumatoid arthritis. Targeted over-expression of SOCS proteins (i.e. SOCS proteins as gene therapeutics) should turn off cytokine signalling and ameliorate cytokine-mediated disease. Rheumatoid arthritis represents a useful example. When over-expressed, SOCS-1 has been demonstrated to interact with and inhibit the activity of JAKs. JAK activation and subsequent action represents an important downstream event in signalling through both IL 6 and GM-CSF receptors. Furthermore SOCS-1 has also been demonstrated to be a potent antagonist of TNFα mediated activities. In work leading up to the present invention, the inventors reasoned that over-expression of SOCS-1 could be expected to interfere in IL-6, GM-CSF and TNF signalling, all key mediators of rheumatoid arthritis.

[0012] For SOCS therapeutics to be effective, it is likely that they will need to be expressed at a high level such as being over-expressed in the majority of target cells within a pathological lesion. Gene based therapies clearly represent the best way to achieve this, with viral vectors such as adenovirus, adeno-associated virus (AAV) and retrovirus likely to represent the delivery mechanism of choice.

SUMMARY OF THE INVENTION

[0013] Nucleotide and amino acid sequences are referred to by a sequence identifier number (SEQ ID NO:). The SEQ

ID NOs: correspond numerically to the sequence identifiers <400>1, <400>2, etc. A sequence listing is provided after the claims.

[0014] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

[0015] The present invention is predicated in part on the use of genetic therapeutic protocols to increase, enhance or otherwise facilitate expression of nucleotide sequences encoding a SOCS molecule in a cell. Over-expression of such nucleotide sequences thereby elevates levels of the SOCS protein or other expression products (e.g. mRNA or spliced out introns from mRNA encoded by genomic DNA). The "over-expression" in this context means, in one particular embodiment, a level of expression statistically greater than a standardized normal control. However, the present invention also contemplates maintenance of normal expression levels. The "level" of expression may readily be determined by, for example, nuclear run-on analysis or determination of SOCS protein levels amongst other methods.

[0016] Accordingly, one aspect of the present invention contemplates a method for modulating cytokine or hormone signalling in an animal, said method comprising up-regulating expression of a genetic sequence encoding a SOCS protein or its derivative or homolog in said animal.

[0017] Another aspect of the present invention provides a method of modulating cytokine or hormone signalling in an animal and in particular a human, said method comprising up-regulating expression of a genetic sequence encoding a SOCS protein in said animal and wherein said SOCS protein comprises a protein:molecule interacting region such as but not limited to an SH2 domain, WD40 repeats and/or ankyrin repeats, N terminal of a SOCS box, wherein said SOCS box comprises the amino acid sequence:

[0018] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}[X_i]_nX_{17}X_{18}X_{19}X_{20}X_{21}X_{22}X_{23}[X_j]_nX_{24}X_{25}X_{26}X_{27}X_{28}$

wherein:

[0019] X is L, I, V, M, A or P;

[0020] X_2 is any amino acid residue;

[0021] X_3 is P, T or S;

[0022] X_4 is L, I, V, M, A or P;

[0023] X_5 is any amino acid;

[0024] X_6 is any amino acid;

[0025] X_7 is L, I, V, M, A, F, Y or W;

[0026] X_8 is C, T or S;

[0027] X_9 is R, K or H;

[0028] X_{10} is any amino acid;

[0029] X_{11} is any amino acid;

[0030] X_{12} is L, I, V, M, A or P;

[0031] X_{13} is any amino acid;

[0032] X_{14} is any amino acid;

[0033] X_{15} is any amino acid;

[0034] X_{16} is L, I, V, M, A, P, G, C, T or S;

[0035] $[X-]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

[0036] X_{17} is L, I, V, M, A or P;

[0037] X_{18} is any amino acid;

[0038] X_{19} is any amino acid;

[0039] X_{20} is L, I, V, M, A or P;

[0040] X_{21} is P;

[0041] X_{22} is L, I, V, M, A, P or G;

[0042] X_{23} is P or N;

[0043] $[X_j]_n$ is a sequence of n amino acids wherein n is from 0 to 50 amino acids and wherein the X_j may comprise the same or different amino acids selected from any amino acid residue;

[0044] X_{24} is L, V, M, A or P;

[0045] X_{25} is any amino acid;

[0046] X_{26} is any ammo acid;

[0047] X_{27} is Y or F;

[0048] X_{28} is L, I, V, M, A or P.

[0049] Still another aspect of the present invention contemplates a method for controlling cytokine or hormone signalling, such as pro-inflammatory cytokine signalling (i.e. IL-6, GM-CSF, TNFα), in an animal such as a human or livestock animal, said method comprising modulating expression of a genetic sequence encoding a SOCS protein comprising a SOCS box and a protein:molecule interacting region N-terminal of said SOCS box wherein said SOCS box comprises the amino acid sequence:

[0050] $X_1X_2X_3X_4X_5X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}[X_i]_nX_{17}X_{18}X_{19}X_{20}X_{21}X_{22}X_{23}[X_j]_nX_{24}X_{25}X_{26}X_{27}X_{28}$

wherein:

[0051] X_1 is L, I, V, M, A or P;

[0052] X_2 is any amino acid residue;

[0053] X_3 is P, T or S;

[0054] X_4 is L, I, V, M, A or P;

[0055] X_5 is any amino acid;

[0056] X_6 is any amino acid;

[0057] X_7 is L, I, V, M, A, F, Y or W;

[0058] X_8 is C, T or S;

[0059] X_9 is R, K or H;

[0060] X_{10} is any amino acid;

[0061] X_{11} is any amino acid;

[0062] X_{12} is L, I, V, M, A or P;

[0063] X_{13} is any amino acid;

[0064] X_{14} is any amino acid;

[0065] X_{15} is any amino acid;

[0066] X_{16} is L, I, V, M, A, P, G, C, T or S;

[0067] $[X_i]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

[0068] X_{17} is L, I, V, M, A or P;

[0069] X_{18} is any amino acid;

[0070] X_{19} is any amino acid;

[0071] X_{20} is L, I, V, M, A or P;

[0072] X_{21} is P;

[0073] X_{22} is L, I, V, M, A, P or G;

[0074] X_{23} is P or N;

[0075] $[X_j]_n$ is a sequence of n amino acids wherein n is from 0 to 50 amino acids and wherein the X_j may comprise the same or different amino acids selected from any amino acid residue;

[0076] X_{24} is L, I, V, M, A or P;

[0077] X_{25} is any amino acid;

[0078] X_{26} is any amino acid;

[0079] X_{27} is Y or F;

[0080] X_{28} is L, I, V, M, A or P.

[0081] Yet another aspect of the present invention contemplates a method for controlling cytokine or hormone signalling in an animal such as human or livestock animal, said method comprising administering to said animal a genetic molecule encoding a SOCS protein for a time and under conditions sufficient to modulate growth hormone signalling.

[0082] Another aspect of the present invention contemplates a method for the treatment of cytokine-mediated disease in an animal, said method comprising modulating cytokine or hormone signalling in an animal by upregulating the expression of a genetic sequence encoding a SOCS protein or its derivative or homologue in said animal.

[0083] In a preferred embodiment, the SOCS gene is expressed at a high level such as being overexpressed.

[0084] A summary of sequence identifiers used throughout the subject specification is provided below.

SUMMARY OF SEQUENCE IDENTIFIERS

SEQUENCE ID NO:	DESCRIPTION
1	Mouse SOCS-1 (nucleotide)
2	Mouse SOCS-1 (amino acid)
3	Mouse SOCS-3 (nucleotide)
4	Mouse SOCS-3 (amino acid)
5	Human SOCS-1 (nucleotide)
6	Human SOCS-1 (amino acid)
7	Rat SOCS-1 (nucleotide)

-continued

SUMMARY OF SEQUENCE IDENTIFIERS

SEQUENCE ID NO:	DESCRIPTION
8	Rat SOCS-1 (amino acid)
9	Primer
10	Primer
11	Primer
12	Primer
13	Primer
14	Primer

BRIEF DESCRIPTION OF THE FIGURES

[0085] FIG. **1** is a graphical representation of SOCS-1^{++} IFN-$\gamma^{-/-}$ mice (■) compared to SOCS-$1^{-/-}$ IFN-$\gamma^{-/-}$ (□) mice following injection of BSA and IL-1 subcutaneously to knee joints in three daily injections. A histological score was measured in oxodate, synovitis, pannus, cartilage and bone.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0086] One aspect of the present invention contemplates a method for modulating cytokine or hormone signalling in an animal, said method comprising up-regulating expression of a genetic sequence encoding a SOCS protein or its derivative or homolog in said animal.

[0087] Reference herein to "SOCS" encompasses any or all members of the SOCS family. Specific SOCS molecules may be defined numerically such as, for example, SOCS-1, SOCS-2 and SOCS-3. The species from which the SOCS has been obtained may be indicated by a preface of single letter abbreviation where "h" is human, "m" is mouse and "r" is rat. Accordingly, "mSOCS-2", for example, is a specific SOCS from a murine animal. Reference herein to "SOCS" is not to imply that the protein solely suppresses cytokine-mediated signal transduction, as the molecule may modulate other effector-mediated signal transductions such as by hormones or other endogenous or exogenous molecules, antigen, microbes and microbial products, viruses or components thereof ions, hormones and parasites. The term "modulates" encompasses up-regulation as well as at least maintenance of particular levels. Preferably, the expression is up-regulated. Reference herein to "murine" includes both mouse and rat.

[0088] Reference herein to a "hormone" includes protein hormones as well as non-proteinaceous hormones. One particularly useful hormone is growth hormone. Another useful hormones are insulin-like growth factor I (IGF-I) and prolactin. A cytokine refers to any cytokine or cytokine-like molecule such as interleukin (e.g. IL-1, IL-6), tumour necrosis factor (e.g. TNFα), a colony stimulating factor (e.g. GM-CSF) or an interferon.

[0089] An "animal" is preferably a mammal such as but not limited to a human, primate, livestock animal (e.g. sheep, cow, pig, horse, donkey), laboratory test animal (e.g. rabbit, mouse, rat, guinea pig), companion animal (e.g. cat, dog) or captive wild animal. The animal may be in the form of an animal model. Useful animals for this purpose are laboratory test animals. Genetically modifying livestock animals is useful in assisting in food production. The pre-

ferred animal is a human, primate animal or laboratory test animal. The most preferred animal is a human.

[0090] Reference herein to "SOCS" includes a protein comprising a SOCS box in its C-terminal region comprising the amino acid sequence:

[0091] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}[X_i]_nX_{17}X_{18}X_{19}X_{20}X_{21}X_{22}X_{23}[X_j]_nX_{24}X_{25}X_{26}X_{27}X_{28}$

wherein:

[0092] X_1 is L, I, V, M, A or P;

[0093] X_2 is any amino acid residue;

[0094] X_3 is P, T or S;

[0095] X_4 is L, I, V, M, A or P;

[0096] X_5 is any amino acid;

[0097] X_6 is any amino acid;

[0098] X_7 is L, I, V, M, A, F, Y or W;

[0099] X_8 is C, T or S;

[0100] X_9 is R, K or H;

[0101] X_{10} is any amino acid;

[0102] X_{11} is any amino acid;

[0103] X_{12} is L, I, V, M, A or P;

[0104] X_{13} is any amino acid;

[0105] X_{14} is any amino acid;

[0106] X_{15} is any amino acid;

[0107] X_{16} is L, I, V, M, A, P, G, C, T or S;

[0108] $[X_i]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X; may comprise the same or different amino acids selected from any amino acid residue;

[0109] X_{17} is L, I, V, M, A or P;

[0110] X_{18} is any amino acid;

[0111] X_{19} is any amino acid;

[0112] X_{20} is L, I, V, M, A or P;

[0113] X_{21} is P;

[0114] X_{22} is L, I, V, M, A, P or G;

[0115] X_{23} is P or N;

[0116] $[X_j]_n$ is a sequence of n amino acids wherein n is from 0 to 50 amino acids and wherein the X_j may comprise the same or different amino acids selected from any amino acid residue;

[0117] X_{24} is L, I, V, M, A or P;

[0118] X_{25} is any amino acid;

[0119] X_{26} is any amino acid;

[0120] X_{27} is Y or F;

[0121] X_{28} is L, I, V, M, A or P.

[0122] The SOCS protein also comprises a protein:molecule interacting region such as but not limited to one or more of an SH2 domain, WD-40 repeats and/or ankyrin repeats, N-terminal of the SOCS box.

[0123] In an important aspect, the present invention contemplates up-regulating expression of a nucleotide sequence encoding a SOCS protein in the treatment of inflammatory diseases such as rheumatic arthritis.

[0124] Another aspect of the present invention provides a method of modulating cytokine or hormone signalling in an animal and in particular a human, said method comprising up-regulating expression of a genetic sequence encoding a SOCS protein in said animal and wherein said SOCS protein comprises a protein:molecule interacting region such as but not limited to an SH2 domain, WD40 repeats and/or ankyrin repeats, N terminal of a SOCS box, wherein said SOCS box comprises the amino acid sequence:

[0125] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}[X_i]_nX_{17}X_{18}X_{19}X_{20}X_{21}X_{22}X_{23}[X_j]_nX_{24}X_{25}X_{26}X_{27}X_{28}$

wherein:

[0126] X_1 is L, I, V, M, A or P;

[0127] X_2 is any amino acid residue;

[0128] X_3 is P, T or S;

[0129] X_4 is L, I, V, M, A or P;

[0130] X_5 is any amino acid;

[0131] X_6 is any amino acid;

[0132] X_7 is L, I, V, M, A, F, Y or W;

[0133] X_8 is C, T or S;

[0134] X_9 is R, K or H;

[0135] X_{10} is any amino acid;

[0136] X_{11} is any amino acid;

[0137] X_{12} is L, I, V, M, A or P;

[0138] X_{13} is any amino acid;

[0139] X_{14} is any amino acid;

[0140] X_{15} is any amino acid;

[0141] X_{16} is L, I, V, M, A, P, G, C, T or S;

[0142] $[X_i]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

[0143] X_{17} is L, I, V, M, A or P;

[0144] X_{18} is any amino acid;

[0145] X_{19} is any amino acid;

[0146] X_{20} is L, I, V, M, A or P;

[0147] X_{21} is P;

[0148] X_{22} is L, I, V, M, A, P or G;

[0149] X_{23} is P or N;

[0150] $[X_j]_n$ is a sequence of n amino acids wherein n is from 0 to 50 amino acids and wherein the X_j may comprise the same or different amino acids selected from any amino acid residue;

[0151] X_{24} is L, I, V, M, A or P;

[0152] X_{25} is any amino acid;

[0153] X_{26} is any amino acid;

[0154] X_{27} is Y or F;

[0155] X_{28} is L, I, V, M, A or P.

[0156] The present invention extends to any SOCS molecule such as those disclosed in International Patent Application No. PCT/AU99/00729 [WO 98/20023] which is incorporated herein by reference. However, in a particularly preferred embodiment, the present invention is directed to manipulating levels of SOCS-1, which murine form (mSOCS-1) comprises the nucleotide and corresponding amino acid sequence as set forth in SEQ ID NO:1 and SEQ ID NO:2, respectively. The present invention is hereinafter described with reference to murine SOCS-1 (mSOCS-1), however, this is done with the understanding that the present invention encompasses the manipulation of levels of any SOCS molecule, such as but not limited to human SOCS-2 (hSOCS-2). Reference herein to a "SOCS" molecule such as SOCS-1 includes any mutants thereof such as functional mutants. An example of a mutant is a single or multiple amino acid substitution, addition and/or deletion or truncation to the SOCS molecule or its corresponding DNA or RNA.

[0157] Accordingly, another aspect of the present invention contemplates a method for controlling cytokine or hormone signalling such as pro-inflammatory cytokine signalling (i.e. IL-6, GM-CSF, TNFα), in an animal such as a human or livestock animal, said method comprising modulating expression of a genetic sequence encoding a SOCS protein comprising a SOCS box and a protein:molecule interacting region N-terminal of said SOCS box wherein said SOCS box comprises the amino acid sequence:

[0158] $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}[X_i]_nX_{17}X_{18}X_{19}X_{20}X_{21}X_{22}X_{23}[X_j]_nX_{24}X_{25}X_{26}X_{27}X_{28}$

wherein:

[0159] X_1 is L, I, V, M, A or P;

[0160] X_2 is any amino acid residue;

[0161] X_3 is P, T or S;

[0162] X_4 is L, I, V, M, A or P;

[0163] X_5 is any amino acid;

[0164] X_6 is any amino acid;

[0165] X_7 is L, I, V, M, A, F, Y or W;

[0166] X_8 is C, T or S;

[0167] X_9 is R, K or H;

[0168] X_{10} is any amino acid;

[0169] X_{11} is any amino acid;

[0170] X_{12} is L, I, V, M, A or P;

[0171] X_{13} is any amino acid;

[0172] X_{14} is any amino acid;

[0173] X_{15} is any amino acid;

[0174] X_{16} is L, I, V, M, A, P, G, C, T or S;

[0175] $[X_i]_n$ is a sequence of n amino acids wherein n is from 1 to 50 amino acids and wherein the sequence X_i may comprise the same or different amino acids selected from any amino acid residue;

[0176] X_{17} is L, I, V, M, A or P;

[0177] X_{18} is any amino acid;

[0178] X_{19} is any amino acid;

[0179] X_{20} is L, I, V, M, A or P;

[0180] X_{21} is P;

[0181] X_{22} is L, I, V, M, A, P or G;

[0182] X_{23} is P or N;

[0183] $[X_j]_n$ is a sequence of n amino acids wherein n is from 0 to 50 amino acids and wherein the X_j may comprise the same or different amino acids selected from any amino acid residue;

[0184] X_{24} is L, I, V, M, A or P;

[0185] X_{25} is any amino acid;

[0186] X_{26} is any amino acid;

[0187] X_{27} is Y or F;

[0188] X_{28} is L, I, V, M, A or P.

[0189] Preferably, the SOCS protein-encoding genetic sequence comprises a nucleotide sequence substantially as set forth in SEQ ID NO:1, SEQ ED NO:3, SEQ ID NO:5 or SEQ ID NO:7 or a nucleotide sequence having at least 60% similarity thereto or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7 or its complementary form under low stringency conditions at 42° C. Even more preferably, the SOCS protein in a human homolog of the nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7.

[0190] The term "similarity" as used herein includes exact identity between compared sequences at the nucleotide or amino acid level. Where there is non-identity at the nucleotide level, "similarity" includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. Where there is non-identity at the amino acid level, "similarity" includes amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. In a particularly preferred embodiment, nucleotide and sequence comparisons are made at the level of identity rather than similarity.

[0191] Terms used to describe sequence relationships between two or more polynucleotides or polypeptides include "reference sequence", "comparison window", "sequence similarity", "sequence identity", "percentage of sequence similarity", "percentage of sequence identity", "substantially similar" and "substantial identity". A "reference sequence" is at least 12 but frequently 15 to 18 and often at least 25 or above, such as 30 monomer units, inclusive of nucleotides and amino acid residues, in length. Because two polynucleotides may each comprise (1) a sequence (i.e. only a portion of the complete polynucleotide

sequence) that is similar between the two polynucleotides, and (2) a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of sequence similarity. A "comparison window" refers to a conceptual segment of typically 12 contiguous residues that is compared to a reference sequence. The comparison window may comprise additions or deletions (i.e. gaps) of about 20% or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by computerized implementations of algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Drive Madison, Wis., USA) or by inspection and the best alignment (i.e. resulting in the highest percentage homology over the comparison window) generated by any of the various methods selected. Reference also may be made to the BLAST family of programs as, for example, disclosed by Altschul et al. (2). A detailed discussion of sequence analysis can be found in Unit 19.3 of Ausubel et al. (3).

[0192] The terms "sequence similarity" and "sequence identity" as used herein refers to the extent that sequences are identical or functionally or structurally similar on a nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a window of comparison. Thus, a "percentage of sequence identity", for example, is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g. A, T, C, G, I) or the identical amino acid residue (e.g. Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. For the purposes of the present invention, "sequence identity" will be understood to mean the "match percentage" calculated by the DNASIS computer program (Version 2.5 for windows; available from Hitachi Software engineering Co., Ltd., South San Francisco, Calif., USA) using standard defaults as used in the reference manual accompanying the software. Similar comments apply in relation to sequence similarity.

[0193] Reference herein to a low stringency includes and encompasses from at least about 0 to at least about 15% v/v formamide and from at least about 1 M to at least about 2 M salt for hybridization, and at least about 1 M to at least about 2 M salt for washing conditions.

[0194] Generally, low stringency is at from about 25-30° C. to about 42° C. The temperature may be altered and higher temperatures used to replace formamide and/or to give alternative stringency conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5 M to at least about 0.9 M salt for hybridization, and at least about 0.5 M to at least about 0.9 M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01 M to at least about 0.15 M salt for hybridization, and at least about 0.01 M to at least about 0.15 M salt for washing conditions. In general, washing is carried out T_m=69.3+0.41 (G+C) % (4). However, the T_m of a duplex DNA decreases by 1° C. with every increase of 1% in the number of mismatch base pairs (5). Formamide is optional in these hybridization conditions. Accordingly, particularly preferred levels of stringency are defined as follows: low stringency is 6×SSC buffer, 0.1% w/v SDS at 25-42° C.; a moderate stringency is 2×SSC buffer, 0.1% w/v SDS at a temperature in the range 20° C. to 65° C.; high stringency is 0.1×SSC buffer, 0.1% w/v SDS at a temperature of at least 65° C.

[0195] Most preferably, an expression vector is administered capable of expressing high levels of a SOCS gene.

[0196] Another aspect of the present invention contemplates a method for the treatment of cytokine-mediated disease in an animal, said method comprising modulating cytokine or hormone signalling in an animal by up-regulating the expression of a genetic sequence encoding a SOCS protein or its derivative or homolog in said animal.

[0197] In accordance with the this and other aspects of the present invention, the expression of a genetic sequence encoding a SOCS protein is preferably up-regulated by the administration to the animal of an expression vector comprising a SOCS gene.

[0198] The present invention contemplates a range of derivatives of the SOCS molecule.

[0199] A "derivative" includes a part, portion or fragment thereof such as a molecule comprising a single or multiple amino acid substitution, deletion and/or addition. A "homolog" includes a functionally similar molecule from either the same species or another species.

[0200] Other derivatives contemplated by the present invention include a range of glycosylation variants from a completely unglycosylated molecule to a modified glycosylated molecule. Altered glycosylation patterns may result from expression of recombinant molecules in different host cells.

[0201] The present invention provides, therefore, the genetic control of SOCS levels in animals in the treatment of a range of physiological conditions. Preferably, the level of SOCS protein is increased by the administration of an expression vector comprising the SOCS gene.

[0202] Preferably, the expression vector is a viral vector, such as an adenovirus, adeno-associated virus (AAV) or retrovirus, although other vectors, including plasmid-based vectors, are contemplated.

[0203] Preferably, the genetic sequence encoding a SOCS protein is the SOCS-1 genetic sequence encoding the SOCS-1 protein.

[0204] For example, compositions comprising antisense RNA or sense or antisense DNA, ribozymes or sense molecules (for co-suppression) may be administered either locally or systemically to manipulate expression of SOCS genes or translation of SOCS mRNA.

[0205] The present invention is further described by the following non-limiting Examples.

Example 1

Construction of Recombinant Adenovirus for Expression of Selected SOCS Proteins

[0206] Recombinant human adenovirus type 5 expressing selected SOCS proteins (for analysis in mouse models of disease mouse SOCS proteins are preferable) are generated following recombination between an adenovirus shuttle vector, into which a SOCS encoding cDNA has been cloned, and a mutant adenovirus. The E1 region has been deleted in the mutant adenovirus rendering it incapable of replication except in a packaging cell line that complements the defect (for example, human 293 cells expressing viral E1A and E1B proteins). Recombination, and subsequent selection of recombinants, can be carried out in the packaging cell line but a bacterial system, referred to as the pAdEasy system is preferred (6)

[0207] The pAdEasy system is used to generate recombinant adenovirus expressing murine SOCS proteins by the following means.

[0208] Murine SOCS-1 cDNA is amplified by the polymerase chain reaction (PCR), using the following primer set: 5' primer—ATATCTCGAGGCCACCATGGTAGCACGCAACCAGG [SEQ ID NO: 9]; 3' primer—ATATAAGCTTTCAGATCTGGAAGGGGAAGG [SEQ ID NO:10]. The 5' primer contains a Kozak sequence and a XhoI restriction site, while the 3' primer contains a HindIII restriction site.

[0209] Murine SOCS-2 cDNA is amplified by PCR, using the following primer set: 5' primer—ATATGCGGCCGCGCCACCATGACCCTGCGGTGCCT [SEQ ID NO:11]; 3' primer—ATATTCTAGATTATACCTGGAATTTATATTCTTCC [SEQ ID NO:12]. The 5' primer contains a Kozak sequence and a NotI restriction site, and the 3' primer contains a XbaI restriction site.

[0210] Murine SOCS-3 cDNA was amplified by PCR, using the following primer set: 5' primer—TATAGCGGCCGCGCCACCATGGTCACCCACAGCAA [SEQ ID NO:13]; 3' primer—ATATAAGCTTTTAAAGTGGAGCATCATACTA [SEQ ID NO:14]. The 5' primer contains a Kozak sequence and a NotI restriction site, and the 3' primer contains a HindIII restriction site.

[0211] All three SOCS genes are amplified under the same PCR conditions: one cycle at 96° C. for 2 mins then 35 cycles of 96° C. for 10 seconds, 55° C. for 10 seconds and 72° C. for 1 minute.

[0212] PCR products are cloned into the adenovirus shuttle vector, pShuttle-CMV, (6) by standard ligation reactions. Generation of recombinant adenovirus plasmids by homologous recombination is then carried out in the *E. coli* strain BJ5183 (6). 1 μg of pShuttle-CMV (containing selected SOCS gene) was linearized with PmeI restriction enzyme and purified with a DNA purification kit (Qiagen), then mixed with 100 ng of the adenovirus backbone plasmid, pAdEasy-1. The DNA was then electroporated into *E.coli* BJ5183, which was then plated out onto LB-agar plates containing 30 μg/ml of kanamycin and left at 37° C. for 18 hrs. The smallest colonies were picked and grown in 2 ml LB broth containing 30 μg/ml of kanamycin and placed at 37° C. for 8 hrs. Adenovirus plasmid DNA was extracted from each culture and was screened for the presence of recombinant adenoviral DNA by restriction enzyme digestion in comparison with pAdEasy-1. Direct sequencing of the recombinant adenovirus DNA clones confirmed the presence of SOCS encoding sequence.

[0213] Production of recombinant adenovirus for in vivo studies is carried out in 293 cells (viral E1 transformed). 93 cells are cultured in 25 cm^2 flasks, in OptiMEM media (Gibco BRL), at 37° C. and 10% CO_2 until they are 70% confluent 4 μg of recombinant adenovirus, digested with the Pac1 restriction enzyme, is transfected into 293 cells with Lipofectamine (Gibco-BRL), according to the manufacturer's instructions. Cells are left for 7-10 days and then harvested by scrapping cells off the bottom of the flask into PBS. Cells are subjected to 5 cycles of a freeze/thawing, and the supernatant can then be used to infect more 293 cells to build up viral stocks. Cell lysis should be evident in the majority of cells approximately 3 days post infection, and should be harvested as described above.

[0214] To purify the recombinant adenovirus, the infected 293 cells are harvested and spun at 7000 g 4° C. for 10 minutes. The supernatant is discarded and the cells are resuspended in 10 ml of PBS and subject to 5 cycles of a freeze/thawing. The recombinant adenovirus is then purified through a CsCl gradient, comprising two layers of 1.5 ml and 2.5 ml at densities of 1.45 g/ml and 1.25 g/ml respectively. The CsCl is made-up in 5 mM Tris Cl, 1 mM EDTA pH 7.8. The CsCl gradient containing the recombinant adenovirus is spun at 90,000 g for 2 hrs and the virus fraction collected with a 19-gauge needle.

[0215] The adenovirus is subject to a second round of CsCl purification. The adenovirus is diluted in CsCl solution at a density of 1.33 g/ml and centrifuged at 105 g for 18 hrs. The adenovirus is recovered with a 19-gauge needle and then placed through a G-25 Sephadex column (Amersham) and the virus fractions collected in PBS containing 10% glycerol. The recombinant adenovirus can then be stored at −70° C. until ready for use.

Example 2

Adenovirus Expressing SOCS-1 have a Beneficial Therapeutic Effect in a Mouse Model of Rheumatoid Arthritis

[0216] Collagen-induced arthritis (CIA) is a model of chronic arthritis that is induced following intradermal immunization of mice with collagen in Complete Freund's Adjuvant. It affects articular joints and is characterized by synovial hyperplasia and inflammation, pannus formation and progressive cartilage and bone degradation. The importance of individual cytokines such as GM-CSF and TNFα in CIA has been extensively studied by antibody neutralisation in vivo over the course of disease or by initiating disease in cytokine gene knockout mice.

[0217] For induction of CIA, type II collagen (of bovine or chick origin for example) is dissolved to a concentration of 2 mg/ml in 10 mM acetic acid (overnight at 4° C.) then emulsified in an equal volume of Complete Freunds Adjuvant. Male DBA/1 mice are injected intradermally at several sights into the base of the tail with a total of 100 microliters of the emulsion containing 100 micrograms of collagen. On day 21 mice are given an intraperitoneal booster injection of 100 microgram of type II collagen dissolved in phosphate buffered saline with onset of arthritis occurring at around day 25-28.

[0218] Just prior to expected onset of CIA, mice are scored visually for appearance of arthritis. Mice without macroscopic signs of arthritis in their paws are selected for treatment groups. Alternatively, to study the impact of treatment on existing disease, mice can be left for longer and those that develop overt arthritis selected for treatment groups.

[0219] For treatment selected mice are anaesthetized and a small incision in the skin of the knee joint is performed for the intra-articular injection procedure. Intra-articular injection is performed with 10^7/6 microlitre of either a SOCS-1 (or other SOCS protein) expressing or an empty or β-galactosidase expressing control recombinant adenovirus. At days 1, 5, 10 and 20 after treatment mice are sacrificed and the skin of the knee joint removed. The appearance of arthritis was assessed and severity score was recorded as per routine methods described elsewhere (7). For histological assessment whole knee joints are removed, fixed, decalcified and paraffin embedded. Tissue sections are stained with hematoxylin and eosin and evaluated without knowledge of the treatment groups. Histological changes can be scored according to standard methods. For example, infiltration of cells is scored on a scale of 0-3, depending on the amount of inflammatory cells in the synovial cavity (exudate) and synovial tissue (infiltrate). A characteristic parameter in CIA is the progressive loss of bone. This destruction can be graded on a scale of 0-3, ranging from no damage to complete loss of bone structure. Additional analysis may encompass, for example, immunohistological determination of other cell surface/tissue specific markers of disease progression and severity.

[0220] Over-expression of SOCS-1 (or other selected SOCS proteins) within the joint may decrease both incidence and severity of CIA and this may be reflected in histological analysis where cellular accumulation within the joint and/or the level of bone and cartilage destruction is significantly ameliorated.

Example 3

Analysis of Arthritis in an Animal Model Demonstrates a Regulatory Role for SOCS-1 and Supports the Use of SOCS-Based Gene Therapy for the Treatment of Human Inflammatory Disease

[0221] Genetically modified mice with a targeted deletion of the SOCS-1 gene (SOCS-$1^{-/-}$) die within 3 weeks of birth. The primary mediator of this lethal phenotype is interferon-γ. SOCS-$1^{-/-}$ animals crossed onto an IFN-$\gamma^{-/-}$ background survive as do SOCS-$1^{-/-}$ treated with an antibody that inhibits IFN-γ activity. SOCS-$1^{-/-}$IFN-$\gamma^{-/-}$ mice are ideal for studying the role of SOCS-1 in the development of various disease pathologies. In the present example, the role of SOCS-1 in regulating the activity of the pro-inflammatory cytokines responsible for the development of arthritis was assessed.

[0222] SOCS-$1^{+/+}$ IFN-$\gamma^{-/-}$ and SOCS-$1^{-/-}$ IFN-$\gamma^{-/-}$ mice were anaesthetized and injected intra-articularly into the knee joint with 10 μl of a 20 mg/ml solution of methylated bovine serum albumin (mBSA). At the same time, mice were also injected with 250 ng recombinant human IL-1β subcutaneously into the rear footpad. The IL-1 injection was repeated on the next 2 days. The mice were sacrificed on day 7 and the knee joints fixed in 10% v/v neutral buffered formalin for at least 2 days, decalcified and embedded in paraffin. Frontal sections of the knee joints were cut at 4 depths, approximately 100 μm apart and stained with haemotoxylin and eosin.

Assessment of Arthritis:

[0223] Joint pathology was assessed in a blinded manner and S parameters of arthritis were graded for severity from 0 (normal) to 5 (severe). Exudate was scored according to the presence and relative numbers of inflammatory cells and fibrin-like debris in the joint space. Synovitis was defined as thickening of the synovial lining layer and soft tissue inflammation in the infrapatellar fat pad, joint capsule and the area adjacent to the periosteal sheath. Pannus was defined as the encroachment of hyperplastic synovium over the articular surface or at the cartilage-bone junction. Cartilage degradation was evaluated on patellofemoral and tibiofemoral articular surfaces. Bone degradation was evaluated as the extent and depth of subchondral and periosteal bone erosion. The Mann-Whitney 2-sample rank test was used to compare mean histologic scores of test and control groups.

[0224] The results demonstrate a role for SOCS-1 in down-regulating/controlling the development of arthritis, in this model of the disease. SOCS-$1^{-/-}$IFN-$\gamma^{-/-}$ animals develop more severe arthritis than control SOCS-1^{++}IFN-$\gamma^{-/-}$ animals FIG. **1**). The severity of the disease in the SOCS-$1^{+/+}$IFN-$\gamma^{-/-}$ animals was identical to that routinely observed in wildtype controls (not shown) indicating that the lack of functional SOCS-1 and not INF-γ was responsible for the exacerbation in disease phenotype. Given the clearly demonstrated role for SOCS-1 in the negative regulation of cytokine signalling it is assumed that the exacerbation of disease is the result of the increased activity of proinflammatory cytokines. Over-expression of SOCS-1, following SOCS-1 based gene therapy would inhibit pro-inflammatory cytokine activity and thus ameliorate disease pathology.

[0225] The results are shown in tabular form in Table 1 and graphically in FIG. **1**.

[0226] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

TABLE 1

	Exudate	Synovitis	Pannus	Cartilage loss	Bone loss	
2980	3	3.75	2.5	2.5	2.5	14.25
2981	3.33	4.67	2.33	2	1.67	14
2982	3	4	3.25	2.5	3.25	16
2983	3	3.75	3	2.5	2.75	15
2984	3	3	2.5	2.75	2	13.25
2985	3.25	3.5	2	1.25	1	11
Average	3.096666667	3.77833333	2.59666667	2.25	2.195	13.9166667
Std. Dev.	0.062003584	0.22576413	0.18577166	0.2236068	0.32943133	0.69721669
2986	2	2.25	1.25	1	1.25	7.75
2987	2	3	3	2.25	2.75	13
2988	1	2	1.75	2	1.25	8
2989	2	4	2.75	2	2	12.75
2990	2	3.75	1.75	1.5	2	11
2991	1.5	2.5	2.75	2.5	2	11.25
2992	2.5	3	2	1.25	1.75	10.5
2993	1	2	2	1	1.5	7.5
2994	2	2.75	2.75	2	1.5	11
2995	2	3	1.75	1.5	1	9.25
Average	1.8	2.825	2.175	1.7	1.7	10.2
Std. Dev	0.152752523	0.21424934	0.18652524	0.16583124	0.16158933	0.63113654
2996	4	4.75	3.5	2.75	2.5	17.5
2997	2.5	4	4	2.5	3.5	16.5
2998	4	5	4	3.5	3.5	20
2999	4	5	4	3.25	3.25	19.5
3000	3	4.5	3.5	3	3	17
3001	2	2.5	2.5	2	2	11
Average	3.25	4.29166667	3.58333333	2.83333333	2.95833333	16.9166667
Std. Dev	0.359397644	0.3895332	0.23863035	0.22047928	0.24509069	1.31286371
Ttest	0.000736214	0.0028622	0.00038333	0.00099983	0.0005242	0.00013435

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           95                  100                 105

ccc cga agc acg cag cca gtt ccc cgc ttc gac tgt gta ctc aag ctg      386
Pro Arg Ser Thr Gln Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu
        110                 115                 120

gtg cac cac tac atg ccg cct cca ggg acc ccc tcc ttt tct ttg cca      434
Val His His Tyr Met Pro Pro Pro Gly Thr Pro Ser Phe Ser Leu Pro
    125                 130                 135

ccc acg gaa ccc tcg tcc gaa gtt ccg gag cag cca cct gcc cag gca      482
Pro Thr Glu Pro Ser Ser Glu Val Pro Glu Gln Pro Pro Ala Gln Ala
140                 145                 150                 155

ctc ccc ggg agt acc ccc aag aga gct tac tac atc tat tct ggg ggc      530
Leu Pro Gly Ser Thr Pro Lys Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly
                160                 165                 170

gag aag att ccg ctg gta ctg agc cga cct ctc tcc tcc aac gtg gcc      578
Glu Lys Ile Pro Leu Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala
            175                 180                 185

acc ctc cag cat ctt tgt cgg aag act gtc aac ggc cac ctg gac tcc      626
Thr Leu Gln His Leu Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser
        190                 195                 200

tat gag aaa gtg acc cag ctg cct gga ccc att cgg gag ttc ctg gat      674
Tyr Glu Lys Val Thr Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp
    205                 210                 215

cag tat gat gct cca ctt taa ggagcaaaag ggtcagaggg gggcctgggt         725
Gln Tyr Asp Ala Pro Leu
220                 225

cggtcggtcg cctctcctcc gaggcacatg gcacaagcac aaaaatccag ccccaacggt    785

cggtagctcc cagtgagcca ggggcagatt ggcttcttcc tcaggccctc cactcccgca    845

gagtagagct ggcaggacct ggaattcgtc tgaggggagg gggagctgcc acctgctttc    905

ccccctcccc cagctccagc ttctttcaag tggagccagc cggcctggcc tggtgggaca    965

ataccttga caagcggact ctcccctccc cttcctccac acccccctctg cttcccaagg   1025

gaggtgggga cacctccaag tgttgaactt agaactgcaa ggggaatctt caaactttcc   1085

cgctggaact tgtttgcgct ttgatttggt ttgatcaaga gcaggcacct gggggaagga   1145

tggaagagaa aagggtgtgt gaagggtttt tatgctggcc aaagaaataa ccactcccac   1205

tgcccaacct aggtgaggag tggtggctcc tggctctggg gagagtggca aggggtgacc   1265

tgaagagagc tatactggtg ccaggctcct ctccatgggg cagctaatga aacctcgcag   1325

atcccttgca ccccagaacc ctccccgttg tgaagaggca gtagcattta gaagggagac   1385

agatgaggct ggtgagctgg ccgccttttc caacaccgaa gggaggcaga tcaacagatg   1445

agccatcttg gagcccaggt ttcccctgga gcagatggag ggttctgctt tgtctctcct   1505

atgtggggct aggagactcg ccttaaatgc cctctgtccc agggatgggg attggcacac   1565

aaggagccaa acacagccaa taggcagaga gttgagggat tcacccaggt ggctacaggc   1625

caggggaagt ggctgcaggg gagagaccca gtcactccag gagactcctg agttaacact   1685

gggaagacat tggccagtcc tagtcatctc tcggtcagta ggtccgagag cttccaggcc   1745

ctgcacagcc ctcctttctc acctgggggg aggcaggagg tgatggagaa gccttcccat   1805

gccgctcaca ggggcctcac gggaatgcag cagccatgca attacctgga actggtcctg   1865

tgttggggag aaacaagttt tctgaagtca ggtatggggc tgggtggggc agctgtgtgt   1925

tggggtggct tttttctctc tgttttgaat aatgtttaca atttgcctca atcactttta   1985
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taaaaatcca cctccagccc gcccctctcc ccactcaggc cttcgaggct gtctgaagat 2045

gcttgaaaaa ctcaaccaaa tcccagttca actcagactt tgcacatata tttatattta 2105

tactcagaaa agaaacattt cagtaattta taataaaaga gcactatttt ttaatgaaaa 2165

aaaaaaaaaa aaaaaaaaaa aa 2187

<210> SEQ ID NO 4
<211> LENGTH: 225
<212> TYPE: PRT
<213> ORGANISM: murine

<400> SEQUENCE: 4

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

Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln
20 25 30

Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp
35 40 45

Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Leu Ser Ala Glu Pro
50 55 60

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

Thr Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln
85 90 95

Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
100 105 110

Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val His His Tyr Met
115 120 125

Pro Pro Pro Gly Thr Pro Ser Phe Ser Leu Pro Pro Thr Glu Pro Ser
130 135 140

Ser Glu Val Pro Glu Gln Pro Pro Ala Gln Ala Leu Pro Gly Ser Thr
145 150 155 160

Pro Lys Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu
165 170 175

Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
180 185 190

Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
195 200 205

Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
210 215 220

Leu
225

<210> SEQ ID NO 5
<211> LENGTH: 1094
<212> TYPE: DNA
<213> ORGANISM: human

<400> SEQUENCE: 5

ctccggctgg ccccttctgt aggatggtag cacacaacca ggtggcagcc gacaatgcag 60

tctccacagc agcagagccc cgacggcggc cagaaccttc ctcctcttcc tcctcctcgc 120

ccgcggcccc cgcgcgcccg cggccgtgcc ccgcggtccc ggccccggcc cccggcgaca 180

cgcacttccg cacattccgt tcgcacgccg attaccggcg catcacgcgc gccagcgcgc 240

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tcctggacgc ctgcggattc tactgggggc ccctgagcgt gcacggggcg cacgagcggc    300

tgcgcgccga gcccgtgggc accttcctgg tgcgcgacag ccgccagcgg aactgctttt    360

tcgcccttag cgtgaagatg gcctcgggac ccacgagcat ccgcgtgcac tttcaggccg    420

gccgctttca cctggatggc agccgcgaga gcttcgactg cctcttcgag ctgctggagc    480

actacgtggc ggcgccgcgc cgcatgctgg gggccccgct gcgccagcgc cgcgtgcggc    540

cgctgcagga gctgtgccgc cagcgcatcg tggccaccgt gggccgcgag aacctggctc    600

gcatccccct caaccccgtc ctccgcgact acctgagctc cttccccttc cagatttgac    660

cggcagcgcc cgccgtgcac gcagcattaa ctgggatgcc gtgttatttt gttattactt    720

gcctggaacc atgtgggtac cctccccggc ctgggttgga gggagcggat gggtgtaggg    780

gcgaggcgcc tcccgccctc ggctggagac gaggccgcag acccccttctc acctcttgag    840

ggggtcctcc ccctcctggt gctccctctg ggtccccctg gttgttgtag cagcttaact    900

gtatctggag ccaggacctg aactcgcacc tcctacctct tcatgtttac atatacccag    960

tatctttgca caaaccaggg gttgggggag ggtctctggc tttatttttc tgctgtgcag   1020

aatcctattt tatatttttt aaagtcagtt taggtaataa actttattat gaaagttttt   1080

ttttttaaaa aaaa                                                     1094
```

<210> SEQ ID NO 6
<211> LENGTH: 211
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 6

```
Met Val Ala His Asn Gln Val Ala Ala Asp Asn Ala Val Ser Thr Ala
1               5                   10                  15

Ala Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser
            20                  25                  30

Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Ala Val Pro Ala Pro
        35                  40                  45

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

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

Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu
                85                  90                  95

Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe
            100                 105                 110

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

His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Ser Phe
    130                 135                 140

Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg
145                 150                 155                 160

Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu
                165                 170                 175

Leu Cys Arg Gln Arg Ile Val Ala Thr Val Gly Arg Glu Asn Leu Ala
            180                 185                 190

Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro
```

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195 200 205

Phe Gln Ile
210

<210> SEQ ID NO 7
<211> LENGTH: 2807
<212> TYPE: DNA
<213> ORGANISM: murine

<400> SEQUENCE: 7

ggaaaccgag gcggggagac caggaggcct tggcctcaga gcttcagagt cgcgtggcag 60

caaacagaga aacctgtaga gggcagtgtg cgtcacttag ctcagggaag ctgcacgcga 120

aactcacccg ccttcattca taaacatcgt cagctaggca cctactcctg ggctttcagg 180

acaaactgaa tcacgaaacc acagtgtcct taaaataggt ctgaccgcct gaatccctgg 240

ccaaggtgtg tacggggcat gggagccctt gtgcagagat gcttgcagga gccttgaggg 300

gctctgtaag acagaggcta ggaagacaaa gttgggggct acagcttctt gtcctgcccg 360

gggcctcagt ttcttcggtt gcccacgtag gagtgcagag agtccagccc ctggggaccc 420

aacccaaccc cgcccagttt ccgaggaact cgtccgggag cgggggcgcc cctcccgcac 480

cgccttaggc ttcctttgaa gcctctgcgg tcaggccacc gcttcctggg aagcccaagc 540

caaggccagg ccgagtggcc aacgggaggg gcccgcgcgc gattctggag gagggcggcg 600

gccccacagg tctccagggc tggctagccg ggctcctaga gcggagactg ccaaggcctt 660

cgggtcctgg gcaggaagga tcctggcagg gaggagttgc ttgggggtg gggggaaag 720

gctccaggcg cggtggagct ctgaccagga gaatgcacac actcggaggg gaggaggcgt 780

gtcagcccca agctagcatc ccacccgggg agcagcgatg tggggcgaag gtagccagag 840

caaaagagca ggcaccaggt gacacgaaac agaagattcc gggtagagcc agaaccccag 900

aagtcccatt cagggaaggt gcgaggcgag aacgagttag gtggaccctc tccaggggca 960

gccaaagaaa tctaaagaga acccgaagga cttgccggaa agagaaaccg aaagcggcgg 1020

tgggcgggat cggtgggcgg ggcctccctg gtttaagagc ttgatgcagg ggcgggcagc 1080

agcagagaga actgcggccg tggcagcggc acggctcccg gccccggagc atgcgcgaca 1140

gcagccccgg aacccccagc cgcggcgccc cgcgtcccgc cgccaggtga gccgaggcag 1200

ctgcgaagga gcaggcggga ggggatggga ggaaggggag cagagcctgg caggactatc 1260

ctcgcagact gcatggcggg gtcgtggatg ctatgcctct ggcgcccgcc ccaccggctg 1320

gcccaggcgg cccctcgcgc gcgcggggcg ccgtcagccc ctcctctccg gccctgagcc 1380

cggatcgtcc gcccgggttc cagttcccgg cgtggccagt aggcggcaac cgcgaggcgg 1440

caagccaccc agcggggacg gcctggagtc gggcccctct ccacgccccc ttctccacgc 1500

gcgcggggag gcagggctcc accgccagtc tggaagggtt ccacatacag gaacggccta 1560

cttcgcagat gagcccaccg aggctcaggc tccgggcgga ttctgcgtgt caccctcgct 1620

ccttggggtc cgctggccgg cctgtgccac ccggacgccc ggttcactgc ctctgtctcc 1680

cccatcagcg cagccccgga cgctatggcc cacccctcca gctggcccct cgagtaggat 1740

ggtagcacgt aaccaggtgg aagccgacaa tgcgatctcc ccggcatcag agccccgacg 1800

gcggccagag ccatcctcgt cctcgtcttc gtcctcgccg gcggccccgg cgcgtccccg 1860

gccctgcccg gtggtcccgg ccccggctcc gggcgacact cacttccgca ccttccgctc 1920

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ccactctgat taccggcgca tcacgcggac cagcgctctc ctggacgcct gcggcttcta   1980

ctggggaccc ctgagcgtgc atggggcgca cgaacggctg cgttccgaac ccgtgggcac   2040

cttcttggtg cgcgacagtc gccagcggaa ctgcttcttc gcgctcagcg tgaagatggc   2100

ttcgggcccc acgagcattc gtgtgcactt ccaggccggc cgcttccacc tggacggcaa   2160

ccgcgagacc ttcgactgcc tcttcgagct gctggagcac tacgtggcgg cgccgcgccg   2220

catgttgggg gccccactgc gccagcgccg cgtgcggccg ctgcaggagc tgtgtcgcca   2280

gcgcatcgtg gccgccgtgg gtcgcgagaa cctggcacgc atccctctta acccggtact   2340

ccgtgactac ctgagttcct tccccttcca gatctgaccg gctgccgccg tgcccgcaga   2400

attaagtggg agcgccttat tatttcttat tattaattat tattattttt ctggaaccac   2460

gtgggagccc tccccgccta ggtcggaggg agtgggtgtg gagggtgaga tccctcccac   2520

ttctggctgg agaccttatc ccgcctctcg gggggcctcc cctcctggtg ctccctcccg   2580

gtccccctgg ttgtagcagc ttgtgtctgg ggccaggacc tgaactccac gcctacctct   2640

ccatgtttac atgttcccag tatctttgca caaaccaggg gtgggggagg gtctctggct   2700

tcatttttct gctgtgcaga atattctatt ttatattttt acatccagtt tagataataa   2760

actttattat gaaagttttt ttttttaaag aaacaaagat ttctaga                2807
```

<210> SEQ ID NO 8
<211> LENGTH: 212
<212> TYPE: PRT
<213> ORGANISM: murine

<400> SEQUENCE: 8

```
Met Val Ala Arg Asn Gln Val Glu Ala Asp Asn Ala Ile Ser Pro Ala
1               5                   10                  15

Ser Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser
            20                  25                  30

Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala
        35                  40                  45

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

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

Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ser
                85                  90                  95

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

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

Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Asn Arg Glu Thr
    130                 135                 140

Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg
145                 150                 155                 160

Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln
                165                 170                 175

Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu
            180                 185                 190

Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe
```

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195 200 205

Pro Phe Gln Ile
210

<210> SEQ ID NO 9
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: primer

<400> SEQUENCE: 9

atatctcgag gccaccatgg tagcacgcaa ccagg 35

<210> SEQ ID NO 10
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: primer

<400> SEQUENCE: 10

atataagctt tcagatctgg aaggggaagg 30

<210> SEQ ID NO 11
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: primer

<400> SEQUENCE: 11

atatgcggcc gcgccaccat gaccctgcgg tgcct 35

<210> SEQ ID NO 12
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: primer

<400> SEQUENCE: 12

atatgcggcc gcgccaccat gaccctgcgg tgcct 35

<210> SEQ ID NO 13
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: primer

<400> SEQUENCE: 13

atatgcggcc gcgccaccat gaccctgcgg tgcct 35

<210> SEQ ID NO 14
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: primer

<400> SEQUENCE: 14

atatgcggcc gcgccaccat gaccctgcgg tgcct 35

1-37. (canceled)

38. A method for modulating cytokine or hormone signaling in an animal to treat an inflammatory disease in said animal, said method comprising over-expressing a genetic sequence encoding a SOCS-1 protein in said animal, wherein said SOCS-1 protein comprises an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 8.

39. A method of treating an inflammatory disease in an animal, said method comprising over-expressing a genetic sequence encoding a SOCS-1 protein in said animal, wherein said SOCS-1 protein comprises an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 8.

40. The method according to claim 38 or 39 wherein said method comprises administering to said animal an expres-

sion vector comprising a SOCS-1 genetic sequence encoding a SOCS-1 protein, wherein said SOCS-1 protein comprises an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 8.

41. The method according to claim 40 wherein the expression vector is a viral vector.

42. The method according to claim 41 wherein the viral vector is an adenovirus, adeno-associated virus or retrovirus.

43. The method according to claim 40 wherein the expression vector is a plasmid-based vector.

44. The method according to claim 38 or 39 wherein the animal is a human, primate, livestock animal, laboratory test animal or a companion animal.

45. The method according to claim 44 wherein the animal is a human.

46. The method according to claim 38 or 39 wherein the hormone is selected from a growth hormone, insulin-like growth factor-I or prolactin.

47. The method according to claim 46 wherein the hormone is growth hormone.

48. The method according to claim 38 or 39 wherein the cytokine is an interleukin, tumor necrosis factor, a colony stimulating factor or an interferon.

49. The method according to claim 38 or 39 wherein said inflammatory disease is rheumatoid arthritis.

* * * * *