



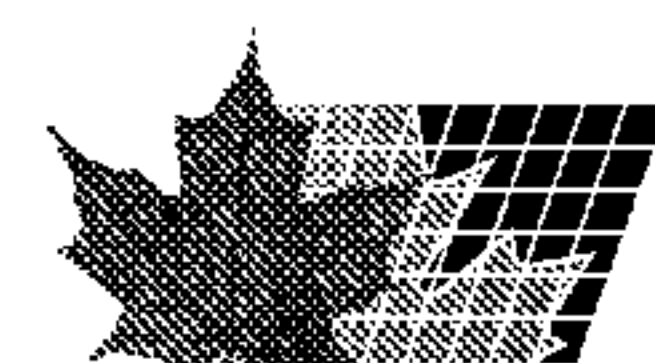
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(54) Title: POLYNUCLEOTIDE AND DEDUCED AMINO ACID SEQUENCES FROM STROMAL CELLS

(57) **Abrégé/Abstract:**

Isolated polynucleotides encoding polypeptides expressed in mammalian fsn -/- lymph node stromal cells are provided, together with expression vectors and host cells comprising such isolated polynucleotides. Methods for the use of such polynucleotides and polypeptides are also provided.



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(54) Title: POLYNUCLEOTIDE AND DEDUCED AMINO ACID SEQUENCES FROM STROMAL CELLS (57) Abstract Isolated polynucleotides encoding polypeptides expressed in mammalian <i>fsn</i> -/- lymph node stromal cells are provided, together with expression vectors and host cells comprising such isolated polynucleotides. Methods for the use of such polynucleotides and polypeptides are also provided.		

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Polynucleotide and deduced amino acid sequences from stromal cells

10 Technical Field of the Invention

This invention relates to genes encoding proteins expressed in lymph node stromal cells from flaky skin (*fsn* $-/-$) mice and their use in therapeutic methods.

Background of the Invention

15 Lymph vessels and nodes are important components of the body's immune system. Lymph nodes are small lymphatic organs that are located in the path of lymph vessels. Large molecules and cells, including foreign substances, enter into the lymphatic vessels and, in circulating through these vessels, pass through the lymph nodes. Here, any foreign substances are concentrated and exposed to lymphocytes. This triggers a cascade of events that constitute
20 an immune response, protecting the body from infection and from cancer.

Lymph nodes are surrounded by a dense connective tissue network that forms a supporting capsule. This network extends into the body of the lymph node, forming an additional framework of support. Throughout the remainder of the organ, a fine meshwork can be identified that comprises reticular fibres and the reticular cells that produce and surround the
25 fibres. These features provide a support for the main functional cells of the lymphatic system, which are T- and B-lymphocytes. Additional cell types found in lymph nodes include macrophages, follicular dendritic cells, and endothelial cells that line the blood vessels servicing the node.

The cells within lymph nodes communicate with each other in order to defend the body
30 against foreign substances. When a foreign substance, or antigen, is present, it is detected by macrophages and follicular dendritic cells that take up and process the antigen, and display parts of it on their cell surface. These cell surface antigens are then presented to T- and B-lymphocytes, causing them to proliferate and differentiate into activated T-lymphocytes and plasma cells, respectively. These cells are released into the circulation in order to seek out and
35 destroy antigen. Some T- and B-lymphocytes will also differentiate into memory cells. Should these cells come across the same antigen at a later date, the immune response will be more rapid.

5 Once activated T- and B-lymphocytes are released into the circulation, they can perform a variety of functions that leads to the eventual destruction of antigen. Activated T-lymphocytes can differentiate into cytotoxic lymphocytes (also known as killer T-cells) which recognise other cells that have foreign antigens on their surface and kill the cell by causing them to lyse. Activated T-lymphocytes can also differentiate into helper T-cells which will then secrete
10 proteins in order to stimulate B-lymphocytes, and other T-lymphocytes, to respond to antigens. In addition, activated T-lymphocytes can differentiate into suppressor T-cells which secrete factors that suppress the activity of B-lymphocytes. Activated B-lymphocytes differentiate into plasma cells, which synthesise and secrete antibodies that bind to foreign antigens. The antibody-antigen complex is then detected and destroyed by macrophages, or by a group of
15 blood constituents known as complement.

 Lymph nodes can be dissociated and the resulting cells grown in culture. Cells that adhere to the tissue culture dishes can be maintained for some length of time and are known as stromal cells. The cultured cells are a heterogeneous population and can be made up of most cells residing within lymph nodes, such as reticular cells, follicular dendritic cells, macrophages
20 and endothelial cells. It is well known that bone marrow stromal cells play a critical role in homing, growth and differentiation of hematopoietic progenitor cells. Proteins produced by stromal cells are necessary for the maintenance of plasma cells *in vitro*. Furthermore, stromal cells are known to secrete factors and present membrane-bound receptors that are necessary for the survival of lymphoma cells.

25 An autosomal recessive mutation, designated flaky skin (*fsn* ^{-/-}), has been described in the inbred A/J mouse strain (The Jackson Laboratory, Bar Harbour, ME). The mice have a skin disorder similar to psoriasis in humans. Psoriasis is a common disease affecting 2% of the population, which is characterised by a chronic inflammation associated with thickening and scaling of the skin. Histology of skin lesions shows increased proliferation of the cells in the
30 epidermis, the uppermost layer of skin, together with the abnormal presence of inflammatory cells, including lymphocytes, in the dermis, the layer of skin below the epidermis. While the cause of the disease is unclear, psoriasis is associated with a disturbance of the immune system involving T lymphocytes. The disease occurs more frequently in family members, indicating the involvement of a genetic factor as well. Mice with the *fsn* gene mutation have not only a
35 psoriatic-like skin disease but also other abnormalities involving cells of the immune and

5 hematopoietic system. These mice have markedly increased numbers of lymphocytes associated with enlarged lymphoid organs, including the spleen and lymph nodes. In addition, their livers are enlarged, and the mice are anaemic. Genes and proteins expressed in abnormal lymph nodes of *fsn*^{-/-} mice may thus influence the development or function of cells of the immune and hematopoietic system, the response of these cells in inflammatory disorders, and the responses of
10 skin and other connective tissue cells to inflammatory signals.

There is a need in the art to identify genes encoding proteins that function to modulate all cells of the immune system. These proteins from normal or abnormal lymph nodes may be useful in modifying the immune responses to tumour cells or infectious agents such as bacteria, viruses, protozoa and worms. Such proteins may be useful in the treatment of disorders where
15 the immune system initiates unfavourable reactions to the body, including Type I hypersensitivity reactions (such as hay fever, eczema, allergic rhinitis and asthma), and Type II hypersensitivity reactions (such as transfusion reactions and haemolytic disease of newborns). Other unfavourable reactions are initiated during Type III reactions, which are due to immune complexes forming in infected organs during persistent infection or in the lungs following
20 repeated inhalation of materials from moulds, plants or animals, and in Type IV reactions in diseases such as leprosy, schistosomiasis and dermatitis.

Novel proteins of the immune system may also be useful in treating autoimmune diseases where the body recognises itself as foreign. Examples of such diseases include rheumatoid arthritis, Addison's disease, ulcerative colitis, dermatomyositis and lupus. Such proteins may
25 also be useful during tissue transplantation, where the body will often recognise the transplanted tissue as foreign and attempt to kill it, and also in bone marrow transplantation when there is a high risk of graft-versus-host disease where the transplanted cells attack their host cells, often causing death.

There thus remains a need in the art for the identification and isolation of genes encoding
30 proteins expressed in cells of the immune system for use in the development of therapeutic agents for the treatment of disorders including those associated with the immune system.

5 Summary of the Invention

The present invention provides polypeptides expressed in lymph node stromal cells of *fsn* -/- mice, together with polynucleotides encoding such polypeptides, expression vectors and host cells comprising such polynucleotides, and methods for their use.

10 In specific embodiments, isolated polypeptides are provided that comprise an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20, 30-38 and 47-53, and variants of such sequences, as defined herein. Isolated polypeptides which comprise at least a functional portion of a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NO: 11-20, 30-38 and 47-53; and (b) variants of a sequence of SEQ ID NO: 11-20, 30-38 and 47-53, as defined herein,
15 are also provided.

In other embodiments, the present invention provides isolated polynucleotides comprising a nucleotide sequence selected from the group consisting of: (a) sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46; (b) complements of sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46; (c) reverse complements of sequences provided in SEQ ID NO: 1-10, 21-
20 29 and 39-46; (d) reverse sequences of sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46; and (e) variants of the sequences of (a) – (d), as defined herein.

In related embodiments, the present invention provides expression vectors comprising the above polynucleotides, together with host cells transformed with such vectors.

25 As detailed below, the isolated polynucleotides and polypeptides of the present invention may be usefully employed in the preparation of therapeutic agents for the treatment of immunological disorders.

In related embodiments, methods for modulating the growth of blood vessels, and for the treatment of disorders such as inflammatory disorders, disorders of the immune system, cancer, tumour-necrosis factor-mediated disorders, and viral disorders are provided. Examples of such
30 disorders include HIV-infection; epithelial, lymphoid, myeloid, stromal and neuronal cancers; arthritis; inflammatory bowel disease; and cardiac failure.

The above-mentioned and additional features of the present invention, together with the manner of obtaining them, will be best understood by reference to the following more detailed description. All references disclosed herein are hereby incorporated by reference in their entirety
35 as if each was incorporated individually.

5

Detailed Description of the Invention

In one aspect, the present invention provides polynucleotides isolated from lymph node stromal cells of *fsn* ^{-/-} mice and isolated polypeptides encoded by such polynucleotides.

The term “polynucleotide(s),” as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of “polynucleotide” therefore includes all such operable anti-sense fragments. Anti-sense polynucleotides and techniques involving anti-sense polynucleotides are well known in the art and are described, for example, in Robinson-Benion *et al.*, *Methods in Enzymol.* 254: 363-375, 1995 and Kawasaki *et al.*, *Artific. Organs* 20: 836-848, 1996.

In specific embodiments, the isolated polynucleotides of the present invention comprise a DNA sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46.

Complements of such isolated polynucleotides, reverse complements of such isolated polynucleotides and reverse sequences of such isolated polynucleotides are also provided, together with polynucleotides comprising at least a specified number of contiguous residues (*x*-mers) of any of the above-mentioned polynucleotides, extended sequences corresponding to any of the above polynucleotides, antisense sequences corresponding to any of the above polynucleotides, and variants of any of the above polynucleotides, as that term is described in this specification.

The definition of the terms “complement”, “reverse complement” and “reverse sequence”, as used herein, is best illustrated by the following example. For the sequence 5’ AGGACC 3’, the complement, reverse complement and reverse sequence are as follows:

5	complement	3' TCCTGG 5'
	reverse complement	3' GGTCCT 5'
	reverse sequence	5' CCAGGA 3'.

Some of the polynucleotides of the present invention are "partial" sequences, in that they do not represent a full length gene encoding a full length polypeptide. Such partial sequences may be extended by analyzing and sequencing various DNA libraries using primers and/or probes and well known hybridization and/or PCR techniques. Partial sequences may be extended until an open reading frame encoding a polypeptide, a full length polynucleotide and/or gene capable of expressing a polypeptide, or another useful portion of the genome is identified. Such extended sequences, including full length polynucleotides and genes, are described as "corresponding to" a sequence identified as one of the sequences of SEQ ID NO: 1-10, 21-29 and 39-46, or a variant thereof, or a portion of one of the sequences of SEQ ID NO: 1-10, 21-29 and 39-46, or a variant thereof, when the extended polynucleotide comprises an identified sequence or its variant, or an identified contiguous portion (x-mer) of one of the sequences of SEQ ID NO: 1-10, 21-29 and 39-46, or a variant thereof. Such extended polynucleotides may have a length of from about 50 to about 4,000 nucleic acids or base pairs, and preferably have a length of less than about 4,000 nucleic acids or base pairs, more preferably yet a length of less than about 3,000 nucleic acids or base pairs, more preferably yet a length of less than about 2,000 nucleic acids or base pairs. Under some circumstances, extended polynucleotides of the present invention may have a length of less than about 1,800 nucleic acids or base pairs, preferably less than about 1,600 nucleic acids or base pairs, more preferably less than about 1,400 nucleic acids or base pairs, more preferably yet less than about 1,200 nucleic acids or base pairs, and most preferably less than about 1,000 nucleic acids or base pairs.

Similarly, RNA sequences, reverse sequences, complementary sequences, antisense sequences, and the like, corresponding to the polynucleotides of the present invention, may be routinely ascertained and obtained using the cDNA sequences identified as SEQ ID NO: 1-10, 21-29 and 39-46.

The polynucleotides identified as SEQ ID NO: 1-10, 21-29 and 39-46 may contain open reading frames ("ORFs") or partial open reading frames encoding polypeptides. Open reading frames may be identified using techniques that are well known in the art. These techniques include, for example, analysis for the location of known start and stop codons, most likely

5 reading frame identification based on codon frequencies, etc. Suitable tools and software for ORF analysis are available, for example, on the Internet at <http://www.ncbi.nlm.nih.gov/gorf/gorf.html>. Open reading frames and portions of open reading frames may be identified in the polynucleotides of the present invention. Once a partial open reading frame is identified, the polynucleotide may be extended in the area of the partial open
10 reading frame using techniques that are well known in the art until the polynucleotide for the full open reading frame is identified. Thus, open reading frames encoding polypeptides may be identified using the polynucleotides of the present invention.

Once open reading frames are identified in the polynucleotides of the present invention, the open reading frames may be isolated and/or synthesized. Expressible genetic constructs
15 comprising the open reading frames and suitable promoters, initiators, terminators, etc., which are well known in the art, may then be constructed. Such genetic constructs may be introduced into a host cell to express the polypeptide encoded by the open reading frame. Suitable host cells may include various prokaryotic and eukaryotic cells, including plant cells, mammalian cells, bacterial cells, algae and the like.

20 In another aspect, the present invention provides isolated polypeptides encoded, or partially encoded, by the above polynucleotides. The term "polypeptide", as used herein, encompasses amino acid chains of any length including full length proteins, wherein amino acid residues are linked by covalent peptide bonds. Polypeptides of the present invention may be naturally purified products, or may be produced partially or wholly using recombinant
25 techniques. The term "polypeptide encoded by a polynucleotide" as used herein, includes polypeptides encoded by a nucleotide sequence which includes the partial isolated DNA sequences of the present invention. In specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20, 30-38, 47-53 and variants of such sequences.

30 Polypeptides encoded by the polynucleotides of the present invention may be expressed and used in various assays to determine their biological activity. Such polypeptides may be used to raise antibodies, to isolate corresponding interacting proteins or other compounds, and to quantitatively determine levels of interacting proteins or other compounds.

All of the polynucleotides and polypeptides described herein are isolated and purified, as
35 those terms are commonly used in the art. Preferably, the polypeptides and polynucleotides are at

5 least about 80% pure, more preferably at least about 90% pure, and most preferably at least about 99% pure.

As used herein, the term "variant" comprehends nucleotide or amino acid sequences different from the specifically identified sequences, wherein one or more nucleotides or amino acid residues is deleted, substituted, or added. Variants may be naturally occurring allelic
10 variants, or non-naturally occurring variants. Variant sequences (polynucleotide or polypeptide) preferably exhibit at least 50%, more preferably at least 75%, and most preferably at least 90% identity to a sequence of the present invention. The percentage identity is determined by aligning the two sequences to be compared, determining the number of identical residues in the aligned portion, dividing that number by the total length of the inventive, or queried, sequence
15 and multiplying the result by 100.

Polynucleotide or polypeptide sequences may be aligned, and percentage of identical residues in a specified region may be determined against another polynucleotide, using computer algorithms that are publicly available. Two exemplary algorithms for aligning and identifying the similarity of polynucleotide sequences are the BLASTN and FASTA algorithms.
20 Polynucleotides may also be analyzed using the BLASTX algorithm, which compares the six-frame conceptual translation products of a nucleotide query sequence (both strands) against a protein sequence database. The similarity of polypeptide sequences may be examined using the BLASTP or FASTX algorithms. Both the BLASTN and BLASTP software are available on the NCBI anonymous FTP server (<ftp://ncbi.nlm.nih.gov>) under `/blast/executables/`. The BLASTN
25 algorithm version 2.0.6 [Sept-16-1998], set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of variants according to the present invention. The use of the BLAST family of algorithms, including BLASTN and BLASTP, is described at NCBI's website at URL <http://www.ncbi.nlm.nih.gov/BLAST/newblast.html> and in the publication of Altschul *et al.*,
30 "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", *Nucleic Acids Res.* 25:3389-3402, 1997. The computer algorithm FASTA is available on the Internet at the ftp site <ftp://ftp.virginia.edu/pub/fasta/>. Version 3.1t11, August 1998, set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of variants according to the present invention. The use of
35 the FASTA algorithm is described in Pearson and Lipman, "Improved Tools for Biological

- 5 Sequence Analysis,” *Proc. Natl. Acad. Sci. USA* 85:2444-2448, 1988 and Pearson, “Rapid and Sensitive Sequence Comparison with FASTP and FASTA,” *Methods in Enzymol.* 183:63-98, 1990. The use of the FASTX algorithm is described in Pearson *et al.*, “Comparison of DNA sequences with protein sequences,” *Genomics* 46:24-36, 1997.

The following running parameters are preferred for determination of alignments and
 10 similarities using BLASTN that contribute to the E values and percentage identity: Unix running command: blastall -p blastn -d embldb -e 10 -G 0 -E 0 -r 1 -v 30 -b 30 -i queryseq -o results; and parameter default values:

- p Program Name [String]
- d Database [String]
- 15 -e Expectation value (E) [Real]
- G Cost to open a gap (zero invokes default behavior) [Integer]
- E Cost to extend a gap (zero invokes default behavior) [Integer]
- r Reward for a nucleotide match (BLAST only) [Integer]
- v Number of one-line descriptions (V) [Integer]
- 20 -b Number of alignments to show (B) [Integer]
- i Query File [File In]
- o BLAST report Output File [File Out] Optional

For BLASTP the following running parameters are preferred: blastall -p blastp -d swissprot -e 10 -G 0 -E 0 -v 30 -b 30 -i queryseq -o results

- 25 -p Program Name [String]
- d Database [String]
- e Expectation value (E) [Real]
- G Cost to open a gap (zero invokes default behavior) [Integer]
- E Cost to extend a gap (zero invokes default behavior) [Integer]
- 30 -v Number of one-line descriptions (v) [Integer]
- b Number of alignments to show (b) [Integer]
- I Query File [File In]
- o BLAST report Output File [File Out] Optional

The “hits” to one or more database sequences by a queried sequence produced by
 35 BLASTN, BLASTP, FASTA, or a similar algorithm, align and identify similar portions of

5 sequences. The hits are arranged in order of the degree of similarity and the length of sequence overlap. Hits to a database sequence generally represent an overlap over only a fraction of the sequence length of the queried sequence.

The BLASTN and FASTA algorithms also produce "Expect" values for alignments. The Expect value (E) indicates the number of hits one can "expect" to see over a certain number of
10 contiguous sequences by chance when searching a database of a certain size. The Expect value is used as a significance threshold for determining whether the hit to a database, such as the preferred EMBL database, indicates true similarity. For example, an E value of 0.1 assigned to a hit is interpreted as meaning that in a database of the size of the EMBL database, one might expect to see 0.1 matches over the aligned portion of the sequence with a similar score simply by
15 chance. By this criterion, the aligned and matched portions of the sequences then have a probability of 90% of being the same. For sequences having an E value of 0.01 or less over aligned and matched portions, the probability of finding a match by chance in the EMBL database is 1% or less using the BLASTN or FASTA algorithm.

According to one embodiment, "variant" polynucleotides, with reference to each of the
20 polynucleotides of the present invention, preferably comprise sequences having the same number or fewer nucleic acids than each of the polynucleotides of the present invention and producing an E value of 0.01 or less when compared to the polynucleotide of the present invention. That is, a variant polynucleotide is any sequence that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using
25 the BLASTN or FASTA algorithms set at the default parameters. According to a preferred embodiment, a variant polynucleotide is a sequence having the same number or fewer nucleic acids than a polynucleotide of the present invention that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or FASTA algorithms set at the default parameters.

30 Alternatively, variant polynucleotide sequences hybridize to the recited polynucleotide sequence under stringent conditions. As used herein, "stringent conditions" refers to prewashing in a solution of 6X SSC, 0.2% SDS; hybridizing at 65°C, 6X SSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1X SSC, 0.1% SDS at 65 °C and two washes of 30 minutes each in 0.2X SSC, 0.1% SDS at 65 °C.

5 The present invention also encompasses polynucleotides that differ from the disclosed sequences but that, as a consequence of the degeneracy of the genetic code, encode a polypeptide which is the same as that encoded by a polynucleotide of the present invention. Thus, polynucleotides comprising sequences that differ from the polynucleotide sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46, or complements, reverse sequences, or reverse
10 complements thereof, as a result of conservative substitutions are contemplated by and encompassed within the present invention. Additionally, polynucleotides comprising sequences that differ from the polynucleotide sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46, or complements, reverse complements or reverse sequences thereof, as a result of deletions and/or insertions totaling less than 10% of the total sequence length are also contemplated by and
15 encompassed within the present invention. Similarly, polypeptides comprising sequences that differ from the polypeptide sequences provided in SEQ ID NO: 11-20, 30-38 and 47-53, as a result of amino acid substitutions, insertions, and/or deletions totaling less than 10% of the total sequence length are contemplated by and encompassed within the present invention.

Polynucleotides of the present invention also comprehend polynucleotides comprising at
20 least a specified number of contiguous residues (x-mers) of any of the polynucleotides identified as SEQ ID NO: 1-10, 21-29 and 39-46, complements, reverse sequences, and reverse complements of such sequences, and their variants. Similarly, polypeptides of the present invention comprehend polypeptides comprising at least a specified number of contiguous residues (x-mers) of any of the polypeptides identified as SEQ ID NO: 11-20, 30-38 and 47-53,
25 and their variants. As used herein, the term "x-mer," with reference to a specific value of "x," refers to a sequence comprising at least a specified number ("x") of contiguous residues of any of the polynucleotides identified as SEQ ID NO: 1-10, 21-29 and 39-46, or the polypeptides identified as SEQ ID NO: 11-20, 30-38 and 47-53. According to preferred embodiments, the value of x is preferably at least 20, more preferably at least 40, more preferably yet at least 60,
30 and most preferably at least 80. Thus, polynucleotides and polypeptides of the present invention comprise a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer, a 250-mer, a 300-mer, 400-mer, 500-mer or 600-mer of a polynucleotide or polypeptide identified as SEQ ID NO: 1-53, and variants thereof.

The inventive polynucleotides may be isolated by high throughput sequencing of cDNA
35 libraries prepared from lymph node stromal cells of *fsn* ^{-/-} mice as described below in Example

5 1. Alternatively, oligonucleotide probes based on the sequences provided in SEQ ID NO: 1-10,
21-29 and 39-46 can be synthesized and used to identify positive clones in either cDNA or
genomic DNA libraries from lymph node stromal cells of *fsn* ^{-/-} mice by means of hybridization
or polymerase chain reaction (PCR) techniques. Probes can be shorter than the sequences
provided herein but should be at least about 10, preferably at least about 15 and most preferably
10 at least about 20 nucleotides in length. Hybridization and PCR techniques suitable for use with
such oligonucleotide probes are well known in the art (see, for example, Mullis *et al.*, *Cold
Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press,
NY, 1989; Sambrook *et al.*, *Molecular cloning –a laboratory manual*, Cold Spring Harbor
Laboratory Press, Cold Spring Harbor, NY, 1989). Positive clones may be analyzed by
15 restriction enzyme digestion, DNA sequencing or the like.

The polynucleotides of the present invention may alternatively be synthesized using
techniques that are well known in the art. The polynucleotides may be synthesized, for example,
using automated oligonucleotide synthesizers (*e.g.*, Beckman Oligo 1000M DNA Synthesizer) to
obtain polynucleotide segments of up to 50 or more nucleic acids. A plurality of such
20 polynucleotide segments may then be ligated using standard DNA manipulation techniques that
are well known in the art of molecular biology. One conventional and exemplary polynucleotide
synthesis technique involves synthesis of a single stranded polynucleotide segment having, for
example, 80 nucleic acids, and hybridizing that segment to a synthesized complementary 85
nucleic acid segment to produce a 5 nucleotide overhang. The next segment may then be
25 synthesized in a similar fashion, with a 5 nucleotide overhang on the opposite strand. The
“sticky” ends ensure proper ligation when the two portions are hybridized. In this way, a
complete polynucleotide of the present invention may be synthesized entirely *in vitro*.

Polypeptides of the present invention may be produced recombinantly by inserting a
DNA sequence that encodes the polypeptide into an expression vector and expressing the
30 polypeptide in an appropriate host. Any of a variety of expression vectors known to those of
ordinary skill in the art may be employed. Expression may be achieved in any appropriate host
cell that has been transformed or transfected with an expression vector containing a DNA
molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast
and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, insect, yeast or a
35 mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may

5 encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In a related aspect, polypeptides are provided that comprise at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20, 30-38 and 47-53 and variants thereof. As used herein, the
10 "functional portion" of a polypeptide is that portion which contains the active site essential for affecting the function of the polypeptide, for example, the portion of the molecule that is capable of binding one or more reactants. The active site may be made up of separate portions present on one or more polypeptide chains and will generally exhibit high binding affinity. Such functional portions generally comprise at least about 5 amino acid residues, more preferably at least about
15 10, and most preferably at least about 20 amino acid residues. Functional portions of the inventive polypeptides may be identified by first preparing fragments of the polypeptide, by either chemical or enzymatic digestion of the polypeptide or mutation analysis of the polynucleotide that encodes for the polypeptide, and subsequently expressing the resultant mutant polypeptides. The polypeptide fragments or mutant polypeptides are then tested to
20 determine which portions retain the biological activity of the full-length polypeptide.

Portions and other variants of the inventive polypeptides may be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any
25 of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (Merrifield, *J. Am. Chem. Soc.* 85:2149-2154, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's
30 instructions. Variants of a native polypeptide may be prepared using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see, for example, Kunkel, *Proc. Natl. Acad. Sci. USA* 82:488-492, 1985). Sections of DNA sequence may also be removed using standard techniques to permit preparation of truncated polypeptides.

Since the polynucleotide sequences of the present invention have been derived from *fsn* -
35 /- mouse lymph node stromal cells, they likely encode proteins that have important role(s) in

5 growth and development of the immune system, and in responses of the immune system to tissue injury and inflammation as well as other disease states. Some of the polynucleotides contain sequences that code for signal sequences, or transmembrane domains, which identify the protein products as secreted molecules or receptors. Such protein products are likely to be growth factors, cytokines, or their cognate receptors. The polypeptide sequence of SEQ ID NO: 13 has
10 more than 25% identity to known members of the tumour necrosis factor (TNF) receptor family of proteins, with the polypeptides of SEQ ID NO: 30, 31, 32 and 33 having more than 25% identity to known members of the fibroblast growth factor (FGF) receptor family of proteins, and the polypeptide of SEQ ID NO: 38 having more than 25% identity to known members of the WDNM1 family of proteins. These inventive polypeptides are thus likely to have similar
15 biological functions.

In particular, the inventive polypeptides may have important roles in processes such as: modulation of immune responses; differentiation of precursor immune cells into specialized cell types; cell migration; cell proliferation and cell-cell interaction. The polypeptides may be important in the defence of the body against infectious agents, and thus be of importance in
20 maintaining a disease-free environment. These polypeptides may act as modulators of skin cells, especially since immune cells are known to infiltrate skin during tissue insult, causing growth and differentiation of skin cells. In addition, these proteins may be immunologically active, making them important therapeutic targets in a large range of disease states.

In one aspect, the present invention provides methods for using one or more of the
25 inventive polypeptides or polynucleotides to treat disorders in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human.

In this aspect, the polypeptide or polynucleotide is generally present within a pharmaceutical composition or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. Vaccines may comprise one or more of the
30 above polypeptides and a non-specific immune response amplifier, such as an adjuvant or a liposome, into which the polypeptide is incorporated.

Alternatively, a vaccine or pharmaceutical composition of the present invention may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is
35 generated *in situ*. In such vaccines and pharmaceutical compositions, the DNA may be present

5 within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, and bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminator signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus Calmette-Guerin*) that expresses an immunogenic
10 portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other poxvirus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic, or defective, replication competent virus. Techniques for incorporating DNA into such expression systems are well known in the art. The DNA may also be "naked," as described, for example, in Ulmer *et al.*, *Science*
15 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual. In general, the pharmaceutical compositions and vaccines may be administered by
20 injection (*e.g.*, intradermal, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg per kg of host, and preferably from about 100 pg to about 1 µg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from
25 about 0.1 ml to about 2 ml.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax or a buffer. For oral
30 administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and
35 5,075,109.

5 Any of a variety of adjuvants may be employed in the vaccines derived from this invention to non-specifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a non-specific stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *M. tuberculosis*. Suitable adjuvants are commercially available as, for example, Freund's
10 Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories, Detroit, MI), and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A and Quil A.

The polynucleotides of the present invention may also be used as markers for tissue, as chromosome markers or tags, in the identification of genetic disorders, and for the design of
15 oligonucleotides for examination of expression patterns using techniques well known in the art, such as the microarray technology available from Synteni (Palo Alto, CA). Partial polynucleotide sequences disclosed herein may be employed to obtain full length genes by, for example, screening of DNA expression libraries, and to isolate homologous DNA sequences from other species using hybridization probes or PCR primers based on the inventive sequences.

20 The isolated polynucleotides of the present invention also have utility in genome mapping, in physical mapping, and in positional cloning of genes. As detailed below, the polynucleotide sequences identified as SEQ ID NO: 1-10, 21-29 and 39-46, and their variants, may be used to design oligonucleotide probes and primers. Oligonucleotide probes designed using the polynucleotides of the present invention may be used to detect the presence and
25 examine the expression patterns of genes in any organism having sufficiently similar DNA and RNA sequences in their cells using techniques that are well known in the art, such as slot blot DNA hybridization techniques. Oligonucleotide primers designed using the polynucleotides of the present invention may be used for PCR amplifications. Oligonucleotide probes and primers designed using the polynucleotides of the present invention may also be used in connection with
30 various microarray technologies, including the microarray technology of Synteni (Palo Alto, California).

As used herein, the term "oligonucleotide" refers to a relatively short segment of a polynucleotide sequence, generally comprising between 6 and 60 nucleotides, and comprehends both probes for use in hybridization assays and primers for use in the amplification of DNA by
35 polymerase chain reaction. An oligonucleotide probe or primer is described as "corresponding

5 to" a polynucleotide of the present invention, including one of the sequences set out as SEQ ID NO: 1-10, 21-29 and 39-46, or a variant thereof, if the oligonucleotide probe or primer, or its complement, is contained within one of the sequences set out as SEQ ID NO: 1-10, 21-29 and 39-46, or a variant of one of the specified sequences. Oligonucleotide probes and primers of the present invention are substantially complementary to a polynucleotide disclosed herein.

10 Two single stranded sequences are said to be substantially complementary when the nucleotides of one strand, optimally aligned and compared, with the appropriate nucleotide insertions and/or deletions, pair with at least 80%, preferably at least 90% to 95% and more preferably at least 98% to 100% of the nucleotides of the other strand. Alternatively, substantial complementarity exists when a first DNA strand will selectively hybridize to a second DNA
15 strand under stringent hybridization conditions. Stringent hybridization conditions for determining complementarity include salt conditions of less than about 1 M, more usually less than about 500 mM, and preferably less than about 200 mM. Hybridization temperatures can be as low as 5°C, but are generally greater than about 22°C, more preferably greater than about 30°C, and most preferably greater than about 37°C. Longer DNA fragments may require higher
20 hybridization temperatures for specific hybridization. Since the stringency of hybridization may be affected by other factors such as probe composition, presence of organic solvents and extent of base mismatching, the combination of parameters is more important than the absolute measure of any one alone.

In specific embodiments, the oligonucleotide probes and/or primers comprise at least
25 about 6 contiguous residues, more preferably at least about 10 contiguous residues, and most preferably at least about 20 contiguous residues complementary to a polynucleotide sequence of the present invention. Probes and primers of the present invention may be from about 8 to 100 base pairs in length or, preferably from about 10 to 50 base pairs in length or, more preferably from about 15 to 40 base pairs in length. The probes can be easily selected using procedures
30 well known in the art, taking into account DNA-DNA hybridization stringencies, annealing and melting temperatures, and potential for formation of loops and other factors, which are well known in the art. Tools and software suitable for designing probes, and especially suitable for designing PCR primers, are available on the Internet, for example, at URL <http://www.horizonpress.com/pcr/>. Preferred techniques for designing PCR primers are also

5 disclosed in Dieffenbach, CW and Dyksler, GS. *PCR Primer: a laboratory manual*, CSHL Press: Cold Spring Harbor, NY, 1995.

A plurality of oligonucleotide probes or primers corresponding to a polynucleotide of the present invention may be provided in a kit form. Such kits generally comprise multiple DNA or oligonucleotide probes, each probe being specific for a polynucleotide sequence. Kits of the
10 present invention may comprise one or more probes or primers corresponding to a polynucleotide of the present invention, including a polynucleotide sequence identified in SEQ ID NO: 1-10, 21-29 and 39-46.

In one embodiment useful for high-throughput assays, the oligonucleotide probe kits of the present invention comprise multiple probes in an array format, wherein each probe is
15 immobilized at a predefined, spatially addressable location on the surface of a solid substrate. Array formats which may be usefully employed in the present invention are disclosed, for example, in U.S. Patents No. 5,412,087 and 5,545,451, and PCT Publication No. WO 95/00450, the disclosures of which are hereby incorporated by reference.

The polynucleotides of the present invention may also be used to tag or identify an
20 organism or reproductive material therefrom. Such tagging may be accomplished, for example, by stably introducing a non-disruptive non-functional heterologous polynucleotide identifier into an organism, the polynucleotide comprising one of the polynucleotides of the present invention.

The polypeptides provided by the present invention may additionally be used in assays to determine biological activity, to raise antibodies, to isolate corresponding ligands or receptors, in
25 assays to quantify levels of protein or cognate corresponding ligand or receptor, as anti-inflammatory agents, and in compositions for the treatment of diseases of skin, connective tissue and the immune system.

Example 1

ISOLATION OF cDNA SEQUENCES FROM LYMPH NODE STROMAL CELL EXPRESSION LIBRARIES

The cDNA sequences of the present invention were obtained by high-throughput sequencing of cDNA expression libraries constructed from rodent *fsn* ^{-/-} lymph node stromal cells as described below.

5 *cDNA Libraries from Lymph Node Stromal Cells (MLSA and MLSE)*

Lymph nodes were removed from flaky skin *fsn* ^{-/-} mice, the cells dissociated and the resulting single cell suspension placed in culture. After four passages, the cells were harvested. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, MD), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, CA),
 10 according to the manufacturer's specifications. A cDNA expression library (referred to as the MLSA library) was then prepared from the mRNA by Reverse Transcriptase synthesis using a Lambda ZAP Express cDNA library synthesis kit (Stratagene, La Jolla, CA). A second cDNA expression library, referred to as the MLSE library, was prepared exactly as above except that the cDNA was inserted into the mammalian expression vector pcDNA3 (Invitrogen, Carlsbad
 15 CA).

The nucleotide sequence of the cDNA clone isolated from the MLSE library is given in SEQ ID NO: 1, with the corresponding amino acid sequence being provided in SEQ ID NO: 11. The nucleotide sequences of the cDNA clones isolated from the MLSA library are given in SEQ ID NO: 2-10, 21-23 and 28, with the corresponding amino acid sequences being provided in
 20 SEQ ID NO: 12-20, 30-32 and 37, respectively.

Subtracted cDNA Library from flaky skin Lymph Node Stromal Cells (MLSS)

Stromal cells from flaky skin mice lymph nodes and 3T3 fibroblasts were grown in culture and the total RNA extracted from these cells using established protocols. Total RNA
 25 from both populations was isolated using TRIzol Reagent (Gibco BRL Life Technologies, Gaithersburg, MD) and used to obtain mRNA using either a Poly (A) Quik mRNA isolation kit (Stratagene, La Jolla, CA) or Quick Prep^(R) Micro mRNA purification kit (Pharmacia, Uppsala, Sweden). Double-stranded cDNA from flaky skin lymph node stromal cell mRNA was prepared by Reverse Transcriptase synthesis using a lambda ZAP cDNA library synthesis kit (Stratagene)
 30 that had been ligated with *Eco*RI adaptors and digested with *Xho*I to produce double-stranded fragments with *Eco*RI and *Xho*I overhanging ends.

Double-stranded cDNA from 3T3 fibroblasts was prepared using the Superscript II reverse transcriptase (Gibco BRL Life Technologies) followed by treatment with DNA polymerase I and RNaseH (Gibco BRL Life Technologies). Double-stranded 3T3 cDNA was
 35 then digested with restriction endonucleases *Alu*I and *Rsa*I (Gibco BRL Life Technologies) to

5 produce blunt-ended fragments. A 20-fold excess of *AluI* /*RsaI*-digested 3T3 cDNA was hybridized with the *EcoRI/XhoI* flaky skin lymph node stromal cell cDNA in the following hybridisation solution: 50% formamide, 5xSSC, 10mM NaH₂PO₄ pH7.5, 1mM EDTA, 0.1% SDS, 200µg yeast tRNA (Boehringer Mannheim) at 37°C for 24 hours. Hybridized flaky skin lymph node stromal cell cDNA and 3T3 cDNA was then phenol/chloroform extracted and
10 ethanol precipitated. The cDNA was size-fractionated over a Sepharose CL-2B gel filtration column as described in the Lambda ZAP cDNA library synthesis protocol (Stratagene). Flaky skin lymph node stromal cell-specific cDNA was preferentially ligated into ZAP Express vector (Stratagene) by virtue of *EcoRI/XhoI* ends. Chimeric cDNA between flaky skin lymph node stromal cell cDNA and 3T3 cDNA would not be cloned due to non-compatible ends, and the
15 subtracted cDNA library was packaged using Gigapack III Gold packaging extract (Stratagene).

The nucleotide sequences of the cDNA clones isolated from the MLSS library are given in SEQ ID NO: 25-27 and 29, with the corresponding amino acid sequences being provided in SEQ ID NO: 34-36 and 38, respectively.

20

Example 2

CHARACTERIZATION OF ISOLATED CDNA SEQUENCES

The isolated cDNA sequences were compared to sequences in the EMBL DNA database using the computer algorithm BLASTN, and the corresponding predicted protein sequences (DNA translated to protein in each of 6 reading frames) were compared to sequences in the
25 SwissProt database using the computer algorithm BLASTP. Specifically, comparisons of DNA sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46 to sequences in the EMBL (Release 60, September 1999) DNA database, and amino acid sequences provided in SEQ ID NO: 11-20, 30-38 and 47-53 to sequences in the SwissProt and TrEMBL (up to October 20, 1999) databases were made as of December 31, 1999. The cDNA sequences of SEQ ID NO: 1-10, 21-24 and 27-
30 28, and their corresponding predicted amino acid sequences (SEQ ID NO: 11-20, 30-33 and 36-37, respectively) were determined to have less than 75% identity (determined as described above) to sequences in the EMBL and SwissProt databases using the computer algorithms BLASTN and BLASTP, respectively.

Isolated cDNA sequences and their corresponding predicted protein sequences, were
35 computer analyzed for the presence of signal sequences identifying secreted molecules. Isolated

5 cDNA sequences that have a signal sequence at a putative start site within the sequence are provided in SEQ ID NO: 4-6, 9-10, 25-26, 39-41 and 43-45. The isolated cDNA sequences were also computer analyzed for the presence of transmembrane domains coding for putative membrane-bound molecules. Isolated cDNA sequences that have one or more transmembrane domain(s) within the sequence are provided in SEQ ID NO: 1-3, 7, 8, 27 and 41-45.

10 Using automated search programs to screen against sequences coding for known molecules reported to be of therapeutic and/or diagnostic use, the isolated cDNA sequences of SEQ ID NO: 3, 21-24 and 29 were determined to encode predicted protein sequences that appear to be members of the tumour necrosis factor (TNF) receptor family of proteins (SEQ ID NO: 13), the fibroblast growth factor (FGF) receptor family (SEQ ID NO: 30-33) and the WDNM1
15 protein family (SEQ ID NO: 38). A family member is here defined to have at least 20% identical amino acid residues in the translated polypeptide to a known protein or member of a protein family.

As noted above, the isolated cDNA sequence of SEQ ID NO: 3 was determined to encode a predicted protein sequence (SEQ ID NO: 13) that appears to be a member of the TNF-receptor
20 family. Proteins of the TNF/NGF-receptor family are involved in the proliferation, differentiation and death of many cell types including B and T lymphocytes. Residues 18-55 of SEQ ID NO: 13 show a high degree of similarity to the Prosite motif for the TNF/NGF receptor family (Banner *et al.*, *Cell* 73:431-445, 1993). This motif contributes to the ligand binding domain of the molecule and is thus essential to its function. (Gruss and Dower, *Blood* 85:3378-
25 3404, 1995). The polypeptide of SEQ ID NO: 13 is therefore likely to influence the growth, differentiation and activation of several cell types, and may be usefully developed as an agent for the treatment of skin wounds, and the treatment and diagnosis of cancers, inflammatory diseases, and growth and developmental defects.

The isolated cDNA sequence of SEQ ID NO: 29 was determined to encode a predicted
30 protein sequence (SEQ ID NO: 38) that appears to be a member of the WDNM1 protein family. The WDNM1 family of proteins has a conserved arrangement of cysteine residues. The family includes several proteinase inhibitors, suggesting that WDNM1 could encode a product with proteinase inhibiting capacity. The WDNM1 gene has been shown to be down-regulated in metastatic rat mammary adenocarcinomas (Dear and Kefford, *Biochem. Biophys. Res. Comm.*
35 176:247-254, 1991).

5 The isolated cDNA sequence of SEQ ID NO: 21 was determined to encode a predicted protein sequence (SEQ ID NO: 30) that appears to be a member of the fibroblast growth factor (FGF) receptor family of proteins, specifically the FGF receptor 3. Fibroblast growth factor receptors belong to a family of four single membrane-spanning tyrosine kinases (FGFR1 to 4). These receptors serve as high-affinity receptors for 17 growth factors (FGF1 to 17). FGF
10 receptors have important roles in multiple biological processes, including mesoderm induction and patterning, cell growth and migration, organ formation and bone growth (Xu, *Cell Tissue Res.* 296:33-43, 1999). Further analysis of the sequence revealed the presence of a putative transmembrane domain and intracellular domain, similar to other FGF receptors.

The isolated cDNA sequence of SEQ ID NO: 44 was determined to encode a predicted
15 protein sequence (SEQ ID NO: 52) that appears to be a lysyl oxidase-related protein. Lysyl oxidase is a copper-dependent amine oxidase that has an important role in the formation of connective tissue matrices. The molecule is involved in crosslinking of the extracellular matrix proteins, collagen and elastin (Smith-Mungo and Kagan, *Matrix Biol.* 16:387-398, 1998). Expression of lysyl oxidase is upregulated in many fibrotic diseases, and down regulated in
20 diseases involving impaired copper metabolism. Identification of new lysyl oxidase-related proteins indicates the existence of a multigene family. Experimental evidence suggests that lysyl oxidase may have other important biological functions in addition to its role in cross-linking of collagen and elastin (Smith-Mungo and Kagan, *Matrix Biol.* 16:387-398, 1998).

The isolated cDNA sequence of SEQ ID NO: 45 was determined to encode a predicted
25 protein sequence (SEQ ID NO: 53) that appears to be a CD99-like protein. CD99, also referred to as MIC2, is a cell surface molecule involved in T cell adhesion processes (Gelin *et al.*, *EMBO J.* 8:3252-3259).

Example 3

ISOLATION OF FULL LENGTH cDNA SEQUENCE OF A MURINE FIBROBLAST GROWTH FACTOR RECEPTOR HOMOLOG

The full-length cDNA sequence of a murine fibroblast growth factor receptor homolog was isolated as follows.

35 The MLSA cell cDNA library (described in Example 1) was screened with an [α 32 P]-

5 dCTP labeled cDNA probe corresponding to nucleotides 1 to 451 of the coding region within SEQ ID NO: 21. Plaque lifts, hybridization and screening were performed using standard molecular biology techniques. The determined polynucleotide sequence of the full-length murine FGFR gene (referred to as muFGFR- β) is provided in SEQ ID NO: 22, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 31.

10 Analysis of the polynucleotide sequence of SEQ ID NO: 22 revealed the presence of a putative transmembrane domain corresponding to nucleotides 1311 to 1370. The polypeptide sequence (SEQ ID NO: 31) has regions similar to the extracellular domain of the fibroblast growth factor receptor family.

A splice variant of SEQ ID NO: 22 was also isolated from the MLSA cDNA library as described in Example 1. The determined polynucleotide sequence of the splice variant (referred to as FGFR- γ) is provided in SEQ ID NO: 23 and the corresponding predicted amino acid sequence is provided in SEQ ID NO: 32. The splice regions are in an equivalent position to splice sites for previously described FGF receptors (Ornitz, *J. Biol. Chem.* 296:15292-15297, 1996; Wilkie, *Current Biology* 5:500-507, 1995; Miki, *Proc. Natl. Acad. Sci. USA* 89:246-250, 1992), thus providing further evidence that this molecule is a FGF receptor homolog.

EXAMPLE 4

ISOLATION OF A HUMAN FGF RECEPTOR HOMOLOG

25 The cDNA EST encoding the partial murine FGF receptor (SEQ ID NO: 21) was used to search the EMBL database (Release 58, March 1999) to identify human EST homologs. The identified EST (Accession Number AI245701) was obtained from Research Genetics, Inc (Huntsville AL) as I.M.A.G.E. Consortium clone ID 1870593. Sequence determination of the complete insert of clone 1870593 resulted in the identification of 520 additional nucleotides.

30 The insert of this clone did not represent the full-length gene. The determined nucleotide sequence of the complete insert of clone 1870593 is given in SEQ ID NO: 24 and the corresponding predicted amino acid sequence in SEQ ID NO: 33.

EXAMPLE 5

CHARACTERIZATION OF MURINE FGF RECEPTOR HOMOLOG

5

The murine FGF receptor homolog, muFGFR- β and splice variant FGFR- γ (SEQ ID NO: 22 and 23, respectively) were expressed in mammalian cells and the purified protein used to determine the ligand binding specificity of the molecules.

10 The extracellular domains of muFGFR- β and FGFR- γ (SEQ ID NO: 22 and 23, respectively) were amplified by PCR using primers MS158 and MS159 (SEQ ID NO: 55 and 56, respectively) and cloned into the expression vector pcDNA3 containing the Fc fragment from human IgG1. These recombinant proteins, referred to as FGFR β Fc and FGFR γ Fc, were expressed in HEK293 cells (ATCC No. CRL-1573, American Type Culture Collection, Manassas, VA) and purified using an Affiprep protein A column (Biorad, Hercules CA).

15 Binding of muFGFR- β to FGF-2 (basic fibroblast growth factor) was demonstrated by co-incubating the purified protein and FGF-2 in the presence of protein G Sepharose (Amersham Pharmacia, Uppsala, Sweden) and resolving complexes formed on denaturing polyacrylamide gels. FGF-2 (2 μ g) was incubated with 5 μ g FGFR β Fc, FGF Receptor 2 (FGFR2Fc) or unrelated protein (MLSA8790Fc) in 5 μ l protein G fast flow beads (Pharmacia, Uppsala, Sweden), PBS and 0.1% Triton X-100 for 60 min at 4°C. The beads were washed three times in 20 0.1% Triton X-100/PBS and resuspended in 20 μ l loading buffer (0.1 M DTT, 10% sucrose, 60 mM Tris.HCl pH 6.8, 5% SDS and 0.01% bromophenol blue). The samples were analysed on a 12% polyacrylamide gel. FGF-2, FGFR2Fc, FGFR β Fc and MLSA8790Fc (1 μ g of each) were loaded on the gel for comparison. After staining of the gel with Coomassie blue, a doublet of 25 bands were visible in the lane containing FGFR β Fc, indicating that a complex formed between the FGF-2 and the murine FGF receptor homolog FGFR β Fc, and that FGF-2 is a ligand for the novel FGF receptor homolog. A doublet was also observed in the lane containing the FGFR2Fc, which was the positive control. No doublet was observed in the negative control lane containing the MLSA8790Fc protein.

30 The binding specificity of the murine FGF receptor homolog FGFR β Fc was further examined by repeating the experiment described above, replacing the FGF-2 with another known growth factor, epidermal growth factor (EGF). In this experiment, EGF did not bind to FGFR2Fc, the FGFR β Fc or MLSA8790Fc, indicating that binding of FGF-2 to the murine FGF receptor homolog FGFR β Fc was specific.

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<211> 196
<212> PRT
<213> Mouse

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35 40 45
Asn Ser Leu Thr Ser Phe Gln Lys Phe Lys Gly Ser Leu Ala Leu Arg
50 55 60
Thr Leu Asp Leu Arg Arg Asn Ser Leu Thr Ala Leu Pro Gln Arg Val
65 70 75 80
Val Ser Glu Gln Pro Leu Arg Gly Leu Gln Thr Ile Tyr Leu Ser Gln
85 90 95
Asn Pro Tyr Asp Cys Cys Gly Val Glu Gly Trp Gly Ala Leu Gln Gln
100 105 110
His Phe Lys Thr Val Ala Asp Leu Ser Met Val Thr Cys Asn Leu Ser
115 120 125
Ser Lys Ile Val Arg Val Val Glu Leu Pro Glu Gly Leu Pro Gln Gly
130 135 140
Cys Lys Trp Glu Gln Val Asp Thr Gly Leu Phe Tyr Leu Val Leu Ile
145 150 155 160
Leu Pro Ser Cys Leu Thr Leu Leu Val Ala Cys Thr Val Val Phe Leu
165 170 175
Thr Phe Lys Lys Pro Leu Leu Gln Val Ile Lys Ser Arg Cys His Trp
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Ser Ser Ile Tyr
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<210> 12
<211> 174
<212> PRT
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<400> 12


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Pro Arg Val Gly Cys Ser Glu Tyr Thr Asn Arg Ser Cys Glu Glu Cys
          35          40          45
Leu Arg Asn Val Ser Cys Leu Trp Cys Asn Glu Asn Lys Ala Cys Met
 50          55          60
Asp Tyr Pro Val Arg Lys Ile Leu Pro Pro Ala Ser Leu Cys Lys Leu
65          70          75          80
Ser Ser Ala Arg Trp Gly Val Cys Trp Val Asn Phe Glu Ala Leu Ile
          85          90          95
Ile Thr Met Ser Val Leu Gly Gly Ser Val Leu Leu Gly Ile Thr Val
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Cys Cys Cys Tyr Cys Cys Arg Arg Lys Lys Ser Arg Lys Pro Asp Lys
          115          120          125
Ser Asp Glu Arg Ala Met Arg Glu Gln Glu Glu Arg Arg Val Arg Gln
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Glu Glu Arg Arg Ala Glu Met Lys Ser Arg His Asp Glu Ile Arg Lys
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Lys Tyr Gly Leu Phe Lys Glu Gln Asn Pro Tyr Glu Lys Phe
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Cys Gly Pro Cys Ser Thr Thr Ser Pro Ser Thr Trp Val Leu Cys Pro
          35          40          45
Leu Pro Met Ser Pro Leu Cys Pro Thr Cys Val Ser Thr Met Thr Leu
 50          55          60
Ala Thr Cys Thr Cys Pro Trp Ser Thr Thr Cys Pro Cys Thr Leu Ala
65          70          75          80
Pro Asn His Gly Ile Ala Ser Asp Thr Gln Ser Pro Val Ser Arg Ala
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Glu Ser Val Gly Gly Pro Ser Leu Ile Phe
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<210> 14
 <211> 268
 <212> PRT
 <213> Mouse

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

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 Arg Gly Leu Leu Leu Trp Asn Gln Gln Asp Gly Thr Leu Ser Ala Thr
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 Gln Arg Gln Leu Ser Glu Glu Glu Arg Gly Arg Leu Arg Asp Val Ala
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 Ala Val Asn Gly Leu Tyr Arg Val Arg Val Pro Arg Arg Pro Gly Thr
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 Cys Ser Leu Val Glu Ser His Leu Ser Asp Gln Leu Thr Leu His Val
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 Asp Val Ala Gly Asn Val Val Gly Leu Ser Val Val Val Tyr Pro Gly
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 Gly Cys Arg Gly Ser Glu Val Glu Asp Glu Asp Leu Glu Leu Phe Asn
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 Thr Ser Val Gln Leu Arg Pro Pro Ser Thr Ala Pro Gly Pro Glu Thr
 195 200 205
 Ala Ala Phe Ile Glu Arg Leu Glu Met Glu Gln Ala Gln Lys Ala Lys
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 Asn Pro Gln Glu Gln Lys Ser Phe Phe Ala Lys Tyr Trp Met Tyr Ile
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 <212> PRT
 <213> Mouse

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 Val Val Leu Gly Gly Ala Gln Val Ala Leu Val Leu Gly Tyr Cys Pro
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 Gly Met
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<210> 16
 <211> 338
 <212> PRT
 <213> Mouse

<400> 16
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 35 40 45
 Ala Ala Pro Gly Asp Gly Pro Gly Gly Gly Gly Ser Gly Gly Leu Ser
 50 55 60
 Pro Glu Pro Ser Asp Arg Glu Leu Val Ser Lys Ala Glu His Leu Arg
 65 70 75 80
 Glu Ser Asn Gly His Leu Ile Ser Glu Ser Lys Asp Leu Gly Asn Leu
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 Pro Glu Ala Gln Arg Leu Gln Asn Val Gly Ala Asp Trp Val Asn Ala
 100 105 110
 Arg Glu Phe Val Pro Val Gly Lys Ile Pro Asp Thr His Ser Arg Ala
 115 120 125
 Asp Ser Glu Ala Ala Arg Asn Gln Ser Pro Gly Ser His Gly Gly Glu
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 Trp Arg Leu Pro Lys Gly Gln Glu Thr Ala Val Lys Val Ala Gly Ser
 145 150 155 160
 Val Ala Ala Lys Leu Ala Ser Ser Ser Leu Leu Val Asp Arg Ala Lys
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 Ala Val Ser Gln Asp Gln Ala Gly His Glu Asp Trp Glu Val Val Ser
 180 185 190
 Arg His Ser Ser Trp Gly Ser Val Gly Leu Gly Gly Ser Leu Glu Ala
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 Ser Arg Leu Ser Leu Asn Gln Arg Met Asp Asp Ser Thr Asn Ser Leu
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 Val Gly Gly Arg Gly Trp Glu Val Asp Gly Lys Val Ala Ser Leu Lys
 225 230 235 240
 Pro Gln Gln Val Ser Ile Gln Phe Gln Val His Tyr Thr Thr Asn Thr
 245 250 255
 Asp Val Gln Phe Ile Ala Val Thr Gly Asp His Glu Ser Leu Gly Arg
 260 265 270
 Trp Asn Thr Tyr Ile Pro Leu His Tyr Cys Lys Asp Gly Leu Trp Ser
 275 280 285
 His Ser Val Phe Leu Pro Ala Asp Thr Val Val Glu Trp Lys Phe Val
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<210> 17
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 <212> PRT
 <213> Mouse

<400> 17

Gly Thr Ser Pro Ala Ser Val Leu Arg Ser Val Ser Ser Asp Pro Ser
 1 5 10 15
 Leu Pro Pro Pro Ser Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu
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 Ala Ala Cys Gly Ile Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile
 35 40 45
 Met Leu Gly Ile Phe Phe Asn Val His Ser Ala Val Leu Ile Glu Asp
 50 55 60
 Val Pro Phe Thr Glu Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr


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<210> 18
<211> 280
<212> PRT
<213> Mouse
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<210> 19
<211> 188
<212> PRT
<213> Mouse
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<400> 19
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 1 5 10 15
 Leu Ala Leu Leu Gly Ala Ala Gln Asp Pro Thr Asp Ala Gln Gly Ser
 20 25 30
 Ala Ser Gly Asn His Ser Val Leu Thr Ser Asn Ile Asn Ile Thr Glu
 35 40 45
 Asn Thr Asn Gln Thr Met Ser Val Val Ser Asn Gln Thr Ser Glu Met
 50 55 60
 Gln Ser Thr Ala Lys Pro Ser Val Leu Pro Lys Thr Thr Thr Leu Ile
 65 70 75 80
 Thr Val Lys Pro Ala Thr Ile Val Lys Ile Ser Thr Pro Gly Val Leu
 85 90 95
 Pro His Val Thr Pro Thr Ala Ser Lys Ser Thr Pro Asn Ala Ser Ala
 100 105 110
 Ser Pro Asn Ser Thr His Thr Ser Ala Ser Met Thr Thr Pro Ala His
 115 120 125
 Ser Ser Leu Leu Thr Thr Val Thr Val Ser Ala Thr Thr His Pro Thr
 130 135 140
 Lys Gly Lys Gly Ser Lys Phe Asp Ala Gly Ser Phe Val Gly Gly Ile
 145 150 155 160
 Gly Val Asn Thr Gly Ser Phe Ile Tyr Ser Leu His Trp Met Gln Asn
 165 170 175
 Val Leu Phe Lys Lys Arg His Ser Val Pro Lys His
 180 185

<210> 20
 <211> 317
 <212> PRT
 <213> Mouse

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

Val	Cys	Arg	Ala	Ala	Pro	Cys	Pro	Val	Pro	Ser	Asn	Pro	Gly	Gln	Glu
		195					200					205			
Leu	Cys	Gly	Asn	Asn	Asn	Val	Thr	Tyr	Ile	Ser	Ser	Cys	His	Leu	Arg
	210					215					220				
Gln	Ala	Thr	Cys	Phe	Leu	Gly	Arg	Ser	Ile	Gly	Val	Arg	His	Pro	Gly
225					230					235					240
Ile	Cys	Thr	Gly	Gly	Pro	Lys	Phe	Leu	Lys	Ser	Gly	Asp	Ala	Ala	Ile
				245					250					255	
Val	Asp	Met	Val	Pro	Gly	Lys	Pro	Met	Cys	Val	Glu	Ser	Phe	Ser	Asp
			260					265					270		
Tyr	Pro	Pro	Leu	Gly	Arg	Phe	Ala	Val	Arg	Asp	Met	Arg	Gln	Thr	Val
		275					280					285			
Ala	Val	Gly	Val	Ile	Lys	Ala	Val	Asp	Lys	Lys	Ala	Ala	Gly	Ala	Gly
	290					295					300				
Lys	Val	Thr	Lys	Ser	Ala	Gln	Lys	Ala	Gln	Lys	Ala	Lys			
305					310					315					

<210> 21
 <211> 384
 <212> DNA
 <213> Mouse

<220>
 <221> unsure
 <222> (369)...(369)

<400> 21
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 120
 tgtgggtggc cagaagtttg tgggtgttgcc cacgggtgat gtgtgggtcac ggcctgatgg
 180
 ctctacctc aacaagctgc tcctctctcg ggcccggcag gatgatgctg gcatgtacat
 240
 ctgcctaggt gcaaatacca tgggctacag tttccgtagc gccttcctca ctgtattacc
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 360
 gcctgtggng atcggcatcc cagc
 384

<210> 22
 <211> 1967
 <212> DNA
 <213> Mouse

<400> 22
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 120
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 180
 ccggcgagat gacgcggagc cccgcgctgc tgctgctgct attggggggc ctcccgtcgg
 240

ctgaggcggc gcgaggaccc ccaagaatgg cagacaaagt ggtcccacgg cagggtggccc
300
gcctgggccc cactgtgcgg ctacagtgcc cagtggaggg ggaccaccca ccgttgacca
360
tgtggaccaa agatggccgc acaatccaca gtggctggag ccgcttccgt gtgctgcccc
420
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480
ccaatggctt tggcagcctc agcgtcaact acactctcat catcatggat gatattagtc
540
caggaagga gagccctggg ccagggtggt cttcgggggg ccaggaggac ccagccagcc
600
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660
ggcctgtggg tagctctgtg cggctcaagt gtgtggccag tgggcaccca cggccagaca
720
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780
agaagtggac actgagcttg aagaacctga agcctgaaga cagtggcaag tacacgtgcc
840
gtgtatctaa caaggccggt gccatcaacg ccacctacaa agtggatgta atccagcgga
900
ctcgttccaa gcctgtgctc acagggacac accctgtgaa cacaacgggtg gacttcgggtg
960
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1080
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1200
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1260
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1320
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1380
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1440
catcccagga acgcagtggg gacaaggacc tgccctcatt ggctgtgggc atatgtgagg
1500
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1560
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1620
acacgtcttc atgtggaggg caaggttcat caacaccagc atgtccacta tcagtgctaa
1680
atacagcgaa tctccaagca ctgtgtcctg aggtaggcat atgggggcca aggcaacagg
1740
ttgggagaat tgagaacaat ggaggaagag tatcttaggg tgccttatgg tggacactca
1800
caaacttggc catatagatg tatgtactac cagatgaaca gccagccaga ttcacacacg
1860
cacatgttta aacgtgtaaa cgtgtgcaca actgcacaca caacctgaga aaccttcagg
1920

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1967

<210> 23
<211> 1742
<212> DNA
<213> Mouse

<400> 23
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120
ggtagcgccg ccccgcccag gccggggccg ggggcgcggg gggcgggatg cggcgcccg
180
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240
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300
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360
cctgagtggc gtccagtcca gctcccagtg accgcgcccc tgcttcaggt ccgaccggcg
420
agatgacgcg gagccccgcg ctgctgctgc tgctattggg ggcctcccg tcggctgagg
480
cggcgcgaga tgatattagt ccagggaagg agagccctgg gccagggtgt tcttcggggg
540
gccaggagga cccagccagc cagcagtggg cacggcctcg cttcacacag ccctccaaga
600
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660
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720
aggctagtga acacagaaag aagaagtgga cactgagctt gaagaacctg aagcctgaag
780
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840
aagtggatgt aatccagcgg actcgttcca agcctgtgct cacagggaca caccctgtga
900
acacaacggt ggacttcggt gggacaacgt ccttccagtg caagggtcgc agtgacgtga
960
agcctgtgat ccagtggctg aagcgggtgg agtacggctc cgagggacgc cacaactcca
1020
ccattgatgt ggggtggccag aagtttgtgg tgttgccac gggatgatgt tggtcacggc
1080
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1140
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1200
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1260
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1320
tgctgctctg gctttgccag accaagaaga agccatgtgc ccagcatct acacttctg
1380

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 1440
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 1500
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 1560
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 1620
 cagcatgtcc actatcagtg ctaaatacag cgaatctcca agcactgtgt cctgaggtag
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 1740
 ag
 1742

<210> 24
 <211> 1004
 <212> DNA
 <213> Human

<400> 24

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 120
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 180
 gtgccagtgg aggggggacc gccgccgctg accatgtgga ccaaggatgg ccgcaccatc
 240
 cacagcggct ggagccgctt ccgcgtgctg ccgcaggggc tgaaggtgaa gcaggtggag
 300
 cgggaggatg ccggcgtgta cgtgtgcaag gccaccaacg gcttcggcag ccttagcgtc
 360
 aactacacc tcgtcgtgct ggatgacatt agcccaggga aggagagcct ggggcccgc
 420
 agtcctctg ggggtcaaga ggaccccgcc agccagcagt gggcacgacc gcgcttcaca
 480
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 540
 aagtgcgtgg ccagcgggca ccctcggccc gacatcacgt ggatgaagga cgaccaggcc
 600
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 660
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 720
 aacgccacct acaaggtgga tgtgatccag cggaccgctt ccaagcccggt gctcacaggc
 780
 acgcaccccg tgaacacgac ggtggacttc ggggggacca cgtccttcca gtgcaagggtg
 840
 cgcagcgacg tgaagccggt gatccagtgg ctgaagcgcg tggagtacgg cgccgagggc
 900
 cgccacaact ccaccatcga tgtgggcggc cagaagtttg tgggtgctgcc cacgggtgac
 960
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 1004

<210> 25
 <211> 478
 <212> DNA
 <213> Mouse

<400> 25
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 120
 gggacagagc ccgaactcag cgagacccag cgcaggagcc tacagggtggc tctggaggag
 180
 ttccacaaac acccacctgt gcagttggcc ttccaagaga tcggtgtgga cagagctgaa
 240
 gaagtgctct tctcagctgg cacctttgtg aggttggaat ttaagctcca gcagaccaac
 300
 tgccccaaga aggactggaa aaagccggag tgcacaatca aaccaaacgg ggcggaaatg
 360
 cctggcctgc attaaaatgg accccaaggg taaaattcta ggccggatag tccactgccc
 420
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 478

<210> 26
 <211> 545
 <212> DNA
 <213> Mouse

<400> 26
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 120
 tctccctagc cctatggctg ggcacagtgg gcacacgtgg gacagagccc gaactcagcg
 180
 agaccacagc caggagccta caggtggctc tggaggagtt ccacaaacac ccacctgtgc
 240
 agttggcctt ccaagagatc ggtgtggaca gagctgaaga agtgctcttc tcagctggca
 300
 cctttgtgag gttggaattt aagctccagc agaccaactg cccaagaag gactggaaaa
 360
 agccggagtg cacaatcaaa ccaaacggga gaaggcggaa atgcctggcc tgcattaaaa
 420
 tggaccccaa gggtaaaatt ctaggccgga tagtccactg cccaattctg aagcaagggc
 480
 ctcaggatcc tcaggagttg caatgcatta agatagcaca ggctggcgaa gacccccacg
 540
 gctac
 545

<210> 27
 <211> 2213
 <212> DNA
 <213> Mouse

<400> 27

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120
gtatcccaat cacatgagag agcacaacca attacgtggc tggctctcgg atgaaaatga
180
atgggatgaa cacctgtatc cagtgtggag gaggggagac ggcagggtgga aggactcctg
240
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300
tatcaccttt gtgggtgaacc tgggtgtccc cagatgccag aaggaagatg ctaatggcaa
360
tatcgtctat gagaagaact gcaggaatga tttgggactg acctctgacc tgcattgtcta
420
caactggact gcagggggcag atgatgggtga ctgggaagat ggcaccagcc gaagccagca
480
tctcaggttc ccggacagga ggcccttccc tcgcccccat ggatggaaga aatggagctt
540
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600
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660
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720
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780
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900
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1020
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1080
ctctttaatg cctactggtt acaaatccat ggagctgagt gacatttcca atgaaaactg
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1560
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1620
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1680

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 1860
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 2040
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 2213

<210> 28
 <211> 412
 <212> DNA
 <213> Mouse

<400> 28
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 cctcggtctgg acggtttcat ccttaccgag cgcttgggca gtggcacgta cgccacggtg
 180
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 240
 aagagtctca acaaggcgtc agtggaaaac ctctgactg agattgagat cctcaagggc
 300
 attcggcacc cccatatcgt gcagctgaaa gacttccagt gggacaatga caatatctac
 360
 ctcacatgg agttctgtgc aggggggtgac ctgtctcgtt tcattcatac cc
 412

<210> 29
 <211> 437
 <212> DNA
 <213> Mouse

<400> 29
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 120
 aatttgtggt gatcaatgct caggagatgg atcctgccct ggcaacatga agtgctgtag
 180
 caatagctgt ggtcatgtct gcaaaactcc tgtcttttaa atgggtgaca gccatgtgga
 240
 agatggattc aatcttcata aacatgaatg atggccagcc ccagaagatt tcttctgaat
 300

tcacagagcc tgtgcttggc tacttcctag ccctagaatt gcattcttgg acaaggaaga
 360 tctatatattgt ggtgacaatg ccctaatatg tctgtgtcca aaataaacta cccttagcat
 420 tcaaaaaaaaa aaaaaaa
 437

<210> 30
 <211> 126
 <212> PRT
 <213> Mouse

 <220>
 <221> UNSURE
 <222> (123)...(123)

<400> 30
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 Val Lys Pro Val Ile Gln Trp Leu Lys Arg Val Glu Tyr Gly Ser Glu
 20 25 30
 Gly Arg His Asn Ser Thr Ile Asp Val Gly Gly Gln Lys Phe Val Val
 35 40 45
 Leu Pro Thr Gly Asp Val Trp Ser Arg Pro Asp Gly Ser Tyr Leu Asn
 50 55 60
 Lys Leu Leu Ile Ser Arg Ala Arg Gln Asp Asp Ala Gly Met Tyr Ile
 65 70 75 80
 Cys Leu Gly Ala Asn Thr Met Gly Tyr Ser Phe Arg Ser Ala Phe Leu
 85 90 95
 Thr Val Leu Pro Asp Pro Lys Pro Pro Gly Pro Pro Met Ala Ser Ser
 100 105 110
 Ser Ser Ser Thr Ser Leu Pro Trp Pro Val Xaa Gly Ile Pro
 115 120 125

<210> 31
 <211> 529
 <212> PRT
 <213> Mouse

<400> 31
 Met Thr Arg Ser Pro Ala Leu Leu Leu Leu Leu Gly Ala Leu Pro
 1 5 10 15
 Ser Ala Glu Ala Ala Arg Gly Pro Pro Arg Met Ala Asp Lys Val Val
 20 25 30
 Pro Arg Gln Val Ala Arg Leu Gly Arg Thr Val Arg Leu Gln Cys Pro
 35 40 45
 Val Glu Gly Asp Pro Pro Pro Leu Thr Met Trp Thr Lys Asp Gly Arg
 50 55 60
 Thr Ile His Ser Gly Trp Ser Arg Phe Arg Val Leu Pro Gln Gly Leu
 65 70 75 80
 Lys Val Lys Glu Val Glu Ala Glu Asp Ala Gly Val Tyr Val Cys Lys
 85 90 95
 Ala Thr Asn Gly Phe Gly Ser Leu Ser Val Asn Tyr Thr Leu Ile Ile
 100 105 110
 Met Asp Asp Ile Ser Pro Gly Lys Glu Ser Pro Gly Pro Gly Gly Ser
 115 120 125

Ser Gly Gly Gln Glu Asp Pro Ala Ser Gln Gln Trp Ala Arg Pro Arg
 130 135 140
 Phe Thr Gln Pro Ser Lys Met Arg Arg Arg Val Ile Ala Arg Pro Val
 145 150 155 160
 Gly Ser Ser Val Arg Leu Lys Cys Val Ala Ser Gly His Pro Arg Pro
 165 170 175
 Asp Ile Met Trp Met Lys Asp Asp Gln Thr Leu Thr His Leu Glu Ala
 180 185 190
 Ser Glu His Arg Lys Lys Lys Trp Thr Leu Ser Leu Lys Asn Leu Lys
 195 200 205
 Pro Glu Asp Ser Gly Lys Tyr Thr Cys Arg Val Ser Asn Lys Ala Gly
 210 215 220
 Ala Ile Asn Ala Thr Tyr Lys Val Asp Val Ile Gln Arg Thr Arg Ser
 225 230 235 240
 Lys Pro Val Leu Thr Gly Thr His Pro Val Asn Thr Thr Val Asp Phe
 245 250 255
 Gly Gly Thr Thr Ser Phe Gln Cys Lys Val Arg Ser Asp Val Lys Pro
 260 265 270
 Val Ile Gln Trp Leu Lys Arg Val Glu Tyr Gly Ser Glu Gly Arg His
 275 280 285
 Asn Ser Thr Ile Asp Val Gly Gly Gln Lys Phe Val Val Leu Pro Thr
 290 295 300
 Gly Asp Val Trp Ser Arg Pro Asp Gly Ser Tyr Leu Asn Lys Leu Leu
 305 310 315 320
 Ile Ser Arg Ala Arg Gln Asp Asp Ala Gly Met Tyr Ile Cys Leu Gly
 325 330 335
 Ala Asn Thr Met Gly Tyr Ser Phe Arg Ser Ala Phe Leu Thr Val Leu
 340 345 350
 Pro Asp Pro Lys Pro Pro Gly Pro Pro Met Ala Ser Ser Ser Ser
 355 360 365
 Thr Ser Leu Pro Trp Pro Val Val Ile Gly Ile Pro Ala Gly Ala Val
 370 375 380
 Phe Ile Leu Gly Thr Val Leu Leu Trp Leu Cys Gln Thr Lys Lys Lys
 385 390 395 400
 Pro Cys Ala Pro Ala Ser Thr Leu Pro Val Pro Gly His Arg Pro Pro
 405 410 415
 Gly Thr Ser Arg Glu Arg Ser Gly Asp Lys Asp Leu Pro Ser Leu Ala
 420 425 430
 Val Gly Ile Cys Glu Glu His Gly Ser Ala Met Ala Pro Gln His Ile
 435 440 445
 Leu Ala Ser Gly Ser Thr Ala Gly Pro Lys Leu Tyr Pro Lys Leu Tyr
 450 455 460
 Thr Asp Val His Thr His Thr His Thr His Thr Cys Thr His Thr Leu
 465 470 475 480
 Ser Cys Gly Gly Gln Gly Ser Ser Thr Pro Ala Cys Pro Leu Ser Val
 485 490 495
 Leu Asn Thr Ala Asn Leu Gln Ala Leu Cys Pro Glu Val Gly Ile Trp
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 Gly Pro Arg Gln Gln Val Gly Arg Ile Glu Asn Asn Gly Gly Arg Val
 515 520 525
 Ser

<210> 32
 <211> 439
 <212> PRT

<213> Mouse

<400> 32

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			20					25					30		
Gly	Pro	Gly	Gly	Ser	Ser	Gly	Gly	Gln	Glu	Asp	Pro	Ala	Ser	Gln	Gln
		35					40					45			
Trp	Ala	Arg	Pro	Arg	Phe	Thr	Gln	Pro	Ser	Lys	Met	Arg	Arg	Arg	Val
	50					55					60				
Ile	Ala	Arg	Pro	Val	Gly	Ser	Ser	Val	Arg	Leu	Lys	Cys	Val	Ala	Ser
65					70					75					80
Gly	His	Pro	Arg	Pro	Asp	Ile	Met	Trp	Met	Lys	Asp	Asp	Gln	Thr	Leu
				85					90					95	
Thr	His	Leu	Glu	Ala	Ser	Glu	His	Arg	Lys	Lys	Lys	Trp	Thr	Leu	Ser
			100					105					110		
Leu	Lys	Asn	Leu	Lys	Pro	Glu	Asp	Ser	Gly	Lys	Tyr	Thr	Cys	Arg	Val
		115					120					125			
Ser	Asn	Lys	Ala	Gly	Ala	Ile	Asn	Ala	Thr	Tyr	Lys	Val	Asp	Val	Ile
	130					135					140				
Gln	Arg	Thr	Arg	Ser	Lys	Pro	Val	Leu	Thr	Gly	Thr	His	Pro	Val	Asn
145					150					155					160
Thr	Thr	Val	Asp	Phe	Gly	Gly	Thr	Thr	Ser	Phe	Gln	Cys	Lys	Val	Arg
				165					170						175
Ser	Asp	Val	Lys	Pro	Val	Ile	Gln	Trp	Leu	Lys	Arg	Val	Glu	Tyr	Gly
			180					185					190		
Ser	Glu	Gly	Arg	His	Asn	Ser	Thr	Ile	Asp	Val	Gly	Gly	Gln	Lys	Phe
		195				200						205			
Val	Val	Leu	Pro	Thr	Gly	Asp	Val	Trp	Ser	Arg	Pro	Asp	Gly	Ser	Tyr
	210					215					220				
Leu	Asn	Lys	Leu	Leu	Ile	Ser	Arg	Ala	Arg	Gln	Asp	Asp	Ala	Gly	Met
225					230					235					240
Tyr	Ile	Cys	Leu	Gly	Ala	Asn	Thr	Met	Gly	Tyr	Ser	Phe	Arg	Ser	Ala
			245					250						255	
Phe	Leu	Thr	Val	Leu	Pro	Asp	Pro	Lys	Pro	Pro	Pro	Gly	Pro	Pro	Met
			260					265					270		
Ala	Ser	Ser	Ser	Ser	Ser	Thr	Ser	Leu	Pro	Trp	Pro	Val	Val	Ile	Gly
		275					280					285			
Ile	Pro	Ala	Gly	Ala	Val	Phe	Ile	Leu	Gly	Thr	Val	Leu	Leu	Trp	Leu
	290					295					300				
Cys	Gln	Thr	Lys	Lys	Lys	Pro	Cys	Ala	Pro	Ala	Ser	Thr	Leu	Pro	Val
305					310					315					320
Pro	Gly	His	Arg	Pro	Pro	Gly	Thr	Ser	Arg	Glu	Arg	Ser	Gly	Asp	Lys
				325					330					335	
Asp	Leu	Pro	Ser	Leu	Ala	Val	Gly	Ile	Cys	Glu	Glu	His	Gly	Ser	Ala
			340					345					350		
Met	Ala	Pro	Gln	His	Ile	Leu	Ala	Ser	Gly	Ser	Thr	Ala	Gly	Pro	Lys
		355					360					365			
Leu	Tyr	Pro	Lys	Leu	Tyr	Thr	Asp	Val	His	Thr	His	Thr	His	Thr	His
	370					375					380				
Thr	Cys	Thr	His	Thr	Leu	Ser	Cys	Gly	Gly	Gln	Gly	Ser	Ser	Thr	Pro
385					390					395					400
Ala	Cys	Pro	Leu	Ser	Val	Leu	Asn	Thr	Ala	Asn	Leu	Gln	Ala	Leu	Cys
				405					410					415	
Pro	Glu	Val	Gly	Ile	Trp	Gly	Pro	Arg	Gln	Gln	Val	Gly	Arg	Ile	Glu

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 <211> 322
 <212> PRT
 <213> Human
 <400> 33
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 35 40 45
 Val Pro Val Glu Gly Asp Pro Pro Pro Leu Thr Met Trp Thr Lys Asp
 50 55 60
 Gly Arg Thr Ile His Ser Gly Trp Ser Arg Phe Arg Val Leu Pro Gln
 65 70 75 80
 Gly Leu Lys Val Lys Gln Val Glu Arg Glu Asp Ala Gly Val Tyr Val
 85 90 95
 Cys Lys Ala Thr Asn Gly Phe Gly Ser Leu Ser Val Asn Tyr Thr Leu
 100 105 110
 Val Val Leu Asp Asp Ile Ser Pro Gly Lys Glu Ser Leu Gly Pro Asp
 115 120 125
 Ser Ser Ser Gly Gly Gln Glu Asp Pro Ala Ser Gln Gln Trp Ala Arg
 130 135 140
 Pro Arg Phe Thr Gln Pro Ser Lys Met Arg Arg Arg Val Ile Ala Arg
 145 150 155 160
 Pro Val Gly Ser Ser Val Arg Leu Lys Cys Val Ala Ser Gly His Pro
 165 170 175
 Arg Pro Asp Ile Thr Trp Met Lys Asp Asp Gln Ala Leu Thr Arg Pro
 180 185 190
 Glu Ala Ala Glu Pro Arg Lys Lys Lys Trp Thr Leu Ser Leu Lys Asn
 195 200 205
 Leu Arg Pro Glu Asp Ser Gly Lys Tyr Thr Cys Arg Val Ser Asn Arg
 210 215 220
 Ala Gly Ala Ile Asn Ala Thr Tyr Lys Val Asp Val Ile Gln Arg Thr
 225 230 235 240
 Arg Ser Lys Pro Val Leu Thr Gly Thr His Pro Val Asn Thr Thr Val
 245 250 255
 Asp Phe Gly Gly Thr Thr Ser Phe Gln Cys Lys Val Arg Ser Asp Val
 260 265 270
 Lys Pro Val Ile Gln Trp Leu Lys Arg Val Glu Tyr Gly Ala Glu Gly
 275 280 285
 Arg His Asn Ser Thr Ile Asp Val Gly Gly Gln Lys Phe Val Val Leu
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 Pro Thr Gly Asp Val Trp Ser Arg Pro Asp Gly Ser Tyr Leu Asn Lys
 305 310 315 320
 Pro Leu

<210> 34
 <211> 102
 <212> PRT

<213> Mouse

<400> 34

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

<210> 35

<211> 147

<212> PRT

<213> Mouse

<400> 35

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

<210> 36

<211> 574

<212> PRT

<213> Mouse

<400> 36

Met	Glu	Ser	Leu	Cys	Gly	Val	Leu	Gly	Phe	Leu	Leu	Leu	Ala	Ala	Gly
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Leu	Pro	Leu	Gln	Ala	Ala	Lys	Arg	Phe	Arg	Asp	Val	Leu	Gly	His	Glu
			20					25					30		
Gln	Tyr	Pro	Asn	His	Met	Arg	Glu	His	Asn	Gln	Leu	Arg	Gly	Trp	Ser

27

				485					490					495			
Pro	Leu	Arg	Ala	Val	Asn	Gly	Val	Leu	Ile	Ser	Ile	Gly	Cys	Leu	Ala		
			500					505					510				
Val	Leu	Val	Thr	Met	Val	Thr	Ile	Leu	Leu	Tyr	Lys	Lys	His	Lys	Ala		
		515					520					525					
Tyr	Lys	Pro	Ile	Gly	Asn	Cys	Pro	Arg	Asn	Thr	Val	Lys	Gly	Lys	Gly		
	530					535					540						
Leu	Ser	Val	Leu	Leu	Ser	His	Ala	Lys	Ala	Pro	Phe	Phe	Arg	Gly	Asp		
545					550					555					560		
Gln	Glu	Lys	Asp	Pro	Leu	Leu	Gln	Asp	Lys	Pro	Arg	Thr	Leu				
				565					570								

<210> 37
 <211> 137
 <212> PRT
 <213> Mouse

				<400> 37													
Ala	Glu	Ser	Arg	Leu	Ala	Ala	Pro	Arg	Ala	Pro	Pro	Ala	Ser	Leu	Leu		
1				5					10				15				
Ala	Gly	Thr	Cys	Thr	Pro	Asn	Gln	Glu	Ala	Pro	Gly	Gly	Gly	Arg	Gly		
			20					25					30				
Met	Ala	Gly	Pro	Ser	Trp	Gly	Leu	Pro	Arg	Leu	Asp	Gly	Phe	Ile	Leu		
		35					40					45					
Thr	Glu	Arg	Leu	Gly	Ser	Gly	Thr	Tyr	Ala	Thr	Val	Tyr	Lys	Ala	Tyr		
	50					55					60						
Ala	Lys	Lys	Asp	Thr	Arg	Glu	Val	Val	Ala	Ile	Lys	Cys	Val	Ala	Lys		
65					70					75					80		
Lys	Ser	Leu	Asn	Lys	Ala	Ser	Val	Glu	Asn	Leu	Leu	Thr	Glu	Ile	Glu		
			85						90					95			
Ile	Leu	Lys	Gly	Ile	Arg	His	Pro	His	Ile	Val	Gln	Leu	Lys	Asp	Phe		
			100					105						110			
Gln	Trp	Asp	Asn	Asp	Asn	Ile	Tyr	Leu	Ile	Met	Glu	Phe	Cys	Ala	Gly		
		115					120					125					
Gly	Asp	Leu	Ser	Arg	Phe	Ile	His	Thr									
	130						135										

<210> 38
 <211> 72
 <212> PRT
 <213> Mouse

				<400> 38													
Thr	Val	Leu	Phe	Leu	Val	Ala	Leu	Ile	Thr	Val	Gly	Met	Asn	Thr	Thr		
1				5					10				15				
Tyr	Val	Val	Ser	Cys	Pro	Lys	Glu	Phe	Glu	Lys	Pro	Gly	Ala	Cys	Pro		
			20					25					30				
Lys	Pro	Ser	Pro	Glu	Ser	Val	Gly	Ile	Cys	Val	Asp	Gln	Cys	Ser	Gly		
		35					40					45					
Asp	Gly	Ser	Cys	Pro	Gly	Asn	Met	Lys	Cys	Cys	Ser	Asn	Ser	Cys	Gly		
	50					55					60						
His	Val	Cys	Lys	Thr	Pro	Val	Phe										
65						70											

<210> 39
 <211> 1587

<212> DNA
<213> Mouse

<400> 39
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120
gagacagcgg cacagcgtg cttctgccag gttagtggtt acctggacga ctgtacctgt
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240
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960
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1560

aaaaaaaaaa aaaaaaaaaa aaaaaaa
1587

<210> 40
<211> 2435
<212> DNA
<213> Mouse

<400> 40

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 2435

<210> 41
 <211> 1720
 <212> DNA
 <213> Mouse

<400> 41

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 360

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<210> 42
 <211> 1008
 <212> DNA
 <213> Mouse

<400> 42

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			245					250					255				
Lys	Glu	Lys	Asp	Lys	Asp	Ala	Lys	Lys	His	Asn	Leu	Gly	Ile	Asn	Asn		
		260				265						270					
Asn	Asn	Ile	Leu	Gln	Pro	Val	Asp	Ser	Lys	Ile	Gln	Glu	Ile	Glu	Tyr		
	275					280					285						
Met	Glu	Asn	His	Ile	Asn	Ser	Lys	Arg	Leu	Asn	Asn	Asp	Leu	Val	Gly		
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Ser	Thr	Glu	Asn	Leu	Leu	Lys	Glu	Asp	Ser	Cys	Thr	Ala	Ser	Ser	Lys		
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Asn	Tyr	Lys	Asn	Ala	Ser	Gly	Val	Val	Asn	Ser	Ser	Pro	Arg	Ser	His		
			325					330						335			
Ser	Ala	Thr	Asn	Gly	Ser	Ile	Pro	Ser	Ser	Ser	Ser	Lys	Asn	Glu	Lys		
			340				345						350				

Lys Gln Lys Cys Thr Ser Lys Gly Pro Ser Ala His Lys Asp Leu Met
 355 360 365
 Glu Asn Cys Ile Pro Asn Asn Gln Leu Ser Lys Pro Asp Ala Leu Val
 370 375 380
 Arg Leu Glu Gln Asp Ile Lys Lys Leu Lys Ala Asp Leu Gln Ala Ser
 385 390 395 400
 Arg Gln Val Glu Gln Glu Leu Arg Ser Gln Ile Ser Ala Leu Ser Ser
 405 410 415
 Thr Glu Arg Gly Ile Arg Ser Glu Met Gly Gln Leu Arg Gln Glu Asn
 420 425 430
 Glu Leu Leu Gln Asn Lys Leu His Asn Ala Val Gln Met Lys Gln Lys
 435 440 445
 Asp Lys Gln Asn Ile Ser Gln Leu Glu Lys Lys Leu Lys Ala Glu Gln
 450 455 460
 Glu Ala Arg Ser Phe Val Glu Lys Gln Leu Met Glu Glu Lys Lys Arg
 465 470 475 480
 Lys Lys Leu Glu Glu Ala Thr Ala Ala Arg Ala Val Ala Phe Ala Ala
 485 490 495
 Ala Ser Arg Gly Glu Cys Thr Glu Thr Leu Arg Ser Arg Ile Arg Glu
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 Leu Glu Ala Glu Gly Lys Lys Leu Thr Met Asp Met Lys Val Lys Glu
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 Glu Gln Ile Arg Glu Leu Glu Leu Lys Val Gln Glu Leu Arg Lys Tyr
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 Lys Glu Asn Glu Lys Asp Thr Glu Val Leu Met Ser Ala Leu Ser Ala
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 565 570 575
 Arg Ile Lys Leu Asp Leu Phe Ser Ala Leu Gly Asp Ala Lys Arg Gln
 580 585 590
 Leu Glu Ile Ala Gln Gly Gln Ile Leu Gln Lys Asp Gln Glu Ile Lys
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 Asp Leu Lys Gln Lys Ile Ala Glu Val Met Ala Val Met Pro Ser Ile
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 Thr Tyr Ser Ala Ala Thr Ser Pro Leu Ser Pro Val Ser Pro His Tyr
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 Ser Val Tyr Gln Pro Leu Lys Lys
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 <212> PRT
 <213> Mouse

<400> 49

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 Gly Ala Ala Lys Asn Phe Glu Asp Val Arg Cys Lys Cys Ile Cys Pro
 35 40 45
 Pro Tyr Lys Glu Asn Pro Gly His Ile Tyr Asn Lys Asn Ile Ser Gln
 50 55 60
 Lys Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly

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

<210> 50
 <211> 227
 <212> PRT
 <213> Mouse

<400> 50

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

<210> 51

<211> 503
<212> PRT
<213> Mouse

<400> 51

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			20					25					30			
Gly	His	Ile	Val	Thr	Ser	Gln	Asp	Ser	Gly	Thr	Met	Thr	Ser	Lys	Asn	
		35					40					45				
Tyr	Pro	Gly	Thr	Tyr	Pro	Asn	Tyr	Thr	Val	Cys	Glu	Lys	Ile	Ile	Thr	
	50					55					60					
Val	Pro	Lys	Gly	Lys	Arg	Leu	Ile	Leu	Arg	Leu	Gly	Asp	Leu	Asn	Ile	
65					70					75					80	
Glu	Ser	Lys	Thr	Cys	Ala	Ser	Asp	Tyr	Leu	Leu	Phe	Ser	Ser	Ala	Thr	
				85					90					95		
Asp	Gln	Tyr	Gly	Pro	Tyr	Cys	Gly	Ser	Trp	Ala	Val	Pro	Lys	Glu	Leu	
			100					105					110			
Arg	Leu	Asn	Ser	Asn	Glu	Val	Thr	Val	Leu	Phe	Lys	Ser	Gly	Ser	His	
		115					120						125			
Ile	Ser	Gly	Arg	Gly	Phe	Leu	Leu	Thr	Tyr	Ala	Ser	Ser	Asp	His	Pro	
	130					135					140					
Asp	Leu	Ile	Thr	Cys	Leu	Glu	Arg	Gly	Ser	His	Tyr	Phe	Glu	Glu	Lys	
145					150					155					160	
Tyr	Ser	Lys	Phe	Cys	Pro	Ala	Gly	Cys	Arg	Asp	Ile	Ala	Arg	Asp	Ile	
				165					170					175		
Ser	Gly	Asn	Thr	Lys	Asp	Gly	Tyr	Arg	Asp	Thr	Ser	Leu	Leu	Cys	Lys	
			180					185					190			
Ala	Ala	Ile	His	Ala	Gly	Ile	Ile	Thr	Asp	Glu	Leu	Gly	Gly	His	Ile	
		195					200					205				
Asn	Leu	Leu	Gln	Ser	Lys	Gly	Ile	Ser	His	Tyr	Glu	Gly	Leu	Leu	Ala	
	210					215					220					
Asn	Gly	Val	Leu	Ser	Arg	His	Gly	Ser	Leu	Ser	Glu	Lys	Arg	Phe	Leu	
225					230					235					240	
Phe	Thr	Thr	Pro	Gly	Met	Asn	Ile	Thr	Thr	Val	Ala	Ile	Pro	Ser	Val	
				245						250					255	
Ile	Phe	Ile	Ala	Leu	Leu	Leu	Thr	Gly	Met	Gly	Ile	Phe	Ala	Ile	Cys	
			260					265					270			
Arg	Lys	Arg	Lys	Lys	Lys	Gly	Asn	Pro	Tyr	Val	Ser	Ala	Asp	Ala	Gln	
		275					280					285				
Lys	Thr	Gly	Cys	Trp	Lys	Gln	Ile	Lys	Tyr	Pro	Phe	Ala	Arg	His	Gln	
	290					295					300					
Ser	Thr	Glu	Phe	Thr	Ile	Ser	Tyr	Asp	Asn	Glu	Lys	Glu	Met	Thr	Gln	
305					310					315					320	
Lys	Leu	Asp	Leu	Ile	Thr	Ser	Asp	Met	Ala	Asp	Tyr	Gln	Gln	Pro	Leu	
				325					330					335		
Met	Ile	Gly	Thr	Gly	Thr	Val	Ala	Arg	Lys	Gly	Ser	Thr	Phe	Arg	Pro	
			340					345					350			
Met	Asp	Thr	Asp	Thr	Glu	Glu	Val	Arg	Val	Asn	Thr	Glu	Ala	Ser	Gly	
	355						360					365				
His	Tyr	Asp	Cys	Pro	His	Arg	Pro	Gly	Arg	His	Glu	Tyr	Ala	Leu	Pro	
	370					375					380					
Leu	Thr	His	Ser	Glu	Pro	Glu	Tyr	Ala	Thr	Pro	Ile	Val	Glu	Arg	His	
385					390					395					400	
Leu	Leu	Arg	Ala	His	Thr	Phe	Ser	Thr	Gln	Ser	Gly	Tyr	Arg	Val	Pro	

				405					410					415			
Gly	Pro	Arg	Pro	Thr	His	Glu	His	Ser	His	Ser	Ser	Gly	Gly	Phe	Pro		
			420					425					430				
Pro	Ala	Thr	Gly	Ala	Thr	Gln	Val	Glu	Ser	Tyr	Gln	Arg	Pro	Ala	Ser		
		435					440					445					
Pro	Lys	Pro	Val	Gly	Gly	Gly	Tyr	Asp	Lys	Pro	Ala	Ala	Ser	Ser	Phe		
	450					455					460						
Leu	Asp	Ser	Arg	Asp	Pro	Ala	Ser	Gln	Ser	Gln	Met	Thr	Ser	Gly	Gly		
465					470					475					480		
Asp	Asp	Gly	Tyr	Ser	Ala	Pro	Arg	Asn	Gly	Leu	Ala	Pro	Leu	Asn	Gln		
				485					490					495			
Thr	Ala	Met	Thr	Ala	Leu	Leu											
			500														

<210> 52
 <211> 757
 <212> PRT
 <213> Mouse

<400> 52

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

Ala	Gly	Pro	His	Phe	Arg	Arg	Gln	Lys	Pro	Lys	Pro	Thr	Arg	Lys	Glu
290						295					300				
Ser	His	Ala	Glu	Glu	Leu	Lys	Val	Arg	Leu	Arg	Ser	Gly	Ala	Gln	Val
305					310					315					320
Gly	Glu	Gly	Arg	Val	Glu	Val	Leu	Met	Asn	Arg	Gln	Trp	Gly	Thr	Val
				325					330					335	
Cys	Asp	His	Arg	Trp	Asn	Leu	Ile	Ser	Ala	Ser	Val	Val	Cys	Arg	Gln
			340					345					350		
Leu	Gly	Phe	Gly	Ser	Ala	Arg	Glu	Ala	Leu	Phe	Gly	Ala	Gln	Leu	Gly
		355					360					365			
Gln	Gly	Leu	Gly	Pro	Ile	His	Leu	Ser	Glu	Val	Arg	Cys	Arg	Gly	Tyr
370						375					380				
Glu	Arg	Thr	Leu	Gly	Asp	Cys	Leu	Ala	Leu	Glu	Gly	Ser	Gln	Asn	Gly
385					390					395					400
Cys	Gln	His	Ala	Asn	Asp	Ala	Ala	Val	Arg	Cys	Asn	Ile	Pro	Asp	Met
				405					410					415	
Gly	Phe	Gln	Asn	Lys	Val	Arg	Leu	Ala	Gly	Gly	Arg	Asn	Ser	Glu	Glu
			420					425						430	
Gly	Val	Val	Glu	Val	Gln	Val	Glu	Val	Asn	Gly	Val	Pro	Arg	Trp	Gly
		435					440					445			
Thr	Val	Cys	Ser	Asp	His	Trp	Gly	Leu	Thr	Glu	Ala	Met	Val	Thr	Cys
450						455					460				
Arg	Gln	Leu	Gly	Leu	Gly	Phe	Ala	Asn	Phe	Ala	Leu	Lys	Asp	Thr	Trp
465					470					475					480
Tyr	Trp	Gln	Gly	Thr	Pro	Glu	Ala	Lys	Glu	Val	Val	Met	Ser	Gly	Val
				485					490					495	
Arg	Cys	Ser	Gly	Thr	Glu	Met	Ala	Leu	Gln	Gln	Cys	Gln	Arg	His	Gly
			500					505					510		
Pro	Val	His	Cys	Ser	His	Gly	Pro	Gly	Arg	Phe	Ser	Ala	Gly	Val	Ala
		515					520					525			
Cys	Met	Asn	Ser	Ala	Pro	Asp	Leu	Val	Met	Asn	Ala	Gln	Leu	Val	Gln
530						535					540				
Glu	Thr	Ala	Tyr	Leu	Glu	Asp	Arg	Pro	Leu	Ser	Met	Leu	Tyr	Cys	Ala
545					550					555					560
His	Glu	Glu	Asn	Cys	Leu	Ser	Lys	Ser	Ala	Asp	His	Met	Asp	Trp	Pro
				565					570					575	
Tyr	Gly	Tyr	Arg	Arg	Leu	Leu	Arg	Phe	Ser	Ser	Gln	Ile	Tyr	Asn	Leu
			580					585					590		
Gly	Arg	Ala	Asp	Phe	Arg	Pro	Lys	Ala	Gly	Arg	His	Ser	Trp	Ile	Trp
		595					600					605			
His	Gln	Cys	His	Arg	His	Tyr	His	Ser	Ile	Glu	Val	Phe	Thr	His	Tyr
610						615					620				
Asp	Leu	Leu	Thr	Leu	Asn	Gly	Ser	Lys	Val	Ala	Glu	Gly	His	Lys	Ala
625					630					635					640
Ser	Phe	Cys	Leu	Glu	Asp	Thr	Asn	Cys	Pro	Ser	Gly	Val	Gln	Arg	Arg
				645					650					655	
Tyr	Ala	Cys	Ala	Asn	Phe	Gly	Glu	Gln	Gly	Val	Ala	Val	Gly	Cys	Trp
			660					665					670		
Asp	Thr	Tyr	Arg	His	Asp	Ile	Asp	Cys	Gln	Trp	Val	Asp	Ile	Thr	Asp
		675					680					685			
Val	Gly	Pro	Gly	Asp	Tyr	Ile	Phe	Gln	Val	Val	Val	Asn	Pro	Thr	Asn
690						695						700			
Asp	Val	Ala	Glu	Ser	Asp	Phe	Ser	Asn	Asn	Met	Ile	Arg	Cys	Arg	Cys
705					710					715					720
Lys	Tyr	Asp	Gly	Gln	Arg	Val	Trp	Leu	His	Asn	Cys	His	Thr	Gly	Asp
				725					730					735	

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 740 745 750
 Arg Asn Asn Leu Ile
 755

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<400> 53
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 35 40 45
 Pro Ser Gly Gly Phe Asp Leu Glu Asp Ala Leu Pro Gly Gly Gly Gly
 50 55 60
 Gly Gly Ala Gly Glu Lys Pro Gly Asn Arg Pro Gln Pro Asp Pro Lys
 65 70 75 80
 Pro Pro Arg Pro His Gly Asp Ser Gly Gly Ile Ser Asp Ser Asp Leu
 85 90 95
 Ala Asp Ala Ala Gly Gln Gly Gly Gly Ala Gly Arg Arg Gly Ser Gly
 100 105 110
 Asp Glu Gly Gly His Gly Gly Ala Gly Gly Ala Glu Pro Glu Gly Thr
 115 120 125
 Pro Gln Gly Leu Val Pro Gly Val Val Ala Ala Val Val Ala Ala Val
 130 135 140
 Ala Gly Ala Val Ser Ser Phe Val Ala Tyr Gln Arg Arg Arg Leu Cys
 145 150 155 160
 Phe Arg Glu Gly Gly Ser Ala Pro Val
 165

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 <212> DNA
 <213> Artificial Sequence

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 <223> Made in a lab

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 30

<210> 55
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 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 55

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35

<210> 56
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 56
ccgctcgagt agatactctt cctccattgt tctcatt
37

<210> 57
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 57
ctgtgcggct caagtgtg
18

5

EXAMPLE 6

SEQUENCE DETERMINATION OF A POLYNUCLEOTIDE FRAGMENT
CONTAINING GENOMIC MURINE FGFR β

10

Mouse genomic DNA was isolated from L929 cells using standard techniques. A genomic polynucleotide fragment containing murine FGFR β was PCR amplified using primers MS157 and MS166 (SEQ ID NO: 56 and 57, respectively). The 1.4 kb polynucleotide fragment was cloned into a T-tailed pBluescript SK²⁺ vector. The sequence of the insert of this plasmid was determined using standard primer walking sequencing techniques. The determined base sequence of the genomic fragment containing murine FGFR β is given in SEQ ID NO: 46.

CLAIMS:

1. An isolated polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 11-20, 30-38 and 47-53.
2. An isolated polypeptide comprising a sequence selected from the group consisting of:
 - (a) sequences having at least 40% identity to a sequence provided in SEQ ID NO: 11-20, 30-38 and 47-49, 51 and 52 as determined using the computer algorithm BLASTP;
 - (b) sequences having at least 60% identity to a sequence provided in SEQ ID NO: 11-20, 30-38 and 47-53 as determined using the computer algorithm BLASTP;
 - (c) sequences having at least 75% identity to a sequence provided in SEQ ID NO: 11-20, 30-38 and 47-53 as determined using the computer algorithm BLASTP; and
 - (d) sequences having at least 90% identity to a sequence provided in SEQ ID NO: 11-20, 30-38 and 47-53 as determined using the computer algorithm BLASTP.
3. An isolated polynucleotide that encodes a polypeptide according to any one of claims 1 and 2.
4. An isolated polynucleotide of claim 3, wherein the polynucleotide comprises a sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-10, 21-29 and 39-46.
5. An isolated polynucleotide comprising a sequence selected from the group consisting of:
 - (a) complements of a sequence provided in SEQ ID NO: 1-10, 21-29 and 39-46;
 - (b) reverse complements of a sequence provided in SEQ ID NO: 1-10, 21-29 and 39-46;
 - (c) reverse sequences of a sequence provided in SEQ ID NO: 1-10, 21-29 and 39-46;
 - (d) sequences having at least 40% identity to a sequence provided in SEQ ID NO: 1-10, 21-29 and 39-46 as determined using the computer algorithm BLASTN;
 - (e) sequences having at least 60% identity to a sequence provided in SEQ ID NO: 1-10, 21-29 and 39-46 as determined using the computer algorithm BLASTN;
 - (f) sequences having at least 75% identity to a sequence provided in SEQ ID NO: 1-10, 21-29 and 39-46 as determined using the computer algorithm BLASTN; and
 - (g) sequences having at least 90% identity to a sequence provided in SEQ ID NO: 1-10, 21-29 and 39-46 as determined using the computer algorithm BLASTN.

6. An isolated polynucleotide comprising a sequence selected from the group consisting of:
(a) sequences that are a 200-mer of an isolated polynucleotide according to any one of claims 3, 4 and 5; (b) sequences that are a 100-mer of an isolated polynucleotide according to any one of claims 3, 4 and 5; and (c) sequences that are a 40-mer of an isolated polynucleotide according to any one of claims 3, 4 and 5.
7. An expression vector comprising an isolated polynucleotide according to any one of claims 3-6.
8. A host cell transformed with an expression vector according to claim 7.
9. An isolated polypeptide comprising at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20, 30-38 and 47-53.
10. A pharmaceutical composition comprising an isolated polypeptide according to any one of claims 1, 2 and 9.
11. A pharmaceutical composition comprising an isolated polynucleotide according to any one of claims 3-6.
12. A method for the treatment of an inflammatory disorder in a patient, comprising administering to the patient a pharmaceutical composition according to any one of claims 10 and 11.
13. A method for modulating the growth of blood vessels in a patient, comprising administering to the patient a pharmaceutical composition according to any one of claims 10 and 11.
14. A method for the treatment of a disorder of the immune system in patient, comprising administering to the patient a pharmaceutical composition according to any one of claims 10 and 11.
15. A method for the treatment of cancer in a patient, comprising administering to the patient a pharmaceutical composition according to any one of claims 10 and 11, wherein the cancer is selected from the group consisting of epithelial, lymphoid, myeloid, stromal and neuronal cancers.
16. A method for the treatment of a tumour necrosis factor-mediated disorder in a patient, comprising administering to the patient a composition comprising an isolated

polypeptide, the polypeptide comprising an amino acid sequence selected from the group consisting of:

- (a) a sequence of SEQ ID NO: 13;
 - (d) sequences having at least 40% identity to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP;
 - (e) sequences having at least 60% identity to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP;
 - (f) sequences having at least 75% identity to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP; and
 - (d) sequences having at least 90% identity to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP.
17. The method of claim 16, wherein the tumour necrosis factor-mediated disorder is selected from the group consisting of arthritis, inflammatory bowel disease and cardiac failure.
18. A method for the treatment of a viral disorder in a patient, comprising administering to the patient a pharmaceutical composition according to any one of claims 10 and 11.
19. The method of claim 18, wherein the viral disorder is HIV-infection.
20. A method for the treatment of a fibroblast growth factor-mediated disorder in a patient, comprising administering to the patient a composition comprising an isolated polypeptide, the polypeptide comprising an amino acid sequence selected from the group consisting of:
- (a) a sequence provided in SEQ ID NO: 30-33;
 - (b) sequences having at least 40% identity to a sequence provided in SEQ ID NO: 30-33 as determined using the computer algorithm BLASTP;
 - (c) sequences having at least 60% identity to a sequence provided in SEQ ID NO: 30-33 as determined using the computer algorithm BLASTP;
 - (d) sequences having at least 75% identity to a sequence provided in SEQ ID NO: 30-33 as determined using the computer algorithm BLASTP; and
 - (e) sequences having at least 90% identity to a sequence provided in SEQ ID NO: 30-33 as determined using the computer algorithm BLASTP.