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

(57) 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.

Polynucleotide and deduced amino acid sequences from stromal cells

Technical Filed 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

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

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 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 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 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 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.

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 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 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 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.

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 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 psoriatic-like skin disease but also other abnormalities involving cells of the immune and 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 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 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 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 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 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.

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.

In specific embodiments, a method for the treatment of an inflammatory disorder in a patient is provided for comprising administering to the patient a composition comprising a polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5. In a preferred embodiment, the sequence has at least 90% identity to a sequence of SEQ ID NO: 30-33 and in another preferred embodiment the sequence is selected from the group consisting of SEQ ID NO: 30-33.

In other embodiments, the present invention provides for a method for the treatment of a disorder of the immune system in a patient, comprising administering to the patient a composition comprising a polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5. In a preferred embodiment, the sequence has at least 90% identity to a sequence of SEQ ID NO: 30-33 and in another preferred embodiment the sequence is selected from the group consisting of SEQ ID NO: 30-33.

In related embodiments, the present invention provides the use of a composition comprising a polypeptide in the manufacture of medicament for the treatment of an inflammatory disorder in a patient, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5. In a preferred embodiment, the sequence has at least 90% identity to a sequence of SEQ ID NO: 30-33 and in another preferred embodiment the sequence is selected from the group consisting of SEQ ID NO: 30-33.

In related embodiments, the present invention provides the use of a composition comprising a polypeptide in the manufacture of medicament for the treatment of a

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disorder of the immune system in a patient, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5. In a preferred embodiment, the sequence has at least 90% identity to a sequence of SEQ ID NO: 30-33 and in another preferred embodiment the sequence is selected from the group consisting of SEQ ID NO: 30-33.

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 as if each was incorporated individually.

Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

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:

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 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 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 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.

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 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.

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 those terms are commonly used in the art. Preferably, the polypeptides and polynucleotides are at 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 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 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. 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 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.*, "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/. Version3.1t11, 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 the FASTA algorithm is described in Pearson and Lipman, "Improved Tools for Biological

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 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]

-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]

-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 swissprotdb –e 10 –G 0 –E 0 –v 30 –b 30 –i queryseq –o results

-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]

-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 BLASTN, BLASTP, FASTA, or a similar algorithm, align and identify similar portions of 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 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 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 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 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.

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.

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 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 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 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, 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, 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 libraries prepared from lymph node stromal cells of *fsn* -/- mice as described below in Example

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 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 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 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 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 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 mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may 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 "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 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 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 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 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* -/- mouse lymph node stromal cells, they likely encode proteins that have important role(s) in 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 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 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 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 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 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 generated *in situ*. In such vaccines and pharmaceutical compositions, the DNA may be present 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 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* 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 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 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 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 5,075,109.

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 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 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.

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 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 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 polymerase chain reaction. An oligonucleotide probe or primer is described as "corresponding 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.

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 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 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 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 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 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 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 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 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 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.

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), 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 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 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 from both populations was isolated using TRIzol Reagent (Gibco BRL Life Technologies, Gaitherburg, 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) 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 then digested with restriction endonucleases *Alu*I and *Rsa*I (Gibco BRL Life Technologies) to produce blunt-ended fragments. A 20-fold excess of *Alu*I /*Rsa*I-digested 3T3 cDNA was hybridized with the *Eco*RI/*Xho*I flaky skin lymph node stromal cell cDNA in the following hybridisation solution: 50% formamide, 5xSSC, 10mM NaH_2PO_4 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 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 *Eco*RI/*Xho*I 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 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.

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 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 27-28, 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 computer analyzed for the presence of signal sequences identifying secreted molecules. Isolated 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.

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 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 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* 85:3378-3404, 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 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.* 176:247-254, 1991).

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 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 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 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 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.

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

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.

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

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. 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

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.

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 FGFRβFc and FGFRγFc, 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).

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 μg) was incubated with 5 μg FGFRβFc, FGF Receptor 2 (FGFR2Fc) or unrelated protein (MLSA8790Fc) in 5 μl 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 0.1% Triton X-100/PBS and resuspended in 20 μl 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, FGFRβFc and MLSA8790Fc (1 μg of each) were loaded on the gel for comparison. After staining of the gel with Coomassie blue, a doublet of bands were visible in the lane containing FGFRβFc, indicating that a complex formed between the FGF-2 and the murine FGF receptor homolog FGFRβFc, 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.

The binding specificity of the murine FGF receptor homolog FGFRβFc 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 FGFRβFc or MLSA8790Fc, indicating that binding of FGF-2 to the murine FGF receptor homolog FGFRβFc was specific.

EXAMPLE 6

SEQUENCE DETERMINATION OF A POLYNUCLEOTIDE FRAGMENT CONTAINING GENOMIC MURINE FGFRβ

Mouse genomic DNA was isolated from L929 cells using standard techniques. A genomic polynucleotide fragment containing murine FGFRβ 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 SK^{2+} 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 FGFRβ is given in SEQ ID NO: 46.

EDITORIAL NOTE

APPLICATION NUMBER 27021/00

The following Sequence Listing pages 1-47 are part of the description. The claims pages follow on pages 26-27

Received 26 January 2001

SEQUENCE LISTING

<110> Strachan, Lorna
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Abernethy, Nevin
Onrust, Rene
Kumble, Anand
Murison, Greg

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<213> Mouse

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<213> Mouse

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Met Asp Phe Ser Ala Phe Gly Asn Leu Arg Ala Leu Asp Leu Ser Gly
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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
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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
100 105 110
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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35 40 45
Leu Pro Met Ser Pro Leu Cys Pro Thr Cys Val Ser Thr Met Thr Leu
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Ala Thr Cys Thr Cys Pro Trp Ser Thr Thr Cys Pro Cys Thr Leu Ala
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Glu Ser Val Gly Gly Pro Ser Leu Ile Phe
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<211> 268
<212> PRT
<213> Mouse

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35 40 45

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Arg Gly Leu Leu Leu Trp Asn Gln Gln Asp Gly Thr Leu Ser Ala Thr
                85                  90                  95
Gln Arg Gln Leu Ser Glu Glu Glu Arg Gly Arg Leu Arg Asp Val Ala
            100                 105                 110
Ala Val Asn Gly Leu Tyr Arg Val Arg Val Pro Arg Arg Pro Gly Thr
        115                 120                 125
Leu Asp Gly Ser Glu Ala Gly Gly His Val Ser Ser Phe Val Pro Ala
    130                 135                 140
Cys Ser Leu Val Glu Ser His Leu Ser Asp Gln Leu Thr Leu His Val
145                 150                 155                 160
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
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            20                  25                  30
Val Val Leu Gly Gly Ala Gln Val Ala Leu Val Leu Gly Tyr Cys Pro
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Asp Val Asn Thr Val Leu Gly Ala Ser Leu Glu Gly Ser Gln Asp Lys
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Gly Met
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<211> 338
<212> PRT
<213> Mouse

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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
85 90 95
Pro Glu Ala Gln Arg Leu Gln Asn Val Gly Ala Asp Trp Val Asn Ala
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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
130 135 140
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
165 170 175
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
195 200 205
Ser Arg Leu Ser Leu Asn Gln Arg Met Asp Asp Ser Thr Asn Ser Leu
210 215 220
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
290 295 300
Leu Val Glu Asn Lys Glu Val Thr Arg Trp Glu Glu Cys Ser Asn Arg
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Phe Leu Gln Thr Gly His Glu Asp Lys Val Val His Gly Trp Trp Gly
325 330 335
Ile His

<210> 17
<211> 119
<212> PRT
<213> Mouse

<400> 17
Gly Thr Ser Pro Ala Ser Val Leu Arg Ser Val Ser Ser Asp Pro Ser
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20 25 30
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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65 70 75 80
Asn Leu Tyr Glu Gln Val Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu
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Tyr Leu Leu Leu Gly Gly Phe Ser Phe Cys Gln Val Arg Leu Asn Lys
100 105 110
Arg Lys Glu Tyr Met Val Arg
115

<210> 18
<211> 280
<212> PRT
<213> Mouse

<400> 18
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20 25 30
Val Ala Gly Ser Gly Glu Ala Glu Gly Ser Ser Ala Ser Ser Pro Ser
35 40 45
Leu Pro Pro Pro Gly Thr Pro Ala Phe Ser Pro Thr Pro Glu Arg Pro
50 55 60
Gln Pro Thr Ala Leu Asp Gly Pro Val Pro Pro Thr Asn Leu Leu Glu
65 70 75 80
Gly Ile Met Asp Phe Phe Arg Gln Tyr Val Met Leu Ile Ala Val Val
85 90 95
Gly Ser Leu Thr Phe Leu Ile Met Phe Ile Val Cys Ala Ala Leu Ile
100 105 110
Thr Arg Gln Lys His Lys Ala Thr Ala Tyr Tyr Pro Ser Ser Phe Pro
115 120 125
Glu Lys Lys Tyr Val Asp Gln Arg Asp Arg Ala Gly Gly Pro Arg Thr
130 135 140
Phe Ser Glu Val Pro Asp Arg Ala Pro Asp Ser Arg His Glu Glu Gly
145 150 155 160
Leu Asp Thr Ser His Gln Leu Gln Ala Asp Ile Leu Ala Ala Thr Gln
165 170 175
Asn Leu Arg Ser Pro Ala Arg Ala Leu Pro Gly Asn Gly Glu Gly Ala
180 185 190
Lys Pro Val Lys Gly Gly Ser Glu Glu Glu Glu Glu Glu Val Leu Ser
195 200 205
Gly Gln Glu Glu Ala Gln Glu Ala Pro Val Cys Gly Val Thr Glu Glu
210 215 220
Lys Leu Gly Val Pro Glu Glu Ser Val Ser Ala Glu Ala Glu Gly Val
225 230 235 240
Pro Ala Thr Ser Glu Gly Gln Gly Glu Ala Glu Gly Ser Phe Ser Leu
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Ala Gln Glu Ser Gln Gly Ala Thr Gly Pro Pro Glu Ser Pro Cys Ala
260 265 270
Cys Asn Arg Val Ser Pro Ser Val
275 280

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<211> 188
<212> PRT
<213> Mouse

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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
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165 170 175
Val Leu Phe Lys Lys Arg His Ser Val Pro Lys His
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<212> PRT
<213> Mouse

<400> 20
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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

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

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tgtgggtggc cagaagtttg tggtgttgcc cacgggtgat gtgtggtcac ggcctgatgg
180
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240
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<210> 22
<211> 1967
<212> DNA
<213> Mouse

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240

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1967

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

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1380

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<212> DNA
<213> Human

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

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

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

<400> 27

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1680

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<213> Mouse

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

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

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

<400> 30

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Val Asp Phe Gly Gly Thr Thr Ser Phe Gln Cys Lys Val Arg Ser Asp
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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
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<210> 31
<211> 529
<212> PRT
<213> Mouse

<400> 31

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Met Thr Arg Ser Pro Ala Leu 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
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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 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
            500   505   510
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

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<213> Mouse

<400> 32

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Ser Ala Glu Ala Ala Arg Asp Asp Ile Ser Pro Gly Lys Glu Ser Pro
            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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            420                     425                     430
Asn Asn Gly Gly Arg Val Ser
        435

      <210> 33
      <211> 322
      <212> PRT
      <213> Human

      <400> 33
Arg Arg Ala Pro Cys Cys Cys Ser Cys Cys Arg Arg Cys Cys Trp Gly
 1               5                  10                  15
Pro Ser His Arg Pro Pro Pro Pro Glu Ala Pro Gln Arg Trp Arg Thr
            20                  25                  30
Arg Trp Ser His Gly Arg Trp Pro Ala Gly Pro His Cys Ala Ala Ala
        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
    290                 295                 300
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
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<213> Mouse

<400> 34
Met Lys Phe Leu Leu Ile Ser Leu Ala Leu Trp Leu Gly Thr Val Gly
1 5 10 15
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
1 5 10 15
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
1 5 10 15
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

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        35                  40                  45
Ser Asp Glu Asn Glu Trp Asp Glu His Leu Tyr Pro Val Trp Arg Arg
    50                  55                  60
Gly Asp Gly Arg Trp Lys Asp Ser Trp Glu Gly Gly Arg Val Gln Ala
65                  70                  75                  80
Val Leu Thr Ser Asp Ser Pro Ala Leu Val Gly Ser Asn Ile Thr Phe
                85                  90                  95
Val Val Asn Leu Val Phe Pro Arg Cys Gln Lys Glu Asp Ala Asn Gly
            100                 105                 110
Asn Ile Val Tyr Glu Lys Asn Cys Arg Asn Asp Leu Gly Leu Thr Ser
        115                 120                 125
Asp Leu His Val Tyr Asn Trp Thr Ala Gly Ala Asp Asp Gly Asp Trp
    130                 135                 140
Glu Asp Gly Thr Ser Arg Ser Gln His Leu Arg Phe Pro Asp Arg Arg
145                 150                 155                 160
Pro Phe Pro Arg Pro His Gly Trp Lys Lys Trp Ser Phe Val Tyr Val
                165                 170                 175
Phe His Thr Leu Gly Gln Tyr Phe Gln Lys Leu Gly Arg Cys Ser Ala
            180                 185                 190
Arg Val Ser Ile Asn Thr Val Asn Leu Thr Ala Gly Pro Gln Val Met
        195                 200                 205
Glu Val Thr Val Phe Arg Arg Tyr Gly Arg Ala Tyr Ile Pro Ile Ser
    210                 215                 220
Lys Val Lys Asp Val Tyr Val Ile Thr Asp Gln Ile Pro Val Phe Val
225                 230                 235                 240
Thr Met Ser Gln Lys Asn Asp Arg Asn Leu Ser Asp Glu Ile Phe Leu
                245                 250                 255
Arg Asp Leu Pro Ile Val Phe Asp Val Leu Ile His Asp Pro Ser His
            260                 265                 270
Phe Leu Asn Asp Ser Ala Ile Ser Tyr Lys Trp Asn Phe Gly Asp Asn
        275                 280                 285
Thr Gly Leu Phe Val Ser Asn Asn His Thr Leu Asn His Thr Tyr Val
    290                 295                 300
Leu Asn Gly Thr Phe Asn Leu Asn Leu Thr Val Gln Thr Ala Val Pro
305                 310                 315                 320
Gly Pro Cys Pro Pro Pro Ser Pro Ser Thr Pro Pro Pro Pro Ser Thr
                325                 330                 335
Pro Pro Ser Pro Pro Pro Ser Pro Leu Pro Thr Leu Ser Thr Pro Ser
            340                 345                 350
Pro Ser Leu Met Pro Thr Gly Tyr Lys Ser Met Glu Leu Ser Asp Ile
        355                 360                 365
Ser Asn Glu Asn Cys Arg Ile Asn Arg Tyr Gly Tyr Phe Arg Ala Thr
    370                 375                 380
Ile Thr Ile Val Glu Gly Ile Leu Glu Val Ser Ile Met Gln Ile Ala
385                 390                 395                 400
Asp Val Pro Met Pro Thr Pro Gln Pro Ala Asn Ser Leu Met Asp Phe
                405                 410                 415
Thr Val Thr Cys Lys Gly Ala Thr Pro Met Glu Ala Cys Thr Ile Ile
            420                 425                 430
Ser Asp Pro Thr Cys Gln Ile Ala Gln Asn Arg Val Cys Ser Pro Val
        435                 440                 445
Ala Val Asp Gly Leu Cys Leu Leu Ser Val Arg Arg Ala Phe Asn Gly
    450                 455                 460
Ser Gly Thr Tyr Cys Val Asn Phe Thr Leu Gly Asp Asp Ala Ser Leu
465                 470                 475                 480
Ala Leu Thr Ser Thr Leu Ile Ser Ile Pro Gly Lys Asp Pro Asp Ser
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                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
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<212> DNA
<213> Mouse

<400> 39
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gttggactcc tgggcgtcgt gtggctgctg cgcttgggcc acggcgagga gcggcggccg
120
gagacagcgg cacagcgctg cttctgccag gttagtggtt acctggacga ctgtacctgt
180
gatgtcgaga ccatcgataa gtttaataac tacagacttt tcccaagact acaaaagctt
240
cttgaaagtg actactttag atattacaag gtgaacttga agaagccttg tcctttctgg
300
aatgacatca accagtgtgg aagaagagac tgtgccgtca aaccctgcca ttctgatgaa
360
gttcctgatg gaattaagtc tgcgagctac aagtattctg aggaagccaa ccgcattgaa
420
gaatgtgagc aagctgagcg acttggagcc gtggatgagt ctctgagtga ggagacccag
480
aaagctgtac ttcagtggac caagcatgat gattcgtcag acagcttctg cgaaattgac
540
gatatacagt cccccgatgc tgagtatgtg gacttactcc ttaaccctga gcgctacaca
600
ggctacaagg ggccagacgc ttggaggata tggagtgtca tctatgaaga aaactgtttt
660
aagccacaga caattcaaag gcctttggct tctgggcgag gaaaaagtaa agagaacaca
720
ttttacaact ggctagaagg cctctgtgta gaaaagagag cattctacag acttatatct
780
ggcctgcacg caagcattaa tgtgcatttg agtgcaaggt atcttttaca agatacttgg
840
ctggaaaaga aatggggtca caatgtcaca gagttccagc agcgctttga tgggattctg
900
actgaaggag aaggcccacg aaggctgagg aacttgtact tcctgtacct gatagagtta
960
agggctctct ccaaagtgct tccatttttt gagcgtccag attttcagct cttcactggg
1020
aataaagttc aggatgcaga aaacaaagcg ttacttctgg agatacttca tgaaatcaag
1080
tcatttcctt tgcacttcga tgagaattct ttttttgctg ggataaaaa cgaagcacat
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1200
ggctgcttca agtgccgcct gtggggcaag cttcagacgc aggggctggg cactgctctg
1260
aagatcttgt tttccgaaaa actgatcgca aatatgccgg aaagcggacc aagttatgag
1320
ttccagctaa ccagacaaga aatagtatca ctgtttaatg catttggaag gatttccaca
1380
agtgtgagag aactagagaa cttcaggcac ttgttacaga atgttcactg aggaggacgg
1440
ttggaatgtg cctgtttctg cacaggggaa tttgaagggc aaaatctctt ttagccccat
1500
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1560

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aaaaaaaaaa aaaaaaaaaa aaaaaaa
1587

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

<400> 40
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120
aggtgagagg cggcggcggc ggcgcggctc gggcaccggc cccccagcgg gaggatgaag
180
cggcggaacg ccgactgcag taagctccgc cgccccctga agcggaaccg gatcaccgag
240
ggtatctacg gcagtacatt tttatacctg aaattcctgg tagtgtgggc acttgtcctc
300
cttgccgact ttgtcctgga gttccgattt gaatacctgt ggccgttctg gcttttcatc
360
agaagcgtct atgattcctt cagataccaa ggactggcct tctcagtatt ttttgtttgt
420
gtagcattca cttcaaatat catatgtctc ctcttcattc ccatacaatg gctttttttc
480
gctgctagca catatgtatg ggtccagtac gtatggcaca cagaaagggg agtgtgtttg
540
cctacagtgt cactctggat cctctttgtt tatattgaag cagcaattag atttaaagat
600
ctgaaaaact ttcatgtaga cctttgtcga ccgtttgctg ctcactgcat tggatacccct
660
gtggtgactt tgggctttgg cttcaaaagt tatgtgagct acaaaatgcg gttaaggaag
720
cagaaggaag ttcagaagga gaacgagttt tacatgcagc ttcttcagca ggccctccct
780
ccagagcagc aaatgttgca gaagcaggag aaggaggctg aggaagcagc caagggattg
840
ccggacatgg attcctcgat ccttatacac cacaacggag gcatcccagc caacaaaaaa
900
ctgtccacaa cgttgccaga gatagaatat cgagaaaaag ggaaagagaa ggacaaggat
960
gccaagaaac acaaccttgg aataaataac aacaacattc tacaacctgt agactctaag
1020
atacaagaga ttgagtatat ggaaaaccat atcaatagta aaagattaaa caatgatctt
1080
gtgggaagta cagaaaatct cttaaaagag gactcatgca ctgcttcctc aaaaaattac
1140
aaaaatgcca gtggagttgt gaactcctcg cctcgaagtc acagcgctac aaatggaagc
1200
attccttcct cgtctagtaa aaacgagaag aagcagaagt gcaccagcaa gggcccgagt
1260
gcacacaagg acttaatgga gaactgtatt cctaacaacc agctgagcaa accagacgcg
1320
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1380

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gtggagcaag agctgcgcag tcagatcagc gccctctcaa gcacagagcg aggcatccgc
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1500
gtgcaaatga agcaaaaaga caagcagaat atcagccagc tagagaagaa gctaaaggct
1560
gagcaggaag cccgaagctt tgtagaaaag cagctaatgg aggagaaaaa aaggaagaag
1620
ttagaagaag ccacagctgc acgggctgtt gcctttgctg ctgcatctag gggagagtgc
1680
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1740
gacatgaaag tgaaggagga gcagatcagg gaactggaac tgaaggttca ggagcttcgg
1800
aagtacaaag aaaacgagaa ggacaccgag gtattgatgt cagccctctc cgccatgcaa
1860
gacaaaacgc aacacctaga gaacagtctc agcgcagaga cgaggatcaa gctggacctc
1920
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1980
aaagaccagg aaatcaagga cctaaaacag aaaatagctg aagtcatggc tgtcatgccc
2040
agcataacat acagtgctgc caccagtccc ctgagccccg tgtcccccca ctactcttcc
2100
aagtttgtgg agaccagccc ctctggactt gaccctaatg cctctgtcta ccagcccttg
2160
aagaagtgaa ggccaactgt gtgctcgccc aacatttgca accaggaggc ttcgaaaagc
2220
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2280
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2340
ttggaagttt ttagaagacc tcacggactt tgcagtttat ttttgttggc caacacatta
2400
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2435

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

<400> 41
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gcgcggggct cggggctcgc aggagcggct ggctcccgcg atggcgagcc tatggtgcgg
120
aaacctgctg cggctgggct cggggctcaa catgtcctgc ctggcgctgt cggtgctgct
180
gctcgcgcag ctgacaggcg ccgccaagaa ttttgaagat gtgagatgta aatgcatctg
240
ccctccctat aaagagaatc ctgggcacat ttataataag aatatatctc agaaagattg
300
tgattgcctt catgtcgtgg agcccatgcc tgtacgggga cctgatgtag aagcatactg
360

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tctacgctgt gaatgcaaat acgaagagag aagctctgtc acaatcaagg ttaccattat
420
aatttatctc tctattttgg gccttctgct tctgtacatg gtatatctta ccttagttga
480
gcccatcctg aagaggcgcc tctttggaca ctcccagctg ttgcagagcg atgatgacgt
540
tggggatcac cagccttttg caaatgccca tgatgtgctg gcccgctctc gcagccgagc
600
caatgttcta aacaaggtgg agtacgctca gcagcgctgg aagctccagg tccaggagca
660
gcgaaagtct gtcttcgacc gacacgttgt cctcagctaa ctgggaactg gaatcaggtg
720
actaggaaga acacgcagac aactgggaag aattgtctgg gtgtccgtgc gttttaatgc
780
catgtttgtt tttacaaatc cttgctggat ggaggaagac tccaaactgg aagcaaaccc
840
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<211> 1008
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<210> 46
<211> 1423

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<400> 47

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Arg Gln Val Glu Gln Glu Leu Arg Ser Gln Ile Ser Ala Leu Ser Ser
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Thr Glu Arg Gly Ile Arg Ser Glu Met Gly Gln Leu Arg Gln Glu Asn
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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
            500   505   510
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
    530   535   540
Lys Glu Asn Glu Lys Asp Thr Glu Val Leu Met Ser Ala Leu Ser Ala
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Met Gln Asp Lys Thr Gln His Leu Glu Asn Ser Leu Ser Ala Glu Thr
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Arg Ile Lys Leu Asp Leu Phe Ser Ala Leu Gly Asp Ala Lys Arg Gln
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Asp Leu Lys Gln Lys Ile Ala Glu Val Met Ala Val Met Pro Ser Ile
    610   615   620
Thr Tyr Ser Ala Ala Thr Ser Pro Leu Ser Pro Val Ser Pro His Tyr
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Ser Ser Lys Phe Val Glu Thr Ser Pro Ser Gly Leu Asp Pro Asn Ala
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Ser Val Tyr Gln Pro Leu Lys Lys
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Gly Ala Ala Lys Asn Phe Glu Asp Val Arg Cys Lys Cys Ile Cys Pro
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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

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65 70 75 80
Pro Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu
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Arg Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile
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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
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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
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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
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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
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IPEA/AU

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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
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Glu Ser Lys Thr Cys Ala Ser Asp Tyr Leu Leu Phe Ser Ser Ala Thr
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Asp Gln Tyr Gly Pro Tyr Cys Gly Ser Trp Ala Val Pro Lys Glu Leu
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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
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Phe Thr Thr Pro Gly Met Asn Ile Thr Thr Val Ala Ile Pro Ser Val
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Ile Phe Ile Ala Leu Leu Leu Thr Gly Met Gly Ile Phe Ala Ile Cys
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Lys Thr Gly Cys Trp Lys Gln Ile Lys Tyr Pro Phe Ala Arg His Gln
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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
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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
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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
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                    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
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Asp Asp Gly Tyr Ser Ala Pro Arg Asn Gly Leu Ala Pro Leu Asn Gln
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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
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Lys Val Ser Asn Ala Leu Gly Pro Gln Gly Arg Arg Leu Glu Glu Val
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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
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Ala Gly Pro His Phe Arg Arg Gln Lys Pro Lys Pro Thr Arg Lys Glu
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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
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Gly Phe Gln Asn Lys Val Arg Leu Ala Gly Gly Arg Asn Ser Glu Glu
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Gly Val Val Glu Val Gln Val Glu Val Asn Gly Val Pro Arg Trp Gly
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Thr Val Cys Ser Asp His Trp Gly Leu Thr Glu Ala Met Val Thr Cys
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Arg Gln Leu Gly Leu Gly Phe Ala Asn Phe Ala Leu Lys Asp Thr Trp
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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
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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
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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
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Lys Tyr Asp Gly Gln Arg Val Trp Leu His Asn Cys His Thr Gly Asp
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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
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18

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for the treatment of an inflammatory disorder in a patient, comprising administering to the patient a composition comprising a polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5.

2. The method of claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 90% identity to a sequence of SEQ ID NO: 30-33.

3. The method of claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 30-33.

4. A method for the treatment of a disorder of the immune system in a patient, comprising administering to the patient a composition comprising a polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5.

5. The method of claim 4, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 90% identity to a sequence of SEQ ID NO: 30-33.

6. The method of claim 4, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 30-33.

7. Use of a composition comprising a polypeptide in the manufacture of medicament for the treatment of an inflammatory disorder in a patient, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5.

8. The use of claim 7, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 90% identity to a sequence of SEQ ID NO: 30-33.

9. The use of claim 7, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 30-33.
10. Use of a composition comprising a polypeptide in the manufacture of medicament for the treatment of a disorder of the immune system in a patient, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 75% identity to a sequence of SEQ ID NO: 30-33 wherein the polypeptide has immune system modulation activity substantially identical to FGFR5.
11. The use of claim 10, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: sequences having at least 90% identity to a sequence of SEQ ID NO: 30-33.
12. The use of claim 10, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 30-33.
13. A method according to any one of claims 1 to 6, substantially as herein described with reference to any one of examples 1 to 4 and/or the sequence listing relating thereto.
14. The use according to any one of claims 7 to 12, substantially as herein described with reference to any one of examples 1 to 4 and/or the sequence listing relating thereto.

DATED this 28th day of July 2005
Shelston IP
Attorneys for: GENESIS RESEARCH AND DEVELOPMENT COPRORATION LIMITED

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