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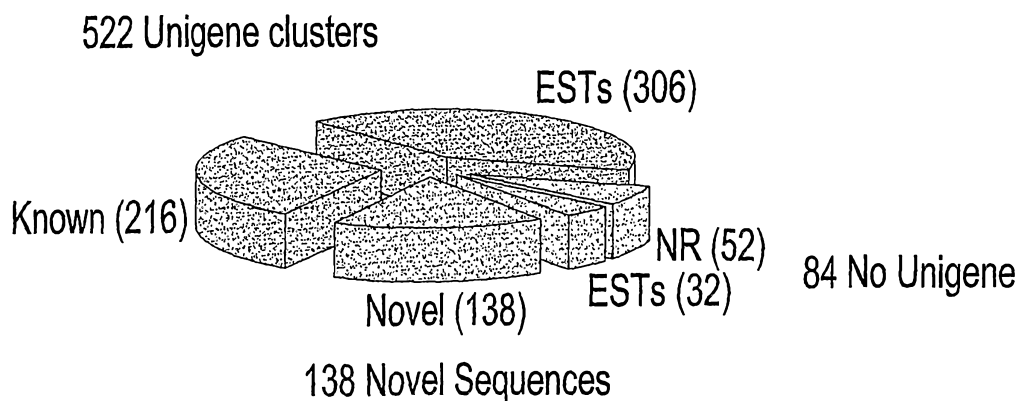
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(54) Title: POLYNUCLEOTIDES AND POLYPEPTIDE SEQUENCES INVOLVED IN THE PROCESS OF BONE REMODELING



(57) Abstract: This invention relates, in part, to unique and newly identified genetic polynucleotides involved in the process of bone remodeling; variants and derivatives of the polynucleotides and corresponding polypeptides; uses of the polynucleotides, polypeptides, variants and derivatives; and methods and compositions for the amelioration of symptoms caused by bone remodeling disorders. Disclosed in particular are, the isolation and identification of polynucleotides, polypeptides, variants and derivatives involved in osteoclast activity, validation of the identified polynucleotides for their potential as therapeutic targets and use of the polynucleotides, polypeptides, variants and derivatives for the amelioration of disease states and research purposes.

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POLYNUCLEOTIDES AND POLYPEPTIDE SEQUENCES INVOLVED IN THE PROCESS OF BONE REMODELING

This application is the Australian national phase of International Patent Application No. PCT/CA2005/001917 filed December 13, 2005, which claims priority from USSN 60/634,981, filed December 13, 2004, which applications are incorporated herein by way of reference in their entirety.

FIELD OF THE INVENTION

This invention relates, in part, to unique and newly identified genetic polynucleotides involved in the process of bone remodeling; variants and derivatives of the polynucleotides and corresponding polypeptides; uses of the polynucleotides, polypeptides, variants and derivatives; methods and compositions for the amelioration of symptoms caused by bone remodeling disorders, including but not limited to osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hypothyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Tumer syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets (including vitamin D dependent, type I and II, and x-linked hypophosphatemic rickets), fibrogenesis imperfecta ossium, osteosclerotic disorders such as pycnodysostosis and damage caused by macrophage-mediated inflammatory processes.

In particular, this invention relates to polynucleotide expression profiles of active osteoclasts, the isolation and identification of polynucleotides, polypeptides, variants and derivatives involved in osteoclast activity, validation of the identified polynucleotides for their potential as therapeutic targets and use of the polynucleotides, polypeptides, variants and derivatives for the amelioration of disease states and research purposes, as well as in diagnosis of disease states or in the predisposition to develop same.

BACKGROUND OF THE INVENTION

Bone is a dynamic connective tissue comprised of functionally distinct cell populations

required to support the structural, mechanical and biochemical integrity of bone and the human body's mineral homeostasis. The principal cell types involved include, osteoblasts responsible for bone formation and maintaining bone mass, and osteoclasts responsible for bone resorption. Osteoblasts and osteoclasts function in a dynamic process termed bone remodeling. The development and proliferation of these cells from their progenitors is governed by networks of growth factors and cytokines produced in the bone microenvironment as well as by systemic hormones. Bone remodeling is ongoing throughout the lifetime of the individual and is necessary for the maintenance of healthy bone tissue and mineral homeostasis. The process remains largely in equilibrium and is governed by a complex interplay of systemic hormones, peptides and downstream signalling pathway proteins, local transcription factors, cytokines, growth factors and matrix remodeling genes.

Any interference or imbalance arising in the bone remodeling process can produce skeletal disease, with the most common skeletal disorders characterized by a net decrease in bone mass. A primary cause of this reduction in bone mass is an increase in osteoclast number and/or activity. The most common such disease, and perhaps the most well known, is osteoporosis occurring particularly in women after the onset of menopause. In fact osteoporosis is the most significant underlying cause of skeletal fractures in late middle-aged and elderly women. While estrogen deficiency has been strongly implicated as a factor in postmenopausal osteoporosis, there is longstanding evidence that remodeling is a locally controlled process being that it takes place in discrete packets throughout the skeleton as first described by Frost over forty years ago (Frost H.M. 1964).

Since bone remodeling takes place in discrete packets, locally produced hormones and enzymes may be more important than systemic hormones for the initiation of bone resorption and the normal remodeling process. Such local control is mediated by osteoblasts and osteoclasts in the microenvironment in which they operate. For example, osteoclasts attach to the bone matrix and form a separate compartment between themselves and the bone surface delimited by a sealing zone formed by a ring of actin surrounding the ruffled border. Multiple small vesicles transport enzymes

toward the bone matrix and internalize partially digested bone matrix. The microenvironment within the sealing zone is rich with the presence of lysosomal enzymes and is highly acidic compared to the normal physiological pH of the body. The ruffled border membrane also expresses RANK, the receptor for RANKL, and
5 macrophage-colony stimulating factor (M-CSF) receptor, both of which are responsible for osteoclast differentiation, as well as the calcitonin receptor capable of rapidly inactivating the osteoclast (Baron, R. 2003).

In a complex pattern of inhibition and stimulation not yet fully understood, growth hormone, insulin-like growth factor-1, the sex steroids, thyroid hormone, calcitrophic
10 hormones such as PTH and prostaglandin E2, various cytokines, such as interleukin-1 beta, interleukin-6, and tumour necrosis factor-alpha, and 1,25-dihydroxyvitamin D (calcitriol) act co-ordinately in the bone remodeling process (Jilka et al. 1992; Poli et al. 1994; Srivastava et al. 1998; de Vemejoul 1996).

Thus, it stands to reason that the unique local environments created by these
15 specialized cells is due to the expression of either unique genetic sequences not expressed in other tissues and/or splice variants of polynucleotides and polypeptides expressed in other tissues. The isolation and identification of polynucleotides, polypeptides and their variants and derivatives specific to osteoclast activity will permit a clearer understanding of the remodeling process and offer tissue specific therapeutic
20 targets for the treatment of disease states related to bone remodeling.

Many diseases linked to bone remodeling are poorly understood, generally untreatable or treatable only to a limited extent. For example, osteoarthritis is difficult to treat as there is no cure and treatment focuses on relieving pain and preventing the affected joint from becoming deformed. Non-steroidal anti-inflammatory drugs (NSAIDs) are
25 generally used to relieve pain.

Another example is osteoporosis where the only current medications approved by the FDA for use in the United States are the anti-resorptive agents that prevent bone

breakdown. Estrogen replacement therapy is one example of an anti-resorptive agent. Others include alendronate (Fosamax- a biphosphonate anti-resorptive), risedronate (Actonel- a bisphosphonate anti-resorptive), raloxifene (Evista- selective estrogen receptor modulator (SERM)), calcitonin (Calcimar- a hormone), and parathyroid hormone/teriparatide (Forteo- a synthetic version of the human hormone, parathyroid hormone, which helps to regulate calcium metabolism).

Bisphosphonates such as alendronate and risedronate bind permanently to the surface of bone and interfere with osteoclast activity. This allows the osteoblasts to outpace the rate of resorption. The most common side effects are nausea, abdominal pain and loose bowel movements. However, alendronate is reported to also cause irritation and inflammation of the esophagus, and in some cases, ulcers of the esophagus. Risedronate is chemically different from alendronate and has less likelihood of causing esophagus irritation. However, certain foods, calcium, iron supplements, vitamins and minerals, or antacids containing calcium, magnesium, or aluminium can reduce the absorption of risedronate, thereby resulting in loss of effectiveness.

The most common side effect of Raloxifen and other SERMS (such as Tamoxifen) are hot flashes. However, Raloxifene and other hormone replacement therapies have been shown to increase the risk of blood clots, including deep vein thrombosis and pulmonary embolism, cardiovascular disease and cancer.

Calcitonin is not as effective in increasing bone density and strengthening bone as estrogen and the other anti-resorptive agents. Common side effects of either injected or nasal spray calcitonin are nausea and flushing. Patients can develop nasal irritations, a runny nose, or nosebleeds. Injectable calcitonin can cause local skin redness at the site of injection, skin rash, and flushing.

A situation demonstrative of the link between several disorders or disease states involving bone remodeling is that of the use of etidronate (Didronel) first approved by

the FDA to treat Paget's disease. Paget's disease is a bone disease characterized by a disorderly and accelerated remodeling of the bone, leading to bone weakness and pain. Didronel has been used 'off-label' and in some studies shown to increase bone density in postmenopausal women with established osteoporosis. It has also been
5 found effective in preventing bone loss in patients requiring long-term steroid medications (such as Prednisone or Cortisone). However, high dose or continuous use of Didronel can cause another bone disease called osteomalacia. Like osteoporosis, osteomalacia can lead to weak bones with increased risk of fractures. Because of osteomalacia concerns and lack of enough studies yet regarding reduction in the rate
10 of bone fractures, the United States FDA has not approved Didronel for the treatment of osteoporosis.

Osteoporosis therapy has been largely focused on antiresorptive drugs that reduce the rate of bone loss but emerging therapies show promise in increasing bone mineral density instead of merely maintaining it or slowing its deterioration. The osteoporosis
15 early stage pipeline consists largely of drug candidates in new therapeutic classes, in particular cathepsin K inhibitors, osteoprotegerin and calcilytics as well as novel bisphosphonates. Some of these are examples where novel drugs exploiting genomics programs are being developed based on a deeper understanding of bone biology and have the potential to change the face of treatment of bone disorders in the long term.

20 The present invention satisfies a need in the art. There thus remains a need to better understand the bone remodeling process and to provide new compositions that are useful for the diagnosis, prognosis, treatment, prevention and evaluation of therapies for bone remodeling and associated disorders. A method for analysing polynucleotide expression patterns has been developed and applied to identify polynucleotides,
25 polypeptides, variants and derivatives specifically involved in bone remodeling.

The present invention seeks to meet these and other needs.

The present description refers to a number of documents, the content of which is

herein incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention relates to polynucleotides comprising sequences involved in the process of bone remodeling including their open reading frame, substantially identical
5 sequences, substantially complementary sequences and fragments thereof.

The present invention relates to polypeptide comprising sequences involved in the process of bone remodeling including biologically active analogs and biologically active fragments thereof.

The present invention also relates to compositions that are useful for the diagnosis,
10 prognosis, treatment, prevention and/or evaluation of therapies for bone remodeling and associated disorders.

In addition, the present invention relates to a method for analyzing polynucleotide expression patterns, and applied to identify polynucleotides, polypeptides, variants and derivatives specifically involved in bone remodeling.

15 Furthermore, the present invention relates to polynucleotide and polypeptide sequences, variants and derivatives thereof which have been validated as potential therapeutic targets.

The identification of gene products involved in regulating osteoclast differentiation and function has led to the discovery of novel targets for the development of new and
20 specific therapies of disease states characterized by abnormal bone remodeling.

The present invention relates to polynucleotide expression profiles of osteoclasts, the isolation and identification of polynucleotides, their corresponding polypeptides, variants and derivatives involved in osteoclast activity, validation of these identified

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elements for their potential as therapeutic targets and use of said polynucleotides, polypeptides, variants and derivatives for the amelioration of disease states.

5 In one example, the present invention provides polynucleotides and related polypeptides that have been isolated and identified. More specifically, the invention provides polynucleotides comprising any one of SEQ. ID. NOs:1 to 57 or 83 to 89, their coding sequence (open reading frame) and related polypeptides comprising any one of SEQ ID NO.: 93 to 155 which have been shown to be upregulated in a highly specific fashion in osteoclasts.

10 The present invention more particularly relates to polynucleotides, their coding sequence (open reading frame), and related polypeptides, which have been demonstrably shown to be necessary or crucial for osteoclast differentiation (e.g. SEQ. ID. NOs:1 to 7, 88 and 89).

15 Of the polynucleotides (e.g. SEQ. ID. NOs:8 to 56) whose gene expression is upregulated, 37 were tested in the model using siRNA for biological validation leaving 12 still to be tested, 28 does not appear to phenotypically perturb osteoclast differentiation in the model used whereas 9 did (SEQ ID NO.:16, SEQ ID NO.:19, SEQ ID NO.:21, SEQ ID NO.:24, SEQ ID NO.:29, SEQ ID NO.:31, SEQ ID NO.:37 and SEQ ID NO.:42). However, a more discrete effect not phenotypically measurable cannot be ruled out for those 28. Without being limited to a particular model, this may be due in
20 part to non-functional siRNA and/or to their roles in the downstream bone remodeling activities of osteoclasts. For example, polynucleotides for cathepsin K (CTSK) and matrix metalloproteinase 9 (MMP-9) are well known markers which are essential for osteoclast activities in bone remodelling but are not required for osteoclast differentiation. NSEQ refers generally to polynucleotide sequences of the present
25 invention and includes for example, SEQ. ID. NOs:1 to 56 and 83 to 89, whereas PSEQ refers generally to polypeptide sequences of the present invention and includes, for example, SEQ ID NO.:93 to 99 and 101 to 155. Of course it will be understood that NSEQ also encompasses polynucleotide sequences which are

designed or derived from SEQ. ID. NOs:1 to 57 and 83 to 89 and more particularly from their coding sequence. Non-limiting examples of such sequences are disclosed herein (e.g. SEQ ID Nos 64-82 and 90).

5 The present invention also provides a method of using a polynucleotide selected from SEQ ID NO's 1 to 57 and 83 to 89 and more particularly their coding sequence and encoded polypeptides thereof to screen a library of molecules or compounds (e.g. DNA molecules, RNA molecules, PNAs, mimetics and proteins) to identify or purify a ligand which specifically binds the polynucleotide by combining a polynucleotide with a library of molecules or compounds under conditions to allow specific binding, and
10 detecting specific binding, thereby identifying or purifying a ligand which specifically binds the polynucleotide.

The present invention relates in one aspect thereof to an isolated polynucleotide sequence having at least from about 80% to about 100% (e.g., 80%, 90%, 95%, etc.) nucleic acid sequence identity to a polynucleotide sequence selected from the group
15 consisting of polynucleotides comprising (a) any one of a SEQ. ID. NOs:1 to 57 and 83 to 89; (b) an open reading frame of (a); (c) a full complement of (a) or (b), and ;(d) a fragment of any one of (a) to (c).

Complements of the isolated polynucleotide sequence encompassed by the present invention may be those, for example, which hybridize under high stringency conditions
20 to any of the nucleotide sequences in (a), or (b). The high stringency conditions may comprise, for example, a hybridization reaction at 65°C in 5X SSC, 5X Denhardt's solution, 1% SDS, and 100 µg/ml denatured salmon sperm DNA.

In accordance with the present invention, the polynucleotide sequence may be used, for example, in the treatment of diseases or disorders involving bone remodelling.

25 Fragments of polynucleotides may be used, for example, as probes for determining the presence of the isolated polynucleotide (or its complement or fragments thereof) in

a sample, cell, tissue, etc. for experimental purposes or for the purpose of diagnostic of a diseases or disorders involving bone remodelling.

The present invention also relates to a combination comprising a plurality of polynucleotides (substantially purified and/or isolated) that may be co-expressed with
5 one or more genes known to be involved in bone remodelling, the plurality of polynucleotides may be selected, for example, from the group consisting of a polynucleotide comprising (a) any one of SEQ. ID. NOs:1 to 57, 83 to 89; (b) an open reading frame (a) ;(c) a full complement of (a) or (b); (d) a sequence that hybridizes under high stringency conditions to any one of the nucleotide sequences in (a), or (b)
10 and; (e) fragments of (a), (b) , (c) or (d).

The present invention further relates to a polynucleotide encoding any one of the polypeptides described herein. In accordance with the present invention, the polynucleotide (RNA, DNA, etc.) may encode a polypeptide which may be selected from the group consisting of any one of SEQ ID NO.:93 to 155, analogs or fragments
15 thereof (e.g., biologically active fragments, immunologically active fragments, etc.).

The present invention also relates to an isolated nucleic acid molecule comprising the polynucleotides of the present invention, operatively linked to a nucleotide sequence encoding a heterologous polypeptide thereby encoding a fusion polypeptide.

The invention further relates to a polypeptide encoded by a polynucleotide of SEQ. ID. NOs:1 to 56 or 83 to 89 and more particularly from the open reading frame of any one of SEQ. ID. NOs:1 to 56 or 83 to 89, or a portion thereof, comprising the product of a gene that is co-expressed with one or more genes known to be involved in bone remodeling.
20

The invention additionally relates to the use of the polypeptide or a portion thereof to screen a library of molecules or compounds (DNA molecules, RNA molecules, PNAs, mimetics, proteins, agonists, antagonists, and antibodies) to identify or purify at least
25

one ligand which specifically binds the polypeptide by combining the polypeptide or a portion thereof with the library of molecules or compounds under conditions to allow specific binding, and detecting specific binding between the polypeptide and ligand, thereby identifying or purifying a ligand which specifically binds the polypeptide.

- 5 Isolated naturally occurring allelic variant are also encompassed by the present invention as well as synthetic variants (e.g., made by recombinant DNA technology or by chemical synthesis, etc.) such as biologically active variant which may comprise one or more conservative amino acid substitutions (compared to a naturally occurring polypeptide).
- 10 The present invention, further provides a vector (mammalian, bacterial, viral, etc.) comprising the polynucleotides described herein or fragments thereof, such as an expression vector. The vector may further comprise a nucleic acid sequence which may help in the regulation of expression of the polynucleotide and/or a nucleotide sequence encoding a tag (e.g., affinity tag; HA, GST, His etc.).
- 15 In accordance with the present invention, an expression vector may comprise, for example, the following operatively linked elements:
- a) a transcription promoter;
 - b) a polynucleotide segment (which may comprise an open reading frame); and
 - 20 c) a transcription terminator.

The invention also relates to an expression vector comprising a polynucleotide described herein, a host cell transformed with the expression vector and a method for producing a polypeptide of the present invention.

- 25 More particularly, the present invention therefore provides a cell which may be genetically engineered to contain and/or to express the polynucleotide (including complements and fragments) and/or polypeptides of the present invention. The cell

may be, for example, a mammalian cell, an insect cell, a bacteria cell, etc.

The present invention, therefore provides a host cell which may comprise a vector as described herein. The cell may be, for example, mammalian cell, an insect cell, a bacteria, etc. The cell may be able to express or expresses a polypeptide encoded by
5 the polynucleotide described herein.

Methods of producing the polypeptides of the present invention encompassed herewith includes for example, culturing the cell in conditions allowing the expression of the polypeptide. The polypeptide may be recovered, for example, from cell lysate or from the cell supernatant.

10 The present invention also relates to a method of using a polynucleotide sequence described herein to screen a library of molecules or compounds including but not limited to, DNA molecules, RNA molecules, PNAs (peptide nucleic acids), peptides, ribozymes, antibodies, agonists, antagonists, immunoglobulins, inhibitors, proteins including transcription factors, enhancers, repressors, and drugs and the like which
15 regulate the activity of the selected polynucleotide sequence in a biological system, to identify or purify a ligand which may specifically bind the polynucleotide by combining a polynucleotide with a library of molecules or compounds under conditions which may allow specific binding, and detecting specific binding, thereby identifying or purifying a ligand which may specifically bind the polynucleotide.

20 The antagonist, agonist, ligand thus identified may be used in the treatment of bone remodelling diseases or disorders.

The invention relates to the use of at least one polynucleotide comprising any one of SEQ. ID. NOs:1 to 57 and/or 83 to 89, their coding sequence, substantially identical sequences, substantially complementary sequences and fragments thereof on an
25 array and for the use of that array in a method for diagnosing a bone remodeling disease or disorder by hybridizing the array with a patient sample under conditions to

allow complex formation, detecting complex formation, and comparing the amount of complex formation in the patient sample to that of standards for normal and diseased tissues wherein the complex formation in the patient sample indicates the presence of a bone remodeling disease or disorder. Of course, the use of a polynucleotide of the present invention in a diagnosis method is not dependent exclusively by way of an assay. The sequence or sequences may be used in conventionally used diagnosis methods known in the art.

The present invention also relates to a method of ameliorating bone remodelling disease or disorder symptoms, or for inhibiting or delaying bone disease or disorder, the method may comprise: contacting a compound capable of specifically inhibiting activity or expression of a polynucleotide sequence described herein or a polypeptide described herein, in osteoclasts so that symptoms of the bone remodelling disease or disorder may be ameliorated, or the disease or disorder may be prevented, delayed or lowered.

The present invention further relates to a method for ameliorating bone remodelling disease or disorder symptoms, or for inhibiting or delaying bone disease or disorder, the method may comprise: contacting a compound capable of specifically promoting activity or expression of a polynucleotide sequence described herein or a polypeptide described herein, in osteoclasts so that symptoms of the bone remodelling disease or disorder may be ameliorated, or the disease or disorder may be prevented, delayed or lowered.

The present invention also relates to a method of treating a condition in a mammal characterized by a deficiency in, or need for, bone growth or replacement and/or an undesirable level of bone resorption, which method may comprise administering to a mammalian subject in need of such treatment an effective amount of a suitable compound described herein.

The present invention further relates to a method of using a polynucleotide sequence

described herein, a polypeptide described herein on an array and for the use of the array in a method for diagnosing a bone remodelling disease or disorder by hybridizing the array with a patient sample under conditions to allow complex formation, detecting complex formation, and comparing the amount of complex formation in the patient sample to that of standards for normal and diseased tissues wherein the complex formation in the patient sample may indicate the presence of a bone remodelling disease or disorder.

In accordance with the present invention the isolated polynucleotide sequence described herein, the antagonist described herein, the ligand described herein, or the method described herein, may be used for diseases or disorders which may be selected from the group consisting of, but not limited to, osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Tumer syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets (including vitamin D dependent, type I and II, and x-linked hypophosphatemic rickets), fibrogenesis imperfecta ossium, osteosclerotic disorders such as pycnodysostosis and damage caused by macrophage-mediated inflammatory processes.

In accordance with the present invention, the method of administration may be selected from, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In accordance with the present invention, the polynucleotide sequence described herein may be used for somatic cell gene therapy or for stem cell gene therapy.

The invention also relates to a pharmaceutical composition comprising a

polynucleotide described herein, a polypeptide encoded by the selected polynucleotide, a portion thereof, a ligand (agonist or antagonist) identified or purified using a selected polynucleotide or a polypeptide encoded by the selected polynucleotide, or a portion thereof, which modulates the activity (activation, enhancement or inhibition) of the selected polynucleotide or a polypeptide encoded thereby, a portion thereof, and a suitable pharmaceutical carrier.

Additionally, the invention relates to products, compositions, processes and methods that comprises a polynucleotide described herein, a polypeptide encoded by the polynucleotides, a portion thereof, their variants or derivatives, for research, biological, clinical and therapeutic purposes.

The NSEQs and PSEQs may be used in diagnosis, prognosis, treatment, prevention, and selection and evaluation of therapies for diseases and disorders involving bone remodeling including, but not limited to, osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Turner syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets (including vitamin D dependent, type I and II, and x-linked hypophosphatemic rickets), fibrogenesis imperfecta ossium, osteosclerotic disorders such as pycnodysostosis and damage caused by macrophage-mediated inflammatory processes.

Use of NSEQ as a Screening Tool

The polynucleotides obtained by the present invention may be used to detect and isolate expression products, for example, mRNA, complementary DNAs (cDNAs) and proteins derived from or homologous to the NSEQs. In one embodiment, the expression of mRNAs homologous to the NSEQs of the present invention may be

detected, for example, by hybridization analysis, reverse transcription and *in vitro* nucleic acid amplification methods. Such procedures permit detection of mRNAs in a variety of tissue types or at different stages of development. The subject nucleic acids which are expressed in a tissue-specific or a developmental-stage-specific manner are
5 useful as tissue-specific markers or for defining the developmental stage of a sample of cells or tissues that may define a particular disease state. One of skill in the art may readily adapt the NSEQs for these purposes.

Those skilled in the art will also recognize that the NSEQs, and its expression products such as cDNA nucleic acids and genomic DNA may be used to prepare short
10 oligonucleotides sequences. For example, oligonucleotides having ten to twelve nucleotides or more may be prepared which hybridize specifically to the present NSEQs and cDNAs and allow detection, identification and isolation of unique nucleic sequences by hybridization. Sequences of for example, at least 15-20 nucleotides may be used and selected from regions that lack homology to other known sequences.
15 Sequences of 20 or more nucleotides that lack such homology show an increased specificity toward the target sequence. Useful hybridization conditions for probes and primers are readily determinable by those of skill in the art. Stringent hybridization conditions encompassed herewith are those that may allow hybridization of nucleic acids that are greater than 90% homologous but which may prevent hybridization of
20 nucleic acids that are less than 70% homologous. The specificity of a probe may be determined by whether it is made from a unique region, a regulatory region, or from a conserved motif. Both probe specificity and the stringency of diagnostic hybridization or amplification (maximal, high, intermediate, or low) reactions may be determined whether the probe identifies exactly complementary sequences, allelic variants, or
25 related sequences. Probes designed to detect related sequences may have at least 50% sequence identity to any of the selected polynucleotides.

It is to be understood herein that the NSEQs (substantially identical sequences and fragments thereof) may hybridize to a substantially complementary sequence found in a test sample. Additionally, a sequence substantially complementary to NSEQ may
30 bind a NSEQ found in a test sample.

Skilled practitioners will also recognize that the NSEQs and PSEQs may be used to screen a library of molecules for specific binding affinity. Typical assays may be used to screen a library of DNA molecules, RNA molecules, PNAs (peptide nucleic acids), peptides, ribozymes, antibodies, agonists, antagonists, immunoglobulins, inhibitors, proteins including transcription factors, enhancers, repressors, and drugs and the like which regulate the activity of the selected polynucleotide sequence in a biological system. Typical assays may involve providing a library of molecules, combining the polynucleotide sequence or a fragment thereof with the library of molecules under conditions suitable to allow specific binding, and detecting specific binding to identify or purify, at least one molecule (ligand) which may specifically bind the polynucleotide sequence. One of skill in the art may readily adapt the NSEQs for these purposes.

Those of skill in the art may readily label the NSEQs and PSEQs by standard methods to add them to a sample from a subject under conditions for the formation and detection of hybridization complexes. After incubation the sample may be washed, and the signal associated with hybrid complex formation may be quantified and compared with a standard or normal value. Standard or normal values may be derived from any control sample, typically one that may be free of a suspect disease. If the amount of signal in the subject sample is altered in comparison to the standard value, then the presence of altered levels of expression in the sample may indicate the presence of the disease. Qualitative and quantitative methods for comparing the hybridization complexes formed in subject samples with previously established standards are well known in the art.

Furthermore, a probe may be labelled by any procedure known in the art, for example by incorporation of nucleotides linked to a "reporter molecule". A "reporter molecule", as used herein, may be a molecule that provides an analytically identifiable signal allowing detection of a hybridized probe. Detection may be either qualitative or quantitative. Commonly used reporter molecules include fluorophores, enzymes, biotin, chemiluminescent molecules, bioluminescent molecules, digoxigenin, avidin, streptavidin or radioisotopes. Commonly used enzymes include horseradish peroxidase, alkaline phosphatase, glucose oxidase and β -galactosidase, among

others. Enzymes may be conjugated to avidin or streptavidin for use with a biotinylated probe. Similarly, probes may be conjugated to avidin or streptavidin for use with a biotinylated enzyme. Incorporation of a reporter molecule into a DNA probe may be by any method known to the skilled artisan, for example by nick translation, primer extension, random oligo priming, by 3' or 5' end labeling or by other means. In addition, hybridization probes include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro. The labelled polynucleotide sequences may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; and in micro arrays utilizing samples from subjects to detect altered expression. Oligonucleotides useful as probes for screening of samples by hybridization assays or as primers for amplification may be packaged into kits. Such kits may contain the probes or primers in a pre-measured or predetermined amount, as well as other suitably packaged reagents and materials needed for the particular hybridization or amplification protocol.

In another embodiment, the invention entails a substantially purified polypeptide encoded by the polynucleotides of NSEQs, polypeptide analogs or polypeptide fragments thereof. The polypeptides whether in a premature, mature or fused form, may be isolated from lysed cells, or from the culture medium, and purified to the extent needed for the intended use. One of skill in the art may readily purify these proteins, polypeptides and peptides by any available procedure. For example, purification may be accomplished by salt fractionation, size exclusion chromatography, ion exchange chromatography, reverse phase chromatography, affinity chromatography and the like.

The invention further provides for a polypeptide encoded by the polynucleotides of NSEQs, or a portion thereof, comprising the product of a gene that is co-expressed with one or more genes known to be involved in bone remodeling. The invention additionally provides for the use of the polypeptide or a portion thereof to screen a library of molecules or compounds (DNA molecules, RNA molecules, PNAs, mimetics, proteins, agonists, antagonists, and antibodies) to identify or purify at least one ligand which specifically binds the polypeptide by combining the polypeptide or a portion

thereof with the library of molecules or compounds under conditions to allow specific binding, and detecting specific binding between the polypeptide and ligand, thereby identifying or purifying a ligand which specifically binds the polypeptide. One of skill in the art may readily adapt the NSEQs for these purposes.

- 5 The portion of a polypeptide employed in such screening may be free in solution, affixed to an abiotic or biotic substrate or located intra-cellularly. Specific binding between the polypeptide and the molecule may be measured. The assay may be used to screen a library of DNA molecules, RNA molecules, PNAs, peptides, mimetics, ribozymes, antibodies, agonists, antagonists, immunoglobulins, inhibitors, peptides,
10 polypeptides, drugs and the like, which may specifically bind the polypeptide. Many such assay methodologies are well known in the art and may be readily adapted by a skilled practitioner.

Use of NSEQ for Development of an Expression System

- In order to express a biologically active polypeptide, NSEQ, or derivatives thereof, may
15 be inserted into an expression vector, i.e., a vector that contains the elements for transcriptional and translational control of the inserted coding sequence in a particular host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' un-translated regions. Methods that are well known to those skilled in the art may be used to construct such expression vectors.
20 These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination.

- A variety of expression vector/host cell systems known to those of skill in the art may be utilized to express NSEQ. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid
25 DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with baculovirus vectors; plant cell systems transformed with viral or bacterial expression vectors; or animal cell systems. For long-term production of

recombinant proteins in mammalian systems, stable expression in cell lines may be effected. For example, NSEQ may be transformed into cell lines using expression vectors that may contain viral origins of replication and/or endogenous expression elements and a selectable or visible marker gene on the same or on a separate vector.

5 The invention is not to be limited by the vector or host cell employed.

In general, host cells that contain NSEQ and that express a polypeptide encoded by the NSEQ, or a portion thereof, may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques that include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or amino acid sequences. Immunological methods for detecting and measuring the expression of polypeptides using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs),
10 radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). Those of skill in the art may readily adapt these methodologies to the present invention.

The present invention additionally relates to a bioassay for evaluating compounds as potential antagonists of the polypeptide described herein, the bioassay may comprise:

- a) culturing test cells in culture medium containing increasing
20 concentrations of at least one compound whose ability to inhibit the action of a polypeptide described herein is sought to be determined, wherein the test cells may contain a polynucleotide sequence described herein in a form having improved trans-activation transcription activity, relative to wild-type polynucleotide, and comprising a response element operatively linked to a reporter gene; and thereafter
- 25 b) monitoring in the cells the level of expression of the product of the reporter gene as a function of the concentration of the potential antagonist compound in the culture medium, thereby indicating the ability of the potential antagonist compound to inhibit activation of the polypeptide encoded by, the polynucleotide sequence described herein.

The present invention further relates to a bioassay for evaluating compounds as potential agonists for a polypeptide encoded by the polynucleotide sequence described herein, the bioassay may comprise:

- 5 a) culturing test cells in culture medium containing increasing concentrations of at least one compound whose ability to promote the action of the polypeptide encoded by the polynucleotide sequence described herein is sought to be determined, wherein the test cells may contain a polynucleotide sequence described herein in a form having improved trans-activation transcription activity, relative to wild-type polynucleotide, and comprising a response element operatively linked to a
10 reporter gene; and thereafter
- b) monitoring in the cells the level of expression of the product of the reporter gene as a function of the concentration of the potential agonist compound in the culture medium, thereby indicating the ability of the potential agonist compound to promote activation of a polypeptide encoded by the polynucleotide sequence
15 described herein.

Host cells transformed with NSEQ may be cultured under conditions for the expression and recovery of the polypeptide from cell culture. The polypeptide produced by a transgenic cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression
20 vectors containing NSEQ may be designed to contain signal sequences that direct secretion of the polypeptide through a prokaryotic or eukaryotic cell membrane. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express the polypeptide encoded by NSEQ. The nucleotide
25 sequences of the present invention may be engineered using methods generally known in the art in order to alter the nucleotide sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide
30 sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation

patterns, change codon preference, produce splice variants, and so forth.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed polypeptide in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing, which cleaves a "prepro" form of the polypeptide, may also be used to specify protein targeting, folding, and/or activity. Different host cells that have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and W138) are available commercially and from the American Type Culture Collection (ATCC) and may be chosen to ensure the correct modification and processing of the expressed polypeptide.

Those of skill in the art will readily appreciate that natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence resulting in translation of a fusion polypeptide containing heterologous polypeptide moieties in any of the aforementioned host systems. Such heterologous polypeptide moieties may facilitate purification of fusion polypeptides using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein, thioredoxin, calmodulin binding peptide, 6-His (His), FLAG, c-myc, hemagglutinin (HA), and monoclonal antibody epitopes.

In yet a further aspect, the present invention relates to an isolated polynucleotide which may comprise a nucleotide sequence encoding a fusion protein, the fusion protein may comprise a fusion partner fused to a peptide fragment of a protein encoded by, or a naturally occurring allelic variant polypeptide encoded by, the polynucleotide sequence described herein, which peptide fragment, when administered to a member of a mammalian species, may be capable of inducing the production of antibodies that bind specifically to the protein encoded by, or a naturally occurring allelic variant polypeptide encoded by, the polynucleotide sequence

described herein.

Those of skill in the art will also readily recognize that the nucleic acid and polypeptide sequences may be synthesized, in whole or in part, using chemical or enzymatic methods well known in the art. For example, peptide synthesis may be performed
5 using various solid-phase techniques and machines such as the ABI 431A Peptide synthesizer (PE Biosystems) may be used to automate synthesis. If desired, the amino acid sequence may be altered during synthesis and/or combined with sequences from other proteins to produce a variant protein.

Use of NSEQ as a Diagnostic Screening Tool

- 10 The skilled artisan will readily recognize that NSEQ may be used for diagnostic purposes to determine the absence, presence, or altered expression (i.e. increased or decreased compared to normal) of the gene. The polynucleotides may be at least 10 nucleotides long or at least 12 nucleotides long, or at least 15 nucleotides long up to any desired length and may comprise complementary RNA and DNA molecules,
15 branched nucleic acids, and/or peptide nucleic acids (PNAs). In one alternative, the polynucleotides may be used to detect and quantify gene expression in samples in which expression of NSEQ is correlated with disease. In another alternative, NSEQ may be used to detect genetic polymorphisms associated with a disease. These polymorphisms may be detected in the transcript cDNA.
- 20 The invention provides for the use of at least one polynucleotide comprising NSEQ (e.g., an open reading frame of NSEQ, a substantially complementary sequence, a substantially identical sequence, and fragments thereof) on an array and for the use of that array in a method for diagnosing a bone remodeling disease or disorder by hybridizing the array with a patient sample under conditions to allow complex
25 formation, detecting complex formation, and comparing the amount of complex formation in the patient sample to that of standards for normal and diseased tissues wherein the complex formation in the patient sample indicates the presence of a bone

remodeling disease or disorder.

In another embodiment, the present invention provides one or more compartmentalized kits for detection of bone resorption disease states. A first kit has a receptacle containing at least one isolated probe. Such a probe may be a nucleic acid
5 fragment which is present/absent in the genomic DNA of normal cells but which is absent/present in the genomic DNA of affected cells. Such a probe may be specific for a DNA site that is normally active/inactive but which may be inactive/active in certain cell types. Similarly, such a probe may be specific for a DNA site that may be abnormally expressed in certain cell types. Finally, such a probe may identify a
10 specific DNA mutation. By specific for a DNA site is meant that the probe may be capable of hybridizing to the DNA sequence which is mutated, or may be capable of hybridizing to DNA sequences adjacent to the mutated DNA sequences. The probes provided in the present kits may have a covalently attached reporter molecule. Probes and reporter molecules may be readily prepared as described above by those of skill
15 in the art.

Use of NSEQ as a Therapeutic

One of skill in the art will readily appreciate that the expression systems and assays discussed above may also be used to evaluate the efficacy of a particular therapeutic treatment regimen, in animal studies, in clinical trials, or to monitor the treatment of an
20 individual subject. Once the presence of disease is established and a treatment protocol is initiated, hybridization or amplification assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate the level observed in a healthy subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to
25 many years.

Therefore, in a further aspect, the present invention relates to an antibody (e.g., isolated antibody), or antigen-binding fragment thereof, that may specifically bind to a

protein or polypeptide described herein. The antibody may be, for example, a monoclonal antibody or a polyclonal antibody. The antibody may originate for example, from a mouse, rat or any other mammal.

5 The antibody may also be a human antibody which may be obtained, for example, from a transgenic non-human mammal capable of expressing human Ig genes. The antibody may also be a humanised antibody which may comprise, for example, one or more complementarity determining regions of non-human origin. It may also comprise a surface residue of a human antibody and/or framework regions of a human antibody. The antibody may also be a chimeric antibody which may comprise, for example,
10 variable domains of a non-human antibody and constant domains of a human antibody.

Suitable antibodies may also include, for example, an antigen-binding fragment, an Fab fragment; an F(ab')₂ fragment, and Fv fragment; or a single-chain antibody comprising an antigen-binding fragment (e.g., a single chain Fv).

15 The antibody of the present invention may be mutated and selected based on an increased affinity and/or specificity for one of a polypeptide described herein and/or based on a reduced immunogenicity in a desired host.

The antibody may further comprise a detectable label attached thereto.

20 The present invention further relates to a method of producing antibodies able to bind to one of a polypeptide, polypeptide fragments, or polypeptide analogs described herein, the method may comprise:

- a) immunizing a mammal (e.g., mouse, a transgenic mammal capable of producing human Ig, etc.) with a suitable amount of a desired polypeptide or a polypeptide fragment thereof;
- 25 b) collecting the serum from the mammal; and

- c) isolating the polypeptide-specific antibodies from the serum of the mammal.

The present invention also relates to a method of producing a hybridoma which secretes an antibody that binds to a polypeptide described herein, the method may
5 comprise:

- a) immunizing a mammal (e.g., mouse, a transgenic mammal capable of producing human Ig, etc.) with a suitable amount of a desired polypeptide, a polypeptide fragment or analog thereof;
- b) obtaining lymphoid cells from the immunized animal obtained
10 from (a);
- c) fusing the lymphoid cells with an immortalizing cell to produce hybrid cells; and
- d) selecting hybrid cells which produce antibody that specifically binds to the polypeptide, a polypeptide fragment or analog thereof.

15 The present invention further relates to a method of producing an antibody that binds to one of the polypeptide described herein, the method may comprise:

- a) synthesizing a library of antibodies on phage or ribosomes;
- b) panning the library against a sample by bringing the phage or ribosomes into contact with a composition comprising a polypeptide or
20 polypeptide fragment described herein;
- c) isolating phage which binds to the polypeptide or polypeptide fragment, and;
- d) obtaining an antibody from the phage or ribosomes.

The antibody of the present invention may thus be obtained, for example, from a
25 library (e.g., bacteriophage library) which may be prepared, for example, by

- a) extracting cells which are responsible for production of antibodies from a host mammal;
- b) isolating RNA from the cells of (a);

- c) reverse transcribing mRNA to produce cDNA;
- d) amplifying the cDNA using a (antibody-specific) primer; and
- e) inserting the cDNA of (d) into a phage display vector or ribosome display cassette such that antibodies are expressed on the phage or ribosomes.

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The host animal may be immunized with polypeptide and/or a polypeptide fragment and/or analog described herein to induce an immune response prior to extracting the cells which are responsible for production of antibodies.

10 The present invention also relates to a kit for specifically assaying a polypeptide described herein, the kit may comprise, for example, an antibody or antibody fragment capable of binding specifically to the polypeptide described herein.

Further, an antagonist, agonist, or an antibody that may bind specifically to a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof, may be administered to a subject to treat or prevent diseases or disorders associated with bone remodeling. The antagonist, antibody, or fragment may be used directly to inhibit the activity of the polypeptide or indirectly to deliver a therapeutic agent to cells or tissues that express the NSEQ. An immunoconjugate comprising a polypeptide-binding site of the antibody or the antagonist and a therapeutic agent may be administered to a subject in need to treat or prevent disease. The therapeutic agent may be a cytotoxic agent selected from a group including, but not limited to, abrin, ricin, doxorubicin, daunorubicin, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, diphtheria toxin, Pseudomonas exotoxin A and 40, radioisotopes, and glucocorticoid. Yet further, an agonist of the polypeptide may be administered to a subject to treat or prevent a disease associated with decreased expression, longevity or activity of NSEQ.

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The present invention further contemplates antibodies that may bind to the polypeptide

encoded by the polynucleotides of NSEQ, polypeptide analogs or portions thereof. Suitable antibodies may bind to unique antigenic regions or epitopes in the polypeptides, or a portion thereof. Epitopes and antigenic regions useful for generating antibodies may be found within the proteins, polypeptides or peptides by procedures
5 available to one of skill in the art. For example, short, unique peptide sequences may be identified in the proteins and polypeptides that have little or no homology to known amino acid sequences. Preferably the region of a protein selected to act as a peptide epitope or antigen is not entirely hydrophobic; hydrophilic regions are preferred because those regions likely constitute surface epitopes rather than internal regions of
10 the proteins and polypeptides. These surface epitopes are more readily detected in samples tested for the presence of the proteins and polypeptides. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. The production of antibodies is well known to one of skill in the art.

15 Peptides may be made by any procedure known to one of skill in the art, for example, by using in vitro translation or chemical synthesis procedures. Short peptides which provide an antigenic epitope but which by themselves are too small to induce an immune response may be conjugated to a suitable carrier. Suitable carriers and methods of linkage are well known in the art. Suitable carriers are typically large
20 macromolecules such as proteins, polysaccharides and polymeric amino acids. Examples include serum albumins, keyhole limpet hemocyanin, ovalbumin, polylysine and the like. One of skill in the art may use available procedures and coupling reagents to link the desired peptide epitope to such a carrier. For example, coupling reagents may be used to form disulfide linkages or thioether linkages from the carrier
25 to the peptide of interest. If the peptide lacks a disulfide group, one may be provided by the addition of a cysteine residue. Alternatively, coupling may be accomplished by activation of carboxyl groups.

The minimum size of peptides useful for obtaining antigen specific antibodies may vary widely. The minimum size must be sufficient to provide an antigenic epitope that is
30 specific to the protein or polypeptide. The maximum size is not critical unless it is

desired to obtain antibodies to one particular epitope. For example, a large polypeptide may comprise multiple epitopes, one epitope being particularly useful and a second epitope being immunodominant. Typically, antigenic peptides selected from the present proteins and polypeptides will range from 5 to about 100 amino acids in length. More typically, however, such an antigenic peptide will be a maximum of about 50 amino acids in length, and preferably a maximum of about 30 amino acids. It is usually desirable to select a sequence of about 10, 12 or 15 amino acids, up to about 20 or 25 amino acids.

Amino acid sequences comprising useful epitopes may be identified in a number of ways. For example, preparing a series of short peptides that taken together span the entire protein sequence may be used to screen the entire protein sequence. One of skill in the art may routinely test a few large polypeptides for the presence of an epitope showing a desired reactivity and also test progressively smaller and overlapping fragments to identify a preferred epitope with the desired specificity and reactivity.

Antigenic polypeptides and peptides are useful for the production of monoclonal and polyclonal antibodies. Antibodies to a polypeptide encoded by the polynucleotides of NSEQ, polypeptide analogs or portions thereof, may be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies, such as those that inhibit dimer formation, are especially preferred for therapeutic use. Monoclonal antibodies may be prepared using any technique that provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma, the human B-cell hybridoma, and the EBV-hybridoma techniques. In addition, techniques developed for the production of chimeric antibodies may be used. Alternatively, techniques described for the production of single chain antibodies may be employed. Fabs that may contain specific binding sites for a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof, may also be generated. Various immunoassays may be used to identify

antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art.

5 To obtain polyclonal antibodies, a selected animal may be immunized with a protein or polypeptide. Serum from the animal may be collected and treated according to known procedures. Polyclonal antibodies to the protein or polypeptide of interest may then be purified by affinity chromatography. Techniques for producing polyclonal antisera are well known in the art.

10 Monoclonal antibodies (Mabs) may be made by one of several procedures available to one of skill in the art, for example, by fusing antibody producing cells with immortalized cells and thereby making a hybridoma. The general methodology for fusion of antibody producing B cells to an immortal cell line is well within the province of one skilled in the art. Another example is the generation of Mabs from mRNA extracted from bone marrow and spleen cells of immunized animals using combinatorial antibody library
15 technology.

The major drawback of Mabs derived from animals or from derived cell lines is that although they may be administered to a patient for diagnostic or therapeutic purposes, they are often recognized as foreign antigens by the immune system and are unsuitable for continued use. Antibodies that are not recognized as foreign antigens by
20 the human immune system have greater potential for both diagnosis and treatment. Methods for generating human and humanized antibodies are now well known in the art.

Chimeric antibodies may be constructed in which regions of a non-human Mab are replaced by their human counterparts. A preferred chimeric antibody is one that has
25 amino acid sequences that comprise one or more complementarity determining regions (CDRs) of a non-human Mab that binds to a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof, grafted to human framework (FW)

regions. Methods for producing such antibodies are well known in the art. Amino acid residues corresponding to CDRs and FWs are known to one of average skill in the art.

- A variety of methods have been developed to preserve or to enhance affinity for antigen of antibodies comprising grafted CDRs. One way is to include in the chimeric antibody the foreign framework residues that influence the conformation of the CDR regions. A second way is to graft the foreign CDRs onto human variable domains with the closest homology to the foreign variable region. Thus, grafting of one or more non-human CDRs onto a human antibody may also involve the substitution of amino acid residues which are adjacent to a particular CDR sequence or which are not contiguous with the CDR sequence but which are packed against the CDR in the overall antibody variable domain structure and which affect the conformation of the CDR. Humanized antibodies of the invention therefore include human antibodies which comprise one or more non-human CDRs as well as such antibodies in which additional substitutions or replacements have been made to preserve or enhance binding characteristics.
- Chimeric antibodies of the invention also include antibodies that have been humanized by replacing surface-exposed residues to make the Mab appear human. Because the internal packing of amino acid residues in the vicinity of the antigen-binding site remains unchanged, affinity is preserved. Substitution of surface-exposed residues of a polypeptide encoded by the polynucleotides of NSEQ (or a portion thereof)-antibody according to the invention for the purpose of humanization does not mean substitution of CDR residues or adjacent residues that influence affinity for a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof.

- Chimeric antibodies may also include antibodies where some or all non-human constant domains have been replaced with human counterparts. This approach has the advantage that the antigen-binding site remains unaffected. However, significant amounts of non-human sequences may be present where variable domains are derived entirely from non-human antibodies.

Antibodies of the invention include human antibodies that are antibodies consisting essentially of human sequences. Human antibodies may be obtained from phage display libraries wherein combinations of human heavy and light chain variable domains are displayed on the surface of filamentous phage. Combinations of variable domains are typically displayed on filamentous phage in the form of Fab's or scFvs. The library may be screened for phage bearing combinations of variable domains having desired antigen-binding characteristics. Preferred variable domain combinations are characterized by high affinity for a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof. Preferred variable domain combinations may also be characterized by high specificity for a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof, and little cross-reactivity to other related antigens. By screening from very large repertoires of antibody fragments, (2-10 x 10¹⁰) a good diversity of high affinity Mabs may be isolated, with many expected to have sub-nanomolar affinities for a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof.

Alternatively, human antibodies may be obtained from transgenic animals into which un-rearranged human Ig gene segments have been introduced and in which the endogenous mouse Ig genes have been inactivated. Preferred transgenic animals contain very large contiguous Ig gene fragments that are over 1 Mb in size but human polypeptide-specific Mabs of moderate affinity may be raised from transgenic animals containing smaller gene loci. Transgenic animals capable of expressing only human Ig genes may also be used to raise polyclonal antiserum comprising antibodies solely of human origin.

Antibodies of the invention may include those for which binding characteristics have been improved by direct mutation or by methods of affinity maturation. Affinity and specificity may be modified or improved by mutating CDRs and screening for antigen binding sites having the desired characteristics. CDRs may be mutated in a variety of ways. One way is to randomize individual residues or combinations of residues so that in a population of otherwise identical antigen binding sites, all twenty amino acids may be found at particular positions. Alternatively, mutations may be induced over a range

of CDR residues by error prone PCR methods. Phage display vectors containing heavy and light chain variable region gene may be propagated in mutator strains of *E. coli*. These methods of mutagenesis are illustrative of the many methods known to one of skill in the art.

- 5 Antibodies of the invention may include complete anti-polypeptide antibodies as well as antibody fragments and derivatives that comprise a binding site for a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof. Derivatives are macromolecules that comprise a binding site linked to a functional domain. Functional domains may include, but are not limited to signalling domains, toxins, enzymes and
10 cytokines.

The antibodies obtained by the means described herein may be useful for detecting proteins, variant and derivative polypeptides in specific tissues or in body fluids. Moreover, detection of aberrantly expressed proteins or protein fragments is probative of a disease state. For example, expression of the present polypeptides encoded by
15 the polynucleotides of NSEQ, or a portion thereof, may indicate that the protein is being expressed at an inappropriate rate or at an inappropriate developmental stage. Hence, the present antibodies may be useful for detecting diseases associated with protein expression from NSEQs disclosed herein.

A variety of protocols for measuring polypeptides, including ELISAs, RIAs, and FACS,
20 are well known in the art and provide a basis for diagnosing altered or abnormal levels of expression. Standard values for polypeptide expression are established by combining samples taken from healthy subjects, preferably human, with antibody to the polypeptide under conditions for complex formation. The amount of complex formation may be quantified by various methods, such as photometric means.
25 Quantities of polypeptide expressed in disease samples may be compared with standard values. Deviation between standard and subject values may establish the parameters for diagnosing or monitoring disease.

Design of immunoassays is subject to a great deal of variation and a variety of these are known in the art. Immunoassays may use a monoclonal or polyclonal antibody reagent that is directed against one epitope of the antigen being assayed. Alternatively, a combination of monoclonal or polyclonal antibodies may be used which are directed against more than one epitope. Protocols may be based, for example, upon competition where one may use competitive drug screening assays in which neutralizing antibodies capable of binding a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof, specifically compete with a test compound for binding the polypeptide. Alternatively one may use, direct antigen-antibody reactions or sandwich type assays and protocols may, for example, make use of solid supports or immunoprecipitation. Furthermore, antibodies may be labelled with a reporter molecule for easy detection. Assays that amplify the signal from a bound reagent are also known. Examples include immunoassays that utilize avidin and biotin, or which utilize enzyme-labelled antibody or antigen conjugates, such as ELISA assays.

Kits suitable for immunodiagnosis and containing the appropriate labelled reagents include antibodies directed against the polypeptide protein epitopes or antigenic regions, packaged appropriately with the remaining reagents and materials required for the conduct of the assay, as well as a suitable set of assay instructions.

The present invention therefore provides a kit for specifically assaying a polypeptide described herein, the kit may comprise, for example, an antibody or antibody fragment capable of binding specifically to the polypeptide described herein.

In accordance with the present invention, the kit may be a diagnostic kit, which may comprise:

- a) one or more antibodies described herein; and
- b) a detection reagent which may comprise a reporter group.

In accordance with the present invention, the antibodies may be immobilized on a solid

support. The detection reagent may comprise, for example, an anti-immunoglobulin, protein G, protein A or lectin etc. The reporter group may be selected, without limitation, from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

- 5 In yet another aspect of the invention, an NSEQ, a portion thereof, or its complement, may be used therapeutically for the purpose of expressing mRNA and polypeptide, or conversely to block transcription or translation of the mRNA. Expression vectors may be constructed using elements from retroviruses, adenoviruses, herpes or vaccinia viruses, or bacterial plasmids, and the like. These vectors may be used for delivery of
- 10 nucleotide sequences to a particular target organ, tissue, or cell population. Methods well known to those skilled in the art may be used to construct vectors to express nucleic acid sequences or their complements.

- Alternatively, NSEQ, a portion thereof, or its complement, may be used for somatic cell or stem cell gene therapy. Vectors may be introduced in vivo, in vitro, and ex vivo. For
- 15 ex vivo therapy, vectors are introduced into stem cells taken from the subject, and the resulting transgenic cells are clonally propagated for autologous transplant back into that same subject. Delivery of NSEQ by transfection, liposome injections, or polycationic amino polymers may be achieved using methods that are well known in the art. Additionally, endogenous NSEQ expression may be inactivated using
- 20 homologous recombination methods that insert an inactive gene sequence into the coding region or other targeted region of NSEQ.

- Vectors containing NSEQ may be transformed into a cell or tissue to express a missing polypeptide or to replace a non-functional polypeptide. Similarly a vector constructed to express the complement of NSEQ may be transformed into a cell to
- 25 down-regulate the over-expression of a polypeptide encoded by the polynucleotides of NSEQ, or a portion thereof. Complementary or anti-sense sequences may consist of an oligonucleotide derived from the transcription initiation site; nucleotides between about positions -10 and +10 from the ATG are preferred. Similarly, inhibition may be

achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See,
5 e.g., Gee et al. 1994)

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the cleavage of mRNA and decrease the levels of particular mRNAs, such as those comprising the polynucleotide sequences of the invention. Ribozymes may cleave mRNA at specific cleavage sites. Alternatively, ribozymes may cleave mRNAs at locations dictated by
10 flanking regions that form complementary base pairs with the target mRNA. The construction and production of ribozymes is well known in the art.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or
15 2' O-methyl rather than phosphodiester linkages within the backbone of the molecule. Alternatively, nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases, may be included.

20 One of skill in the art will readily appreciate that antibodies and antibody conjugates of the invention, where used in the human body for the purpose of the therapeutic applications discussed above, may be administered in the form of a composition. Such pharmaceutical compositions may consist of a polypeptide encoded by the polynucleotides of NSEQ, a portion thereof, or antibodies, mimetics, agonists,
25 antagonists, or inhibitors of the polypeptide. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The

compositions may be administered to a subject alone or in combination with other agents, drugs, or hormones.

In addition to the active ingredients, these pharmaceutical compositions may contain pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that may be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton Pa.).

For any compound, the therapeutically effective dose may be estimated initially either in cell culture assays or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the concentration range and route of administration. Such information may then be used to determine useful doses and routes for administration in humans. These techniques are well known to one skilled in the art and a therapeutically effective dose refers to that amount of active ingredient that ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating and contrasting the ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population) statistics. Any of the therapeutic compositions described above may be applied to any subject in need of such therapy, including, but not limited to, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

The term "Treatment" for purposes of this disclosure refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent

or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

Use of NSEQ in General Research

- 5 The invention finally provides products, compositions, processes and methods that utilize an NSEQ, their open reading frame, or a polypeptide encoded by the polynucleotides of NSEQ or their open reading frame, or a portion thereof, their variants, analogs and derivatives for research, biological, clinical and therapeutic purposes. For example, to identify splice variants, mutations, and polymorphisms
- 10 NSEQ may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences such as promoters and other regulatory elements. Additionally, one may use an XL-PCR kit (PE Biosystems, Foster City Calif.), nested primers, and commercially available cDNA libraries (Life Technologies, Rockville Md.) or genomic libraries (Clontech, Palo Alto
- 15 Calif.) to extend the sequence.

- The polynucleotides may also be used as targets in a micro-array. The micro-array may be used to monitor the expression patterns of large numbers of genes simultaneously and to identify splice variants, mutations, and polymorphisms. Information derived from analyses of the expression patterns may be used to
- 20 determine gene function, to understand the genetic basis of a disease, to diagnose a disease, and to develop and monitor the activities of therapeutic agents used to treat a disease. Microarrays may also be used to detect genetic diversity, single nucleotide polymorphisms which may characterize a particular population, at the genomic level.

- In yet another embodiment, polynucleotides may be used to generate hybridization
- 25 probes useful in mapping the naturally occurring genomic sequence. Fluorescent *in situ* hybridization (FISH) may be correlated with other physical chromosome mapping

techniques and genetic map data.

The present invention more particularly relates in one aspect thereof to a method of representatively identifying an endogeneously differentially expressed sequence involved in osteoclast differentiation. The sequence may be, for example, differentially
5 expressed in a differentiated osteoclast cell compared to an undifferentiated osteoclast precursor cell.

The method of the present invention may comprise;

- 10 a) separately providing total messenger RNA from differentiated osteoclast cell and undifferentiated osteoclast precursor cell, the total messenger RNA may comprise, for example, at least one endogeneously differentially expressed sequence,
- 15 b) generating (e.g., single copy of a) single-stranded cDNA from each messenger RNA of differentiated osteoclast cell and (e.g., randomly) tagging the 3'-end of the single-stranded cDNA with a RNA polymerase promoter sequence and a first sequence tag;
- c) generating (e.g., single copy of a) single-stranded cDNA from each messenger RNA of undifferentiated osteoclast precursor cell and (e.g., randomly) tagging the 3'-end of the single-stranded cDNA with a RNA polymerase promoter sequence and a second sequence tag;
- 20 d) separately generating partially or completely double-stranded 5'-tagged-DNA from each of b) and c), the double-stranded 5'-tagged-DNA may thus comprise in a 5' to 3' direction, a double-stranded RNA polymerase promoter, a first or second sequence tag and an endogeneously expressed sequence,
- 25 e) separately linearly amplifying a first and second tagged sense RNA from each of d) with a RNA polymerase enzyme (which may be selected based on the promoter used for tagging),

- f) generating single-stranded complementary first or second tagged DNA from one of e),
- g) hybridizing the single-stranded complementary first or second tagged DNA of f) with the other linearly amplified sense RNA of e),
- 5 h) recovering unhybridized RNA with the help of the first or second sequence tag (for example by PCR or hybridization), and;
- i) identifying (determining) the nucleotide sequence of unhybridized RNA.

10 The method may further comprise the step of comparatively determining the presence of the identified endogeneously and differentially expressed sequence in a differentiated osteoclast cell relative to an undifferentiated osteoclast precursor cell.

A sequence which is substantially absent (e.g., totally absent or present in very low quantity) from one of differentiated osteoclast cell or an undifferentiated osteoclast precursor cell and present in the other of differentiated osteoclast cell or an undifferentiated osteoclast precursor cell may thus be selected.

15

In accordance with the present invention, the sequence may be further selected based on a reduced or substantially absent expression in other normal tissue, therefore representing a candidate sequence specifically involved in osteoclast differentiation and bone remodeling.

20 The method may also further comprise a step of determining the complete sequence of the nucleotide sequence and may also comprise determining the coding sequence of the nucleotide sequence.

The present invention also relates in a further aspect, to the isolated endogeneously and differentially expressed sequence (polynucleotide and polypeptide) identified by the method of the present invention.

25

More particularly, the present invention encompasses a polynucleotide which may

comprise the identified polynucleotide sequence, a polynucleotide which may comprise the open reading frame of the identified polynucleotide sequence, a polynucleotide which may comprise a nucleotide sequence substantially identical to the polynucleotide identified by the method of the present invention, a polynucleotide
5 which may comprise a nucleotide sequence substantially complementary to the polynucleotide identified by the method of the present invention, fragments and splice variant thereof, provided that the sequence does not consist in or comprise SEQ ID NO.:57.

10 In accordance with the present invention, the isolated endogeneously and differentially expressed sequence of the present invention may be a complete or partial RNA molecule.

Isolated DNA molecule able to be transcribed into the RNA molecule of the present invention are also encompassed herewith as well as vectors (including expression vectors) comprising the such DNA or RNA molecule.

15 The present invention also relates to libraries comprising at least one isolated endogeneously and differentially expressed sequence identified herein (e.g., partial or complete RNA or DNA, substantially identical sequences or substantially complementary sequences (e.g., probes) and fragments thereof (e.g., oligonucleotides)).

20 In accordance with the present invention, the isolated endogeneously and differentially expressed sequence may be selected, for example, from the group consisting of a polynucleotide which may consist in or comprise;

- a) any one of SEQ ID NO.:1 to SEQ ID NO.56, SEQ ID NO.: 83, SEQ ID NO.:84 or SEQ ID NO.:87,
- 25 b) the open reading frame of any one of SEQ ID NO.:1 to SEQ ID NO.56, SEQ ID NO.: 83, SEQ ID NO.:84 or SEQ ID NO.:87,

- c) a polynucleotide which may comprise a nucleotide sequence substantially identical to a) or b), and;
- d) fragments of any one of a) to c).

5 Exemplary substantially identical sequence of a) or b) may comprise, for example, a sequence which may be selected from the group consisting of SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:88, SEQ ID NO.:89 and the open reading frame of the SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:88, SEQ ID NO.:89.

10 In a further aspect the present invention relates to a polypeptide which may be encoded by the isolated endogeneously and differentially expressed sequence of the present invention.

Exemplary polypeptides may comprise a sequence selected from the group consisting of any one of SEQ ID NO.: 93 to 99, 101 to 155.

15 In accordance with the present invention, when the sequence is from a non-human mammal, the method further comprises identifying a corresponding human ortholog polynucleotide sequence using a method described herein or other methods known in the art.

20 The present invention therefore also relates to an isolated human ortholog polynucleotide sequence (involved in bone remodeling), the open reading frame of the human ortholog, substantially identical sequences, substantially complementary sequences, fragments and splice variants thereof.

The present invention as well relates to an isolated polypeptide encoded by the human ortholog polynucleotide as well as biologically active analogs and biologically active fragments thereof.

Exemplary embodiments of human ortholog polynucleotides encompassed herewith include, for example, a sequence selected from the group consisting of SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:88, SEQ ID NO.:89 and the open reading frame of the SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:88, SEQ ID NO.:89.

- 5 Exemplary embodiments of isolated polypeptide encoded by some human orthologs identified herein include for example, a polypeptide selected from the group consisting of SEQ ID NO.:150, SEQ ID NO.:153, SEQ ID NO.:154 and SEQ ID NO.:155.

The present invention also more particularly relates, in an additional aspect thereof, to an isolated polynucleotide which may be differentially expressed in differentiated
10 osteoclast cell compared to undifferentiated osteoclast precursor cell.

The isolated polynucleotide may comprise a member selected from the group consisting of;

- a) a polynucleotide which may comprise any one of SEQ ID NO.:1 to SEQ ID NO.56, SEQ ID NO.: 83, SEQ ID NO.:86 or SEQ ID NO.:87,
15 b) a polynucleotide which may comprise the open reading frame of any one of SEQ ID NO.:1 to SEQ ID NO.56, SEQ ID NO.: 83, SEQ ID NO.:86 or SEQ ID NO.:87,
c) a polynucleotide which may comprise a sequence substantially identical (e.g., from about 50 to 100%, or about 60 to 100% or about 70 to 100% or about 80 to 100% or about 85, 90, 95 to 100% identical over the
20 entire sequence or portion of sequences) to a) or b),
d) a polynucleotide which may comprise a sequence substantially complementary (e.g., from about 50 to 100%, or about 60 to 100% or about 70 to 100% or about 80 to 100% or about 85, 90, 95 to 100% complementarity over the entire sequence or portion of sequences) to
25 a) or b), and;
e) a fragment of any one of a) to d)

f) including polynucleotides which consist in the above.

Exemplary polynucleotides which are substantially identical to those listed above, includes for example, polynucleotides selected from the group consisting of SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:88, SEQ ID NO.:89 and the open reading frame of any one of SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:88 or SEQ ID NO.:89.

Exemplary polynucleotides fragments of those listed above comprises polynucleotides of at least 10 nucleic acids which may be substantially complementary to the nucleic acid sequence of any one of SEQ ID NO.: 1 to 56 or SEQ ID NO.: 83 to SEQ ID NO.:89, such as, for example, fragments selected from the group consisting of any one of SEQ ID NO.: 64 to 80 or 90.

The present invention also relates to an isolated polynucleotide involved in osteoclast differentiation, the isolated polynucleotide may be selected, for example, from the group consisting of;

- a) a polynucleotide comprising any one of SEQ ID NO.: 1 to 56 or 83 to 89,
- b) a polynucleotide comprising the open reading frame of any one of SEQ ID NO.: 1 to 56 or 83 to 89, and;
- c) a polynucleotide substantially identical to a) or b).

The present invention also further relates to an isolated polynucleotide which may be able to promote osteoclast differentiation (e.g., in a mammal or mammalian cell thereof). The polynucleotide may be selected, for example, from the group consisting of polynucleotides which may comprise;

- a) any one of SEQ ID NO.:1 to 5, 8 to 56 or 83 to 89;
- b) the open reading frame of any one of SEQ ID NO.:1 to 5, 8 to 56 or 83 to 89, and;

- c) a sequence of at least 10 nucleic acids which may be complementary to the nucleic acid sequence of any one of SEQ ID NO.:6 or SEQ ID NO.:7.

5 In yet a further aspect, the present invention relates to an isolated polynucleotide which may be able to inhibit osteoclast differentiation (e.g., in a mammal or mammalian cell thereof). The polynucleotide may be selected, for example, from the group consisting of polynucleotides which may comprise;

- a) any one of SEQ ID NO.:6 or SEQ ID NO.:7,
- 10 b) the open reading frame of any one of SEQ ID NO.:6 or SEQ ID NO.:7, and;
- c) a sequence of at least 10 nucleic acids which is complementary to the nucleic acid sequence of any one of SEQ ID NO.:1 to 5 or 8 to 57 or 83 to 89.

15

Suitable polynucleotides include, for example, a polynucleotide having or comprising those which are selected from the group consisting of SEQ ID NO. 64 to 82 and 90.

20

Suitable polynucleotides may be those which may be able to inhibit osteoclast differentiation which has been induced by an inducer of osteoclast differentiation such as those listed herein.

In accordance with the present invention, the polynucleotide may be, for example, a RNA molecule, a DNA molecule, including those which are partial or complete, single-stranded or double-stranded, hybrids, etc.

25

The present invention also relates to a vector (e.g., an expression vector) comprising the polynucleotide of the present invention.

The present invention additionally relates in an aspect thereof to a library of

polynucleotide sequences which may be differentially expressed in a differentiated osteoclast cell compared to an undifferentiated osteoclast precursor cell. The library may comprise, for example, at least one member selected from the group consisting of

- 5 a) a polynucleotide which may comprise any one of SEQ ID NO.:1 to SEQ ID NO.57 and 83 to 89,
- b) a polynucleotide which may comprise the open reading frame of any one of SEQ ID NO.:1 to SEQ ID NO.57 and 83 to 89,
- c) a polynucleotide which may comprise a sequence substantially identical (e.g., from about 50 to 100%, or about 60 to 100% or about 70 to 100% or about 80 to 100% or about 85, 90, 95 to 100% identical over the
10 entire sequence or portion of sequences) to a) or b),
- d) a polynucleotide which may comprise a sequence substantially complementary (e.g., from about 50 to 100%, or about 60 to 100% or about 70 to 100% or about 80 to 100% or about 85, 90, 95 to 100%
15 complementarity over the entire sequence or portion of sequences) to a) or b), and;
- e) a fragment of any one of a) to d).

20 The present invention also relates to an expression library which may comprise a library of polynucleotides described herein. In accordance with the present invention, each of the polynucleotide may be contained within an expression vector.

Arrays and kits comprising a library of polynucleotide sequences (comprising at least one polynucleotide including complementary sequences) of the present invention are also encompassed herewith.

25 The present invention also provides in an additional aspect, a pharmaceutical composition for inhibiting osteoclast differentiation (bone resorption and bone resorption related diseases or disorders), the pharmaceutical composition may comprise, for example;

- a) an isolated polynucleotide as defined herein (e.g., able to inhibit osteoclast differentiation) and;
- b) a pharmaceutically acceptable carrier.

5 The present invention also provides in yet an additional aspect, a method for inhibiting osteoclast differentiation (e.g., for inhibiting bone resorption or for ameliorating bone resorption) in a mammal (individual) in need thereof (or in a mammalian cell), the method may comprise administering an isolated polynucleotide (e.g., able to inhibit osteoclast differentiation) or a suitable pharmaceutical composition.

10 In accordance with the present invention, the mammal in need may suffer, for example and without limitation, from a condition selected from the group consisting of osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's
15 disease/syndrome, Tumer syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets (including vitamin D dependent, type I and II, and x-linked hypophosphatemic rickets), fibrogenesis imperfecta ossium, osteosclerotic disorders such as pycnodysostosis and
20 damage caused by macrophage-mediated inflammatory processes, etc.

In a further aspect, the present invention relates to the use of an isolated polynucleotide (e.g., able to inhibit osteoclast differentiation) for the preparation of a medicament for the treatment of a bone resorption disease.

The present invention in another aspect thereof, provides a pharmaceutical
25 composition for promoting osteoclast differentiation in a mammal in need thereof. The pharmaceutical composition may comprise, for example;

- a. an isolated polynucleotide (e.g., able to promote osteoclast differentiation) and;
- b. a pharmaceutically acceptable carrier.

5 The present invention also further provides a method for promoting osteoclast differentiation in a mammal in need thereof (or in a mammalian cell), the method may comprise, for example, administering an isolated polynucleotide (e.g., able to promote osteoclast differentiation) or a suitable pharmaceutical composition as described above.

10 The present invention additionally relates to the use of an isolated polynucleotide (e.g., able to promote osteoclast differentiation) for the preparation of a medicament for the treatment of a disease associated with insufficient bone resorption (e.g., hyperostosis).

15 The present invention also relates to the use of at least one polynucleotide which may be selected from the group consisting of;

- a) a polynucleotide comprising the any one of SEQ ID NO.:1 to SEQ ID NO.57 and 83 to 89,
- b) a polynucleotide comprising the open reading frame of any one of SEQ ID NO.:1 to SEQ ID NO.57 and 83 to 89,
- 20 c) a polynucleotide comprising a sequence substantially identical (e.g., from about 50 to 100%, or about 60 to 100% or about 70 to 100% or about 80 to 100% or about 85, 90, 95 to 100% identical over the entire sequence or portion of sequences) to a) or b),
- 25 d) a polynucleotide comprising a sequence substantially complementary (e.g., from about 50 to 100%, or about 60 to 100% or about 70 to 100% or about 80 to 100% or about 85, 90, 95 to 100% complementarity over the entire sequence or portion of sequences) to a) or b),
- e) a fragment of any one of a) to d) and;

f) a library comprising any one of a) to d)
in the diagnosis of a condition related to bone remodeling.

5 Also encompassed by the present invention are kits for the diagnosis of a condition related to bone remodeling. The kit may comprise, for example, at least one sequence substantially complementary to any one of SEQ ID NO.:1 to SEQ ID NO.57 or 83 to 89, the open reading frame of any one of SEQ ID NO.:1 to SEQ ID NO.57 or 83 to 89 and fragments thereof.

10 The present invention also provides in an additional aspect, an isolated polypeptide (polypeptide sequence) which may be able to promote osteoclast differentiation (in a mammal or a mammalian cell thereof). The polypeptide may comprise (or consist in) a sequence selected from the group consisting of;

- 15 a) any one of SEQ ID NO.: 93 to 97 or 101 to 155,
b) a biologically active fragment of any one of a),
c) a biologically active analog of any one of a).

In accordance with the present invention, the biologically active analog may comprise, for example, at least one conservative amino acid substitution compared to the original sequence.

20 In yet a further aspect, the present invention provides a pharmaceutical composition for promoting osteoclast differentiation (e.g., for promoting bone resorption). The pharmaceutical composition may comprise, for example a polypeptide (e.g., able to promote osteoclast differentiation) and a pharmaceutically acceptable carrier.

25 Methods for promoting osteoclast differentiation in a mammal in need thereof (or in a mammalian cell) are also provided by the present invention, which methods may comprise administering an isolated polypeptide (e.g., able to promote osteoclast differentiation) or suitable pharmaceutical composition described herein.

In additional aspects, the present invention relates to the use of an isolated polypeptide (e.g., able to promote osteoclast differentiation) for the preparation of a medicament for the treatment of a disease associated with insufficient bone resorption.

5 In a further aspect, the present invention relates to an isolated polypeptide able to inhibit osteoclast differentiation (in a mammal or mammalian cell thereof), the polypeptide may comprise, for example, a sequence selected from the group consisting of

- 10 a) a sequence which may comprise or consist in any one of SEQ ID NO.:98 and SEQ ID NO.:99,
b) a biologically active fragment of any one of a),
c) a biologically active analog of any one of a).

15 In accordance with the present invention, the biologically active analog may comprise, for example, at least one conservative amino acid substitution in the amino acid sequence in comparison to another polypeptide

The present invention further encompasses pharmaceutical compositions which may comprise the isolated polypeptide described herein.

20 Methods for ameliorating bone resorption in an individual in need thereof are also encompassed herewith, which method may comprise, for example, administering an isolated polypeptide (e.g., able to inhibit osteoclast differentiation) or suitable pharmaceutical compositions which may comprise such polypeptide.

25 In a further aspect the present invention provides a method for ameliorating bone resorption in an individual in need thereof which may comprise administering a compound capable of inhibiting (e.g., in an osteoclast precursor cell) the activity or expression of a polypeptide involved in (or able to promote) osteoclast differentiation

such as for example, a polypeptide selected from the group consisting of SEQ ID NO.: 93 to 97 and 101 to 155.

5 In accordance with the present invention, the mammal may suffer, for example, from a condition selected from the group consisting of osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Tumer syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, 10 periodontal disease, rickets (including vitamin D dependent, type I and II, and x-linked hypophosphatemic rickets), fibrogenesis imperfecta ossium, osteosclerotic disorders such as pycnodysostosis and damage caused by macrophage-mediated inflammatory processes, etc.

15 In yet a further aspect, the present invention relates to the use of a polypeptide able to inhibit osteoclast differentiation in the preparation of a medicament for the treatment of a bone resorption disease in an individual in need thereof.

The present invention also relates to the use of a compound able to inhibit (e.g., in an osteoclast precursor cell) the activity or expression of a polypeptide which may be selected, for example, from the group consisting of SEQ ID NO.: 93 to 97 and 101 to 155 in the preparation of a medicament for the treatment of a bone resorption disease in an individual in need thereof. 20

Antibodies and antigen-binding fragment thereof which are able to bind to any of the polypeptide described herein, including those which may be selected from the group consisting of SEQ ID NO.: 93 to 97 and 101 to 155 are also encompassed by the present invention. 25

In accordance with the present invention, the antibody may be able, for example, to

inhibit osteoclast differentiation.

The present invention also relates to a composition (e.g., pharmaceutical composition) which may comprise;

- a) the antibody of claim 40 and;
- b) a pharmaceutically acceptable carrier.

The present invention relates in a further aspect to a method of inhibiting osteoclast differentiation which may comprise administering to a mammal in need thereof the antibody described herein or a pharmaceutical composition comprising such antibody.

The present invention relates in yet a further aspect to the use of an antibody as defined herein for the preparation of a medicament for the treatment of a bone resorption disease in an individual in need thereof.

In an additional aspect, the present invention relates to an immunizing composition which may comprise a polypeptide, such as a polypeptide selected from the group consisting of SEQ ID NO.: 93 to 155, analogs or fragments thereof or a nucleic acid (polynucleotide) selected, for example, from the group consisting of those comprising or consisting in (a) SEQ ID NO.: 1 to 56 and 83 to 89, (b) a polynucleotide which may comprise the open reading frame of SEQ ID NO.: 1 to 56 and 83 to 89, (c) substantially identical sequences of any one of (a) or (b) or fragments of any one of (a), (b) or (c) able to encode immunologically active polypeptides thereof.

In yet an additional aspect, the present invention relates to a method of diagnosing a condition related to a bone resorption disorder or disease in an individual in need thereof. The method may comprise, for example, quantifying a polynucleotide described herein, such as, for example, those selected from the group consisting of those comprising or consisting of (a) SEQ ID NO.: 1 to 56 and 83 to 89 (b) a

polynucleotide which may comprise the open reading frame of SEQ ID NO.: 1 to 56 and 83 to 89, (c) substantially identical sequences of any one of (a) or (b), or a polypeptide sequence which may be selected, for example, from the group consisting of 93 to 155 and analogs thereof in a sample from the individual compared to a standard or normal value.

In an additional aspect, the present invention provides a method for identifying an inhibitory compound (inhibitor, antagonist) which may be able to impair the function (activity) or expression of a polypeptide described herein, such as, for example, those which may be selected from the group consisting of SEQ ID NO.: 93 to 97 and 100 to 155 and analogs thereof. The method may comprise contacting the polypeptide or a cell expressing the polypeptide with a candidate compound and measuring the function (activity) or expression of the polypeptide. A reduction in the function or activity of the polypeptide (compared to the absence of the candidate compound) may positively identify a suitable inhibitory compound.

In accordance with the present invention, the impaired function or activity may be associated with a reduced ability of the polypeptide to promote osteoclast differentiation, such as osteoclast differentiation induced by an inducer described herein or known in the art.

In accordance with the present invention the cell may not naturally (endogenously) express (polypeptide may substantially be unexpressed in a cell) the polypeptide or analog or alternatively, the expression of a naturally expressed polypeptide analog may be repressed.

For example, suitable method of screening for an inhibitor of SEQ ID NO.:153, may comprise repressing the expression of SEQ ID NO.:93 in a mouse osteoclast cell and evaluating differentiation of the osteoclast cell in the presence or absence of a candidate inhibitor.

The impaired function or activity may also be associated with a reduced ability of the polypeptide to interact with a known partner.

For example, suitable method of screening for an inhibitor of SEQ ID NO.: 154 may comprise measuring (evaluating) the interaction of the polypeptide with the v-ATPase- α 3 subunit in the presence or absence of a candidate inhibitor.

The present invention also provides a method for identifying an inhibitory compound (inhibitor, antagonist) able to impair the function (activity) or expression of a polypeptide such as, for example SEQ ID NO.: 98 or SEQ ID NO.:99. The method may comprise, for example, contacting the polypeptide or a cell expressing the polypeptide with a candidate compound and measuring the function (activity) or expression of the polypeptide. A reduction in the function or activity of the polypeptide (compared to the absence of the candidate compound) may thus positively identify a suitable inhibitory compound.

In accordance with the present invention, the impaired function or activity may be associated, for example, with a reduced ability of the polypeptide to inhibit osteoclast differentiation.

The cell used to carry the screening test may not naturally (endogenously) express the polypeptide or analogs, or alternatively the expression of a naturally expressed polypeptide analog may be repressed.

As used herein the term "sequence identity" relates to (consecutive) nucleotides of a nucleotide sequence which with reference to an original nucleotide sequence. The identity may be compared over a region or over the total sequence of a nucleic acid sequence.

Thus, "identity" may be compared, for example, over a region of 3, 4, 5, 10, 19, 20

nucleotides or more (and any number there between). It is to be understood herein that gaps of non-identical nucleotides may be found between identical nucleic acids. For example, a polynucleotide may have 100% identity with another polynucleotide over a portion thereof. However, when the entire sequence of both polynucleotide is compared, the two polynucleotides may have 50% of their overall (total) sequence identical to one another.

Polynucleotides of the present invention or portion thereof having from about 50 to about 100%, or about 60 to about 100% or about 70 to about 100% or about 80 to about 100% or about 85%, about 90%, about 95% to about 100% sequence identity with an original polynucleotide are encompassed herewith. It is known by those of skill in the art, that a polynucleotide having from about 50% to 100% identity may function (e.g., anneal to a substantially complementary sequence) in a manner similar to an original polynucleotide and therefore may be used in replacement of an original polynucleotide. For example a polynucleotide (a nucleic acid sequence) may comprise or have from about 50% to 100% identity with an original polynucleotide over a defined region and may still work as efficiently or sufficiently to achieve the present invention.

Percent identity may be determined, for example, with n algorithm GAP, BESTFIT, or FASTA in the Wisconsin Genetics Software Package Release 7.0, using default gap weights.

As used herein the terms " sequence complementarity" refers to (consecutive) nucleotides of a nucleotide sequence which are complementary to a reference (original) nucleotide sequence. The complementarity may be compared over a region or over the total sequence of a nucleic acid sequence.

Polynucleotides of the present invention or portion thereof having from about 50 to about 100%, or about 60 to about 100% or about 70 to about 100% or about 80 to about 100% or about 85%, about 90%, about 95% to about 100% sequence

complementarity with an original polynucleotide are thus encompassed herewith. It is known by those of skill in the art, that an polynucleotide having from about 50% to 100% complementarity with an original sequence may anneal to that sequence in a manner sufficient to carry out the present invention (e.g., inhibit expression of the original polynucleotide).

An "analogue" is to be understood herein as a molecule having a biological activity and chemical structure similar to that of a polypeptide described herein. An "analogue" may have sequence similarity with that of an original sequence or a portion of an original sequence and may also have a modification of its structure as discussed herein. For example, an "analogue" may have at least 90 % sequence similarity with an original sequence or a portion of an original sequence. An "analogue" may also have, for example; at least 70 % or even 50 % sequence similarity (or less, i.e., at least 40%) with an original sequence or a portion of an original sequence.

Also, an "analogue" may have, for example, at least 50 % sequence similarity to an original sequence with a combination of one or more modification in a backbone or side-chain of an amino acid, or an addition of a group or another molecule, etc.

"Polynucleotide" generally refers to any polyribonucleotide or polydeoxyribonucleotide, which may be unmodified RNA or DNA, or modified RNA or DNA. "Polynucleotides" include, without limitation single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is a mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated

bases and unusual bases such as inosine. A variety of modifications may be made to DNA and RNA; thus "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells.

5 "Polynucleotide" includes but is not limited to linear and end-closed molecules. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

"Polypeptides" refers to any peptide or protein comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds (i.e., peptide isosteres).

10 "Polypeptide" refers to both short chains, commonly referred as peptides, oligopeptides or oligomers, and to longer chains generally referred to as proteins. As described above, polypeptides may contain amino acids other than the 20 gene-encoded amino acids.

As used herein the term "polypeptide analog" relates to mutants, variants, chimeras, fusions, deletions, additions and any other type of modifications made relative to a

15 given polypeptide.

As used herein the term "biologically active" refers to a variant or fragment which retains some or all of the biologicval activity of the natural polypeptide, i.e., to be able to promote or inhibit osteoclast differentiation.

20 Thus, biologically active polypeptides in the form of the original polypeptides, fragments (modified or not), analogues (modified or not), derivatives (modified or not), homologues, (modified or not) of the polypeptides described herein are encompassed by the present invention.

Therefore, any polypeptide having a modification compared to an original polypeptide

25 which does not destroy significantly a desired biological activity is encompassed herein. It is well known in the art, that a number of modifications may be made to the

polypeptides of the present invention without deleteriously affecting their biological activity. These modifications may, on the other hand, keep or increase the biological activity of the original polypeptide or may optimize one or more of the particularity (e.g. stability, bioavailability, etc.) of the polypeptides of the present invention which, in some instance might be desirable. Polypeptides of the present invention may comprise for example, those containing amino acid sequences modified either by natural processes, such as posttranslational processing, or by chemical modification techniques which are known in the art. Modifications may occur anywhere in a polypeptide including the polypeptide backbone, the amino acid side-chains and the amino- or carboxy-terminus. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. It is to be understood herein that more than one modification to the polypeptides described herein are encompassed by the present invention to the extent that the biological activity is similar to the original (parent) polypeptide.

As discussed above, polypeptide modification may comprise, for example, amino acid insertion (i.e., addition), deletion and substitution (i.e., replacement), either conservative or non-conservative (e.g., D-amino acids, desamino acids) in the polypeptide sequence where such changes do not substantially alter the overall biological activity of the polypeptide..

Example of substitutions may be those, which are conservative (i.e., wherein a residue is replaced by another of the same general type or group) or when wanted, non-conservative (i.e., wherein a residue is replaced by an amino acid of another type). In addition, a non-naturally occurring amino acid may substitute for a naturally occurring amino acid (i.e., non-naturally occurring conservative amino acid substitution or a non-naturally occurring non-conservative amino acid substitution).

As is understood, naturally occurring amino acids may be sub-classified as acidic, basic, neutral and polar, or neutral and non-polar. Furthermore, three of the encoded

amino acids are aromatic. It may be of use that encoded polypeptides differing from the determined polypeptide of the present invention contain substituted codons for amino acids, which are from the same type or group as that of the amino acid to be replaced. Thus, in some cases, the basic amino acids Lys, Arg and His may be
5 interchangeable; the acidic amino acids Asp and Glu may be interchangeable; the neutral polar amino acids Ser, Thr, Cys, Gln, and Asn may be interchangeable; the non-polar aliphatic amino acids Gly, Ala, Val, Ile, and Leu are interchangeable but because of size Gly and Ala are more closely related and Val, Ile and Leu are more closely related to each other, and the aromatic amino acids Phe, Trp and Tyr may be
10 interchangeable.

It should be further noted that if the polypeptides are made synthetically, substitutions by amino acids, which are not naturally encoded by DNA (non-naturally occurring or unnatural amino acid) may also be made.

A non-naturally occurring amino acid is to be understood herein as an amino acid
15 which is not naturally produced or found in a mammal. A non-naturally occurring amino acid comprises a D-amino acid, an amino acid having an acetaminomethyl group attached to a sulfur atom of a cysteine, a pegylated amino acid, etc. The inclusion of a non-naturally occurring amino acid in a defined polypeptide sequence will therefore generate a derivative of the original polypeptide. Non-naturally
20 occurring amino acids (residues) include also the omega amino acids of the formula $\text{NH}_2(\text{CH}_2)_n\text{COOH}$ wherein n is 2-6, neutral nonpolar amino acids, such as sarcosine, t-butyl alanine, t-butyl glycine, N-methyl isoleucine, norleucine, etc. Phenylglycine may substitute for Trp, Tyr or Phe; citrulline and methionine sulfoxide are neutral nonpolar, cysteic acid is acidic, and ornithine is basic. Proline may be substituted
25 with hydroxyproline and retain the conformation conferring properties.

It is known in the art that analogues may be generated by substitutional mutagenesis and retain the biological activity of the polypeptides of the present invention. These analogues have at least one amino acid residue in the protein molecule removed and

- a different residue inserted in its place. For example, one site of interest for substitutional mutagenesis may include but are not restricted to sites identified as the active site(s), or immunological site(s). Other sites of interest may be those, for example, in which particular residues obtained from various species are identical.
- 5 These positions may be important for biological activity. Examples of substitutions identified as "conservative substitutions" are shown in Table A. If such substitutions result in a change not desired, then other type of substitutions, denominated "exemplary substitutions" in Table A, or as further described herein in reference to amino acid classes, are introduced and the products screened.
- 10 In some cases it may be of interest to modify the biological activity of a polypeptide by amino acid substitution, insertion, or deletion. For example, modification of a polypeptide may result in an increase in the polypeptide's biological activity, may modulate its toxicity, may result in changes in bioavailability or in stability; or may modulate its immunological activity or immunological identity. Substantial
- 15 modifications in function or immunological identity are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation. (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into
- 20 groups based on common side chain properties:
- (1) hydrophobic: norleucine, methionine (Met), Alanine (Ala), Valine (Val), Leucine (Leu), Isoleucine (Ile)
 - (2) neutral hydrophilic: Cysteine (Cys), Serine (Ser), Threonine (Thr)
 - (3) acidic: Aspartic acid (Asp), Glutamic acid (Glu)
 - 25 (4) basic: Asparagine (Asn), Glutamine (Gln), Histidine (His), Lysine (Lys), Arginine (Arg)
 - (5) residues that influence chain orientation: Glycine (Gly), Proline (Pro); and aromatic: Tryptophan (Trp), Tyrosine (Tyr), Phenylalanine (Phe)
- 30 Non-conservative substitutions will entail exchanging a member of one of these classes for another.

TABLE A. Exemplary amino acid substitution

Original residue	Exemplary substitution	Conservative substitution
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln, His, Lys, Arg	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser	Ser
Gln (Q)	Asn	Asn
Glu (E)	Asp	Asp
Gly (G)	Pro	Pro
His (H)	Asn, Gln, Lys, Arg	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala	Leu
Pro (P)	Gly	Gly
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Leu, Met, Phe, Ala, norleucine	Leu

It is to be understood herein, that if a "range" or "group" of substances (e.g. amino acids), substituents" or the like is mentioned or if other types of a particular characteristic (e.g. temperature, pressure, chemical structure, time, etc.) is mentioned,

the present invention relates to and explicitly incorporates herein each and every specific member and combination of sub-ranges or sub-groups therein whatsoever. Thus, any specified range or group is to be understood as a shorthand way of referring to each and every member of a range or group individually as well as each and every possible sub-ranges or sub-groups encompassed therein; and similarly with respect to any sub-ranges or sub-groups therein. Thus, for example, with respect to a percentage (%) of identity of from about 80 to 100%, it is to be understood as specifically incorporating herein each and every individual %, as well as sub-range, such as for example 80%, 81%, 84.78%, 93%, 99% etc.; and similarly with respect to other parameters such as, concentrations, elements, etc...

It is in particular to be understood herein that the methods of the present invention each include each and every individual steps described thereby as well as those defined as positively including particular steps or excluding particular steps or a combination thereof; for example an exclusionary definition for a method of the present invention, may read as follows: "provided that said polynucleotide does not comprise or consist in SEQ ID NO.:57 or the open reading frame of SEQ ID NO.:57" or "provided that said polypeptide does not comprise or consist in SEQ ID NO.:100" or "provided that said polynucleotide fragment or said polypeptide fragment is less than X unit (e.g., nucleotides or amino acids) long or more than X unit (e.g., nucleotides or amino acids) long".

Other objects, features, advantages, and aspects of the present invention will become apparent to those skilled in the art from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Fig. 1 is a picture of a Southern blot hybridization analysis of the "STAR" subtracted libraries with probes specific for MMP-9, TRAP and GAPDH demonstrating RNA subtraction using STAR;

Fig. 2 shows a pie chart annotation of the clones isolated and sequenced from the SL22 subtracted library;

Fig. 3 is a picture illustrating the representative macroarray results of osteoclast specificity of the differentially expressed sequences selected for biological validation;

Fig. 4A is a picture showing the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for SEQ. ID. NO:1;

Fig. 4B is a picture showing the phenotypic effect on osteoclast differentiation in the presence of a mixture of siRNAs specific for SEQ. ID. NO:1;

Fig. 5 is a picture of a Northern blot showing the attenuation of SEQ. ID. NO:1 gene expression in RAW cells in the presence of specific siRNAs compared to osteoclast-specific marker genes, TRAP and CTSK;

Fig. 6 are pictures illustrating the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for SEQ. ID. NO:2, panel *a*; control RAW-hU6 cells, panel *b*; RAW-hU6 treated with RANK ligand, panel *c*; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:2 (RAW-0179.1), panel *d*; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:2 (RAW-0179.2) and panel *e*; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:2 (RAW-0179.3);

Fig. 7 is a picture of a Northern blot showing the attenuation of SEQ. ID. NO:2 gene expression in RAW cells in the presence of specific siRNAs. Also shown is the effect on the osteoclast-specific marker genes, TRAP and Cathepsin K;

5 Fig. 8 are pictures illustrating the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for SEQ. ID. NO:3 panel a; control RAW-hU6 cells, panel b; RAW-hU6 treated with RANK ligand, panel c; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:3 (RAW-0799.1), panel d; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:3 (RAW-0799.2) and panel e; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:3(RAW-0799.3);

10 Fig. 9 are pictures illustrating the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for SEQ. ID. NO:4 panel a; control RAW-hU6 cells, panel b; RAW-hU6 treated with RANK ligand, and panel c; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:4 (RAW-0351.1);

15 Fig. 10 are pictures illustrating the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for SEQ. ID. NO:5 panel a; control RAW-hU6 cells, panel b; RAW-hU6 treated with RANK ligand, and panel c; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:5 (RAW-01035.1);

20 Fig. 11A are pictures illustrating the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for SEQ. ID. NO:6 panel a; control RAW-hU6 cells, panel b; RAW-hU6 treated with RANK ligand, panel c; RAW-hU6 treated with siRNA specific for SEQ ID NO.:6 (RAW-1200.mix) and panel d; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:6 (RAW-1200.mix);

25 Fig. 11B are pictures illustrating a time-course of the phenotypic effect on osteoclast differentiation of RAW-hU6 observed in the presence or absence of RANK ligand and in the presence or absence siRNAs specific for SEQ. ID. NO:6 (RAW-1200.mix);

Fig. 12 are pictures illustrating the stimulation of the osteoclast-specific marker genes, TRAP and Cathepsin K, in RAW cells expressing specific siRNAs for SEQ. ID. NO:6 in the presence or absence of RANK ligand.

5 Fig. 13 are pictures illustrating the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for SEQ. ID. NO:8, panel a; control RAW-hU6 cells, panel b; RAW-hU6 treated with RANK ligand, and panel c; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:8 (RAW-0682.1);

10 Fig. 14A are pictures illustrating the reduced resorptive activity of osteoclasts expressing specific siRNAs for SEQ. ID. NO:1 panel a; control RAW-hU6 cells, panel b; RAW-hU6 treated with RANK ligand, panel c; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:1 (RAW-0440.1), panel d; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:1 (RAW-0440.2) and panel e; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:1 (RAW-0440.3);

Fig. 14B is an histogram illustrating the results of Fig. 14A in a quantitative manner;

15 Fig. 15A shows the reduced resorptive activity of osteoclasts expressing specific siRNAs for SEQ. ID. NO:2 panel a; control RAW-hU6 cells, panel b; RAW-hU6 treated with RANK ligand, panel c; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:2 (RAW-0179.1), panel d; RAW-hU6 treated with RANK ligand and siRNA specific for SEQ ID NO.:2 (RAW-0179.2) and panel e; RAW-hU6 treated with RANK
20 ligand and siRNA specific for SEQ ID NO.:2 (RAW-0179.3);

Fig. 15B is an histogram illustrating the results of Fig. 15A in a quantitative manner;

Fig. 16A is a picture representing an exemplary embodiment of a macroarray hybridization results of differential expression of some human orthologues in the different human tissues and human osteoclasts samples;

Fig. 16B is a picture of an agarose gel of RT-PCR-amplified SEQ ID NO.:1 in human precursor and osteoclast samples;

Fig. 17 is a picture illustrating the phenotypic effect on osteoclast differentiation in the presence of siRNAs specific for the human orthologue for SEQ ID NO.:1 (SEQ. ID. NO:88) right panel; control siRNA, left panel AB0440 siRNA;

Fig. 18 are pictures illustrating the efficiency of the functional complementation assay for SEQ. ID. NO. 88 to screen for inhibitors of osteoclastogenesis;

Fig. 19 is a picture of a Western blot from cell lysate obtained from cells expressing a SEQ ID NO.:88 fusion protein and treated or not with tunicamycin or phosphoinositol phospholipase C;

Fig. 20A is an histogram quantifying the inhibition of RAW264.7 differentiation into osteoclast using a monoclonal anti-Tsp50 (SEQ. ID. NO. 1) antibody;

Fig. 20B are pictures representing the phenotypic inhibition of RAW264.7 differentiation into osteoclast using a monoclonal anti-Tsp50 (SEQ. ID. NO. 1) antibody

Fig. 21A is a picture of a Northern blot illustrating that SEQ. ID. NO. 89 (d2) expression is upregulated in osteoclasts compared to the d1 isoform,

Fig. 21B are pictures of Western blots of a pull-down assay illustrating interaction of d2 with the v-ATPase a3 subunit but not the a4 subunit and;

Figs. 22 to 87 represents some polynucleotides and polypeptides identified using an exemplary method of the present invention.

SEQ ID NOs: 1-7, and 57 show differentially expressed sequences found in osteoclasts and demonstrated to have an effect on osteoclastogenesis following inhibition with specific siRNAs. SEQ ID NOs: 8-56 show differentially expressed sequences found in osteoclasts with putative roles in bone remodelling. SEQ ID NOs:
5 58-82 show the nucleotide sequences of plasmids, oligonucleotide primers and siRNAs used for experiments performed herein.

SEQ ID NOs: 83-87 show the mRNA sequence of spliced variants isolated from RNA prepared from osteoclasts for some of the osteoclast-specific sequences identified. SEQ ID NOs 83-87 thus show by way of examples that unique spliced variants exist
10 and strongly suggest that others also exist for the model system under study and others. More specifically, SEQ ID NO: 83 is a variant of SEQ ID NO: 1; SEQ ID NO: 84 is a human sequence of the corresponding mouse variant #1 for SEQ ID NO: 2; SEQ ID NO: 85 is a human sequence of the corresponding mouse variant #2 for SEQ ID NO: 2; SEQ ID NO: 86 is a variant of SEQ ID NO: 3; and SEQ ID NO: 87 is a
15 variant of SEQ ID NO: 3.

SEQ ID NO.: 88 and 89 shows the mRNA sequence of human orthologs of SEQ ID NO.:1 and 2 respectively.

SEQ ID NO.: 64 to 82 and 90 shows fragments which are complementary to a portion of a sequence of selected polynucleotides described herein.

20 SEQ ID NO.: 93 to 155 shows polypeptides encoded by the polynucleotides of the present invention.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The applicant employed a carefully planned strategy to identify and isolate genetic sequences involved in osteoclastogenesis and bone remodeling. The process involved

the following steps: 1) preparation of highly representative cDNA libraries using mRNA isolated from precursors and osteoclasts; 2) isolation of sequences upregulated during osteoclastogenesis; 3) identification and characterization of upregulated sequences; 4) selection of upregulated sequences for tissue specificity; 5) determination of knock-down effects on osteoclastogenesis and 6) determination of knock-down effects on bone resorption.

The results discussed in this disclosure demonstrate the advantage of targeting osteoclast genes that are specific to this differentiated cell type and provide a more efficient screening method when studying the genetic basis of diseases and disorders. Genes that are known to have a role in other areas of biology have been shown to play a critical role in osteoclastogenesis and osteoclast function. Genes that are known but have not had a role assigned to them until the present disclosure have also been isolated and shown to have a critical role in osteoclastogenesis and osteoclast function. Finally, novel genes have been identified and play a role, however, applicant reserves their disclosure until further study has been completed.

The present invention is illustrated in further details below in a non-limiting fashion.

A- Material and Methods

Commercially available reagents referred to in the present disclosure were used according to supplier's instructions unless otherwise indicated. Throughout the present disclosure certain starting materials were prepared as follows:

B - Preparation of osteoclast differentiated cells

The RAW 264.7 (RAW) osteoclast precursor cell line and human CD34+ progenitors are well known in the art as murine and human models of osteoclastogenesis. These murine and human osteoclasts are therefore excellent sources of materials for

isolating and characterizing genes specialized for osteoclast function.

RAW cells were purchased from American Type Culture Collection and maintained in high glucose DMEM containing 10% fetal bovine serum and antibiotics. The cells were sub-cultured bi-weekly to a maximum of 10-12 passages. For osteoclast differentiation experiments, RAW cells were seeded in 96-well plates at a density of 4×10^3 cells/well and allowed to plate for 24h. Differentiation was induced in high glucose DMEM, 10% charcoal-treated foetal bovine serum (Hyclone, Logan, UT), 0.05% BSA, antibiotics, 10 ng/ml macrophage colony stimulating factor (M-CSF), and 100 ng/ml receptor activator of NF- κ B (RANK) ligand. The plates were re-fed on day 3 and osteoclasts were clearly visible by day 4. Typically, the cells were stained for tartrate-resistant acid phosphatase (TRAP) on day 4 or 5 unless otherwise indicated. For TRAP staining, the cells were washed with PBS and fixed in 10% formaldehyde for 1 h. After two PBS washes, the cells were rendered lightly permeable in 0.2% Triton X-100 in PBS for 5 min before washing in PBS. Staining was conducted at 37°C for 20-25 min in 0.01% Naphtol AS-MX phosphate, 0.06% Fast Red Violet, 50 mM sodium tartrate, 100 mM sodium acetate, pH 5.2. Cells were visualized microscopically.

Human osteoclasts were differentiated from G-CSF-mobilized peripheral blood mononuclear cells (Cambrex, East Rutherford, NJ) as described by the supplier in the presence of 35 ng/ml M-CSF and 100 ng/ml RANK ligand. Multinucleated TRAP-staining osteoclasts were visible by 11-14 days. Osteoclasts from human cells were also derived from human osteoclasts precursor cells (Cambrex, East Rutherford, NJ) and cultured as described by the supplier. In the latter case, osteoclasts are obtained after 7 days.

C- Method of Isolating Differentially Expressed mRNA

Key to the discovery of differentially expressed sequences unique to osteoclasts is the use of the applicant's patented STAR technology (Subtractive Transcription-based Amplification of mRNA; U.S. Patent No. 5,712,127 Malek et al., January 27, 1998). In

this procedure, mRNA isolated from fully differentiated osteoclasts is used to prepare "tester RNA", which is hybridized to complementary single-stranded "driver DNA" prepared from osteoclast precursor mRNA and only the un-hybridized "tester RNA" is recovered, and used to create cloned cDNA libraries, termed "subtracted libraries".

- 5 Thus, the "subtracted libraries" are enriched for differentially expressed sequences inclusive of rare and novel mRNAs often missed by micro array hybridization analysis, which are anticipated to be among the important gene targets for the development of better diagnostic and therapeutic strategies.

- 10 The clones contained in the enriched "subtracted libraries" are identified by DNA sequence analysis and their potential function assessed by database analysis. The non-redundant clones are then used to prepare DNA micro-arrays, which are used to quantify their relative differential expression patterns by hybridization to fluorescent cDNA probes. Two classes of cDNA probes are used, which are generated from either RNA transcripts prepared from the same subtracted libraries (subtracted probes) or
- 15 mRNA isolated from different osteoclast samples (standard probes). The use of subtracted probes provides increased sensitivity for detecting the low abundance mRNA sequences that are preserved and enriched by STAR. Furthermore, the specificity of the differentially expressed sequences to osteoclast is measured by hybridizing radio-labeled probes prepared from each selected sequence to
- 20 macroarrays containing RNA from different osteoclast samples and different murine and/or human tissues. Additionally, Northern blot analysis is performed so as to confirm the presence of one or more specific mRNA species in the osteoclast samples. Following this, the full-length cDNAs representative of the mRNA species and/or spliced variants are cloned in E. coli DH10B.

- 25 A major challenge in gene expression profiling is the limited quantities of RNA available for molecular analysis. The amount of RNA isolated from many osteoclast samples or human specimens (needle aspiration, laser capture micro-dissection (LCM) samples and transfected cultured cells) is often insufficient for preparing: 1) conventional tester and driver materials for STAR; 2) standard cDNA probes for DNA
- 30 micro-array analysis; 3) RNA macroarrays for testing the specificity of expression; 4)

Northern blots and; 5) full-length cDNA clones for further biological validation and characterization. Thus, the applicant has developed a proprietary technology called RAMP (RNA Amplification Procedure) (U.S. Patent Application No. 11/000,958 published under No. US 2005/0153333A1 on July 14, 2005 and entitled "Selective
5 Terminal Tagging of Nucleic Acids"), which linearly amplifies the mRNA contained in total RNA samples yielding microgram quantities of amplified RNA sufficient for the various analytical applications. The RAMP RNA produced is largely full-length mRNA-like sequences as a result of the proprietary method for adding a terminal sequence tag to the 3'-ends of single-stranded cDNA molecules, for use in linear transcription
10 amplification. Greater than 99.5% of the sequences amplified in RAMP reactions show <2-fold variability and thus, RAMP provides unbiased RNA samples in quantities sufficient to enable the discovery of the unique mRNA sequences involved in osteoclastogenesis.

D- Preparation of Murine Osteoclasts Subtracted Library

15 RAW precursor cells and the corresponding fully differentiated (day 5) osteoclasts were prepared as described above. Isolation of cellular RNA followed by mRNA purification from each was performed using standard methods (Qiagen, Mississauga, ON). Following the teachings of Malek et al. (U.S. Patent No. 5,712,127), 2 µg of poly A+ mRNA from each sample were used to prepare highly representative ($>2 \times 10^6$ CFU)
20 cDNA libraries in specialized plasmid vectors necessary for preparing tester and driver materials. In each case, first-strand cDNA was synthesized using an oligo dT₁₁ primer with 3' locking nucleotides (e.g., A, G or C) and containing a Not I recognition site. Next, second-strand cDNA synthesis was performed according to the manufacturer's procedure for double-stranded cDNA synthesis (Invitrogen, Burlington, ON) and the
25 resulting double-stranded cDNA ligated to linkers containing an Asc I recognition site (New England Biolabs, Pickering, ON). The double-stranded cDNAs were then digested with Asc I and Not I restriction enzymes (New England Biolabs, Pickering, ON), purified from the excess linkers using the cDNA fractionation column from Invitrogen (Burlington, ON) as specified by the manufacturer and each ligated into
30 specialized plasmid vectors - p14 (SEQ. ID. NO:58) and p17+ (SEQ. ID. NO:59) used

for preparing tester and driver materials respectively. Thereafter, the ligated cDNAs were transformed into *E. coli* DH10B resulting in the desired cDNA libraries (RAW 264.7-precursor-p14, RAW 264.7-precursor-p17+, RAW 264.7-osteoclasts-p14 and RAW 264.7-osteoclasts-p17+). The plasmid DNA pool for each cDNA library was purified and a 2- μ g aliquot of each linearized with Not I restriction enzyme. In vitro transcription of the Not I digested p14 and p17+ plasmid libraries was then performed with T7 RNA polymerase and sp6 RNA polymerase respectively (Ambion, Austin, TX).

Next, in order to prepare 3'-represented tester and driver libraries, a 10- μ g aliquot of each of the in vitro synthesized RNA was converted to double-stranded cDNA by performing first-strand cDNA synthesis as described above followed by primer-directed (primer OGS 77 for p14 (SEQ. ID. NO:62) and primer OGS 302 for p17+ (SEQ. ID. NO:63)) second-strand DNA synthesis using Advantage-2 Taq polymerase (BD Biosciences Clontech, Mississauga, ON). The sequences corresponding to OGS 77 and OGS 302 were introduced into the in vitro synthesized RNA by way of the specialized vectors used for preparing the cDNA libraries. Thereafter, 6x 1- μ g aliquots of each double-stranded cDNA was digested individually with one of the following 4-base recognition restriction enzymes Rsa I, Sau3A1, Mse I, Msp I, MinPI I and Bsh 1236I (MBI Fermentas, Burlington, ON), yielding up to six possible 3'-fragments for each RNA species contained in the cDNA library. Following digestion, the restriction enzymes were inactivated with phenol and the set of six reactions pooled. The restriction enzymes sites were then blunted with T4 DNA polymerase and ligated to linkers containing an Asc I recognition site. Each linker-adapted pooled DNA sample was digested with Asc I and Not I restriction enzymes, desalted and ligated to specialized plasmid vectors, p14 and p17 (p17 plasmid vector is similar to the p17+ plasmid vector except for the sequence corresponding to SEQ. ID. NO:63), and transformed into *E. coli* DH10B. The plasmid DNA pool for each p14 and p17 3'-represented library was purified (Qiagen, Mississauga, ON) and a 2-mg aliquot of each digested with Not I restriction enzyme, and transcribed in vitro with either T7 RNA polymerase or sp6 RNA polymerase (Ambion, Austin, TX). The resulting p14 3'-represented RNA was used directly as "tester RNA" whereas, the p17 3'-represented RNA was used to synthesize first-strand cDNA as described above, which then served

as "driver DNA". Each "driver DNA" reaction was treated with RNase A and RNase H to remove the RNA, phenol extracted and desalted before use.

The following 3'-represented libraries were prepared:

- Tester 1 - RAW 264.7-osteoclast-3' in p14
- 5 Tester 2 - RAW 264.7-precursor-3' in p14
- Driver 1 - RAW 264.7-precursor-3' in p17
- Driver 2 - RAW 264.7-osteoclast-3' in p17

10 The tester RNA samples were subtracted following the teachings of U.S. patent No. 5,712,127 with the corresponding driver DNA in a ratio of 1:100 for either 1- or 2-rounds following the teachings of Malek et al. (U.S. Patent No. 5,712,127). Additionally, control reactions containing tester RNA and no driver DNA, and tester RNA plus driver DNA but no RNase H were prepared. The tester RNA remaining in each reaction after subtraction was converted to double-stranded DNA, and 5%
15 removed and amplified in a standard PCR reaction for 30-cycles for analytical purposes. The remaining 95% of only the driver plus RNase H subtracted samples were amplified for 4-cycles in PCR, digested with Asc I and Not I restriction enzymes, and one half ligated into the pCATRMAN (SEQ. ID. NO:60) plasmid vector and the other half, into the p20 (SEQ. ID. NO:61) plasmid vector. The ligated materials were
20 transformed into E. coli DH10B and individual clones contained in the pCATRMAN libraries were picked for further analysis (DNA sequencing and hybridization) whereas, clones contained in each p20 library were pooled for use as subtracted probes. Each 4-cycles amplified cloned subtracted library contained between 25,000 and 40,000 colonies.

25 The following cloned subtracted libraries were prepared:

- T04-22 - tester 1 (osteoclast) minus driver 1 (precursor) (1-round) in pCATRMAN
- SL22 - tester 1 (osteoclast) minus driver 1 (precursor) (2-rounds) in pCATRMAN

SL22 - tester 1 (osteoclast) minus driver 1 (precursor) (2-rounds) in p20

SL27 - tester 2 (precursor) minus driver 2 (osteoclast) (2-rounds) in pCATRMAN

SL27 - tester 2 (precursor) minus driver 2 (osteoclast) (2-rounds) in p20

- 5 A 5- μ L aliquot of the 30-cycles PCR amplified subtracted materials described above were visualized on a 1.5% agarose gel containing ethidium bromide and then transferred to Hybond N+ (Amersham Biosciences, Piscataway, NJ) nylon membrane for Southern blot analysis. Three identical Southern transfers were prepared and were hybridized separately to radiolabeled probes specific to the MMP-9 (matrix metalloproteinase 9; NM_013599.2) and TRAP (tartrate resistant acid phosphatase; NM_007388.1) genes, which are known to be upregulated in osteoclasts, and GAPDH (glyceraldehyde-3-phosphate dehydrogenase; M32599.1), which is a non-differentially expressed house-keeping gene. The results of the hybridization analysis are shown in Fig. 1 where the following lanes contain the following materials:
- 10

- 15 AO 1 - tester 1 RNA plus driver 1 DNA plus RNase H (1-round)
 AO 2 - tester 1 RNA plus driver 1 DNA plus RNase H (2-rounds)
 AP 1 - tester 2 RNA plus driver 2 DNA plus RNase H (1-round)
 AP 2 - tester 2 RNA plus driver 2 DNA plus RNase H (2-rounds)
 BO 1 - tester 1 RNA plus driver 1 DNA minus RNase H (1-round)
 20 BO 2 - tester 1 RNA plus driver 1 DNA minus RNase H (2-rounds)
 BP 1 - tester 2 RNA plus driver 2 DNA minus RNase H (1-round)
 BP 2 - tester 2 RNA plus driver 2 DNA minus RNase H (2-rounds)
 CO 1 - tester 1 RNA minus driver 1 DNA plus RNase H (1-round)
 CO 2 - tester 1 RNA minus driver 1 DNA plus RNase H (2-rounds)
 25 CP 1 - tester 2 RNA minus driver 2 DNA plus RNase H (1-round)
 CP 2 - tester 2 RNA minus driver 2 DNA plus RNase H (2-rounds)
 DP - tester 2 RNA
 DO - tester 1 RNA

- These results clearly show reduction of the GAPDH mRNA levels, representative of a non-differentially expressed gene, when both driver DNA and RNase H were present
- 30

in the reactions (complete) (GAPDH panel: Lanes AO 1, AO 2, AP 1 and AP 2) in comparison to the incomplete reactions (GAPDH panel: BO 1, BO 2, BP 1, BP 2, CO 1, CO 2, CP 1 and CP 2). Additionally, there was better subtraction of GAPDH after 2-rounds (GAPDH panel: AO 2 and AP 2) compared to 1-round (GAPDH panel: AO 1 and AP 1). On the other hand, the differentially expressed upregulated genes (MMP-9 and TRAP) were enriched in the complete reactions (MMP-9 and TRAP panels: Lanes AO 1 and AO 2) in comparison to the incomplete reactions (MMP-9 and TRAP panels: BO 1, BO 2, CO 1 and CO 2), which showed amounts similar to the intact tester RNA (MMP-9 and TRAP panels: Lane DO).

Based on these results, it was anticipated that the subtracted libraries would be enriched for differentially expressed sequences. Thus, for T04-22 and SL22 libraries, genes up regulated in osteoclasts would be represented whereas, for SL27, the down-regulated genes would be represented.

E - Sequence identification and annotation of clones contained in the T04-22 and SL22 subtracted libraries:

Since GAPDH (see above) was most efficiently subtracted after 2-rounds (SL-22), it was anticipated that this library would be most enriched for differentially expressed osteoclast-related sequences. Thus, more exhaustive DNA sequence analysis was performed on clones contained in SL22 (1536 clones) compared to T04-22 (576 clones).

The individual colonies contained in the T04-22- and SL22-pCATRMAN libraries prepared as described previously were randomly picked using a Qbot (Genetix Inc., Boston, MA) into 60 µL of autoclaved water. Then, 42 µL of each was used in a 100-µL standard PCR reaction containing oligonucleotide primers, OGS 1 and OGS 142 and amplified for 40-cycles (94oC for 10 minutes, 40x (94oC for 40 seconds, 55oC for 30 seconds and 72oC for 2 minutes) followed by 72oC for 7 minutes) in 96-wells microtitre plates using HotStart™ Taq polymerase (Qiagen, Mississauga, ON). The

completed PCR reactions were desalted using the 96-well filter plates (Corning) and the amplicons recovered in 100 μ L 10mM Tris (pH 8.0). A 5- μ L aliquot of each PCR reaction was visualized on a 1.5% agarose gel containing ethidium bromide and only those reactions containing a single amplified product were selected for DNA sequence
5 analysis using standard DNA sequencing performed on an ABI 3100 instrument (Applied Biosystems, Foster City, CA). Each DNA sequence obtained was given a Sequence Identification Number and entered into a database for subsequent tracking and annotation.

For the purpose of illustrating the ensuing strategies for identification of the clones,
10 only the DNA sequences obtained for clones contained in SL22 will be discussed further. Of those sequences, 1408 were selected for BLAST analysis of public databases (e.g. NCBI), which yielded 744 unique sequences representing a redundancy of approximately 53% and thus, a sufficiently representative sampling of the subtracted library. Absent from these sequences were the standard housekeeping
15 genes (GAPDH, actin, most ribosomal proteins etc.), which was a good indication that the subtracted library was depleted of at least the relatively abundant non-differentially expressed sequences. A limited survey of 96 clones from a corresponding un-subtracted library resulted in largely known and abundant housekeeping sequences such as GAPDH and beta-actin (data not shown). The 744 unique sequences were
20 broadly classified into three categories shown in Fig. 2: 522 genes with Unigene clusters (70.2%), 84 genes with no Unigene cluster (11.3%) and 138 novel sequences (18.5%). Of the Unigene-clustered genes, only 114 were associated with GO (Gene Ontology) functional categories. Thus, it was evident from these results that the subtracted library (SL22) was enriched for known and novel sequences.

25 Once sequencing and annotation of the selected clones were completed, the next step involved identifying those sequences that were actually upregulated in osteoclasts compared to precursors.

F - Hybridization analysis for identifying upregulated sequences

The PCR amplicons representing the annotated sequences from the T04-22 and SL22 libraries were used to prepare DNA microarrays. The purified PCR amplicons from contained in 70 µL prepared in the previous section was lyophilized and each
5 reconstituted in 20 µL of spotting solution comprising 3xSSC and 0.1% sarkosyl. DNA micro-arrays of each amplicon in triplicate were then prepared using CMT-GAP2 slides (Corning, Corning, NY) and the GMS 417 spotter (Affymetrix, Santa Clara, CA).

The DNA micro-arrays were then hybridized with either standard or subtracted cy3 and cy5 labelled cDNA probes as recommended by the supplier (Amersham Biosciences,
10 Piscataway, NJ). The standard cDNA probes were synthesized using RAMP amplified RNA prepared from five different murine osteoclast samples and the corresponding precursors. It is well known to the skilled artisan that standard cDNA probes only provide limited sensitivity of detection and consequently, low abundance sequences contained in the cDNA probes are usually missed. Thus, the hybridization analysis
15 was also performed using subtracted cDNA probes. These subtracted cDNA probes were synthesized from in vitro transcribed RNA prepared from the SL22-p20 and SL25-p20 subtracted libraries described above in D. These subtracted libraries may be enriched for low abundance sequences as a result of following the teachings of Malek et al., and therefore, may provide increased detection sensitivity.

20 All hybridization reactions were performed using the dye-swap procedure as recommended by the supplier (Amersham Biosciences, Piscataway, NJ). Following analysis of the hybridization results obtained using the standard cDNA probes, 161 of the 744 unique sequences contained in SL22 appeared to be upregulated in the osteoclasts, showing >2-fold difference compared to the precursors. On the other
25 hand, when the subtracted cDNA probes were used, 289 additional SL22-sequences appeared to be upregulated in the osteoclast samples as well.

Thus, it was evident from these results that the SL22 subtracted library was highly

enriched for upregulated sequences (>60%), which were probably involved in osteoclastogenesis. A similar analysis was performed for the T04-22 clones, which showed a lower percentage of differentially expressed sequences likely due to insufficient subtraction after only 1-round of the STAR procedure.

5 ***G - Determining osteoclast specificity of the differentially expressed sequences identified:***

The differentially expressed sequences identified in Section F for both SL22 and T04-22 libraries were tested for osteoclast specificity by hybridization to nylon membrane-based macroarrays. The macroarrays were prepared using RAMP amplified RNA from
10 murine precursors and osteoclasts of five independent experiments, and various normal murine tissues (liver, brain, thymus, heart, lung, testicle, ovary, kidney and embryo) purchased commercially (Ambion, Austin, TX). Because of the limited quantities of mRNA available for many of these samples, it was necessary to first amplify the mRNA using the RAMP methodology. Each amplified RNA sample was
15 reconstituted to a final concentration of 250 ng/μL in 3xSSC and 0.1% sarkosyl in a 96-well microtitre plate and 1 μL spotted onto Hybond N+ nylon membranes using the specialized MULTI-PRINT™ apparatus (VP Scientific, San Diego, CA), air dried and UV-cross linked. A total of 556 different sequences selected from SL22 and T04-22 were individually radiolabeled with α-³²P-dCTP using the random priming procedure
20 recommended by the supplier (Amersham, Piscataway, NJ) and used as probes on the macroarrays. Hybridization and washing steps were performed following standard procedures well known to those skilled in the art.

Of the 556 sequences tested, approximately 80% were found to be upregulated in at least the primary osteoclast RNA sample that was used to prepare the subtracted
25 libraries. However, many of these sequences were also readily detected in the different murine tissues. Based on these results, those sequences that appeared to be associated with experimental variability and those that were detected in many of the other murine tissues were eliminated. Consequently, only 73 sequences, which

appeared to be highly osteoclast-specific, were selected for biological validation studies. This subset of 73 sequences included sequences present in two or less murine tissues relative to the precursor levels since it is entirely possible that the hybridization signals obtained for these tissues maybe due to family members or
5 spliced variants.

Fig. 3 shows examples of the macroarray patterns representative of the sequences selected for validation. Subsequently, RNA from 8 additional normal murine tissues (lymph node, eye, prostate, smooth muscle, spinal cord, stomach, uterus and bone marrow) were incorporated into secondary macroarrays and used to further test the
10 specificity of many of the 73 selected sequences (data not shown). Amongst the 73 selected sequences were 41 genes with functional annotation of which, only two were previously linked to osteoclastogenesis (Unigene Clusters Mm.103560 and Mm.271689), 20 genes with no functional annotation and 12 novel sequences (data not disclosed). Representative sequences are characterized as follows:

15 **SEQ. ID. NO:1:**

The candidate protein encoded by SEQ. ID. NO:1 is a previously identified gene with the designation, testis-specific protease or Tsp50. The mouse polynucleotide contains an open reading frame of 1317 bp and encodes a polypeptide of 439 amino acids. The human polynucleotide contains an open reading frame of 1155 bp and encodes a
20 polypeptide of 385 amino acids. It was originally described and cloned because of its expression in a hypomethylated region of genomic DNA in human breast cancer cells (Yuan et al., 1999). Analysis of the primary amino acid sequence suggests the presence of an amino-terminal signal peptide that will presumably target the protein to the plasma membrane, a carboxy-terminal transmembrane domain to anchor the
25 protein in the plasma membrane, and a predicted catalytic domain homologous to serine proteases (Shan et al., 2002; Netzel-Arnett et al., 2003). The nature of the predicted catalytic activity and the exact cellular localization of Tsp50 have yet to be conclusively established. Applicant directs the reader's attention to US Patent

6,617,434 (Duffy, September 9, 2003) and US Patent 6,451,555 (Duffy, September 17, 2002) where Tsp50 is the subject matter. Despite all of the above information, no functional association with osteoclasts or bone remodeling disorders has been described prior to the present disclosure.

5 **SEQ. ID. NO:2:**

The candidate protein encoded by SEQ. ID. NO:2 is a previously identified gene that encodes the d2 subunit of the vacuolar (V-) ATPase multi-subunit complex. Although the d2 subunit does not span the membrane, it is part of the membrane-spanning complex and interacts directly with the larger a subunit that contains the transmembrane properties (Nishi and Forgac, 2002). The cDNA encoding the mouse V-ATPase d2 protein has recently been described but its function in bone physiology has yet to be established (Nishi et al., 2003). No functional association with osteoclasts or bone remodeling disorders has been described prior to the present disclosure.

15 **SEQ. ID. NO:3:**

The candidate protein encoded by SEQ. ID. NO:3 is a previously identified gene that encodes the cartilage-associated protein, Crtap (Morello et al., 1999; Tonachini et al., 1999). The gene was originally cloned from chick embryo and localized to cartilaginous tissues (Morello et al., 1999). No functional association with osteoclasts or bone remodeling disorders has been described prior to the present disclosure.

SEQ. ID. NO:4:

The candidate protein encoded by SEQ. ID. NO:4 is found in current databases and was cloned as part of the RIKEN Genome Exploration Research Group (Kawai et al., 2001). Although the mRNA contains a predicted open reading frame, no function has

been assigned to this sequence prior to the present disclosure.

SEQ. ID. NO:5:

5 The candidate protein encoded by SEQ. ID. NO:5 is found in current databases and was cloned as part of the RIKEN Genome Exploration Research Group (Strausberg et al., 2002). Although the mRNA contains a predicted open reading frame, no function has been assigned to this sequence prior to the present disclosure.

SEQ. ID. NO:6:

10 The candidate protein encoded by SEQ. ID. NO:6 is found in current databases and was cloned as part of the RIKEN Genome Exploration Research Group (Strausberg et al., 2002). Although the mRNA contains a predicted open reading frame, no function has been assigned to this sequence prior to the present disclosure.

SEQ. ID. NO:7:

15 The candidate protein encoded by SEQ. ID. NO:7 is a previously identified gene that encodes the linker for activation of B cells. The gene has been reported as playing a role in thymocytes (Janssen et al., 2003). No functional association with osteoclasts or bone resorption disorders has been described prior to the present disclosure.

SEQ. ID. NO:57

20 The candidate protein encoded by SEQ. ID. NO:57 is a previously identified gene that encodes the jun dimerization protein 2. This gene has been shown to be involved in osteoclastogenesis using antisense technology (Kawaida et al., 2003). This example serves as further proof of concept of applicant's approach in identifying osteoclast-specific genes.

H- Cloning of full-length cDNAs of selected sequences from osteoclast mRNA:

It was necessary to obtain full-length cDNA sequences in order to perform functional studies of the expressed proteins. Spliced variants are increasingly being implicated in tissue specific functions and as such, it is critically necessary to work with cDNA clones from the system under study. Applicant also recognizes that spliced variants may not always be involved. Thus, the applicant's approach has been to isolate the relevant full-length cDNA sequences directly from osteoclasts in order to identify variants and their potential role with respect to specificity.

Coding cDNA clones were isolated using both a 5'-RACE strategy (Invitrogen, Burlington, ON) and a standard two-primer gene specific approach in PCR. The 5'-RACE strategy used cDNA prepared from cap-selected osteoclast RNA and/or RAMP amplified osteoclast RNA. For amplification using gene specific primers, either cDNA prepared from RAMP RNA or total RNA was used. All cDNAs were synthesized following standard reverse transcription procedures (Invitrogen, Burlington, ON). The cDNA sequences obtained were cloned in E.coli DH10B and the nucleotide sequences for multiple clones determined. Thereafter, the cDNA sequences for each set were aligned and the open reading frame(s) (ORF) identified using standard software (e.g. ORF Finder-NCBI). Table 3 shows examples of cDNA clones of spliced variants, which were obtained for some of the sequences under investigation.

I- RNA Interference Studies

RNA interference is a recently discovered gene regulation mechanism that involves the sequence-specific decrease in a gene's expression by targeting the mRNA for degradation and although originally described in plants, it has been discovered across many animal kingdoms from protozoans and invertebrates to higher eukaryotes (reviewed in Agrawal et al., 2003). In physiological settings, the mechanism of RNA interference is triggered by the presence of double-stranded RNA molecules that are cleaved by an RNase III-like protein active in cells, called Dicer, which releases the

21-23 bp siRNAs. The siRNA, in a homology-driven manner, complexes into a RNA-protein amalgamation termed RISC (RNA-induced silencing complex) in the presence of mRNA to cause degradation resulting in attenuation of that mRNA's expression (Agrawal et al., 2003).

- 5 Current approaches to studying the function of genes, such as gene knockout mice and dominant negatives, are often inefficient, and generally expensive, and time-consuming. RNA interference is proving to be a method of choice for the analysis of a large number of genes in a quick and relatively inexpensive manner. Although transfection of synthetic siRNAs is an efficient method, the effects are often transient
- 10 at best (Hannon G.J., 2002). Delivery of plasmids expressing short hairpin RNAs by stable transfection has been successful in allowing for the analysis of RNA interference in longer-term studies (Brummelkamp et al., 2002; Elbashir et al., 2001). In addition, more recent advances have permitted the expression of siRNA molecules, in the form of short hairpin RNAs, in primary human cells using viral delivery methods
- 15 such as lentivirus (Lee et al., 2004; Robinson et al., 2003).

J- Determination of knockdown effects on osteoclastogenesis

- The design and subcloning of individual siRNA expression cassettes and the procedure utilized for the characterization of each nucleotide sequence is described below. Selection of polynucleotides were chosen based on their RANK ligand-
- 20 dependent upregulation in osteoclasts and the selective nature of their expression in osteoclasts compared to other tissues (see sections F and G above). The design of siRNA sequences was performed using web-based software that is freely available to those skilled in the art (Qiagen for example). These chosen sequences, usually 19-mers, were included in two complimentary oligonucleotides that form the template for
- 25 the short hairpin RNAs, i.e. the 19-nt sense sequence, a 9-nt linker region (loop), the 19-nt antisense sequence followed by a 5-6 poly-T tract for termination of the RNA polymerase III. Appropriate restriction sites were inserted at the ends of these oligonucleotides to facilitate proper positioning of the inserts so that the transcriptional

start point is at a precise location downstream of the hU6 promoter. For each sequence selected, at least two different siRNA expression vectors were constructed to increase the chance of observing RNA interference.

5 The transfection plasmids expressing the siRNAs under the control of the human U6 promoter were constructed as follows. Two primers containing an *Asel* site (forward) and a *KpnI* site (reverse) were used to PCR amplify a 330-bp fragment containing the human U6 promoter from 5 ng of human genomic DNA. This fragment was ligated in similarly digested pd2EGFP-N1 (BD Biosciences Clontech, Mississauga, ON) resulting in the replacement of the CMV E1 promoter of pd2EGFP-N1 by the human (h)U6
10 promoter sequence. Digesting with *AgeI* and *NotI* and religating the blunted ends to generate pd2-hU6 accomplished removal of the d2EGFP fragment. The template for the siRNA hairpin was designed by annealing two oligonucleotides yielding a 57-bp fragment blunt at the 5'-end and having a *BamHI* overhang at the 3'-end. The annealed oligonucleotides were ligated into pd2-hU6 that had been previously
15 digested with *KpnI* (blunted) and *BamHI* resulting in pd2-hU6/siRNA. All plasmids were verified by sequencing to confirm presence of the siRNA hairpin sequence and proper positioning of the transcriptional start site following the hU6 promoter.

RAW cells were seeded in 6-well plates in high glucose DMEM containing 10% fetal bovine serum at a density of 6×10^5 cells/well, allowed to plate overnight and
20 transfected with 1 μ g of pd2-hU6/siRNA plasmid using the Fugene 6 reagent (Roche, Laval, QC). After 16h of incubation, fresh medium was added containing 400 μ g/ml G418 to select for stable transfectants. Control cells were transfected with pd2-hU6. After approximately 10 days, pools and/or individual clones of cells were isolated and analyzed for their ability to form osteoclasts in 96-well plates. The resulting
25 phenotypes were observed microscopically by viewing cells assayed for TRAP staining. The efficacy of RNA interference was also assessed by conducting Northern blots on total RNA isolated from cells subjected to in vitro osteoclastogenesis.

K- Results of RNA Interference studies**SEQ. ID. NO:1:**

The sequences used for RNA interference were derived from the polynucleotide SEQ. ID. NO:1 and have the SEQ. ID. NOs: 64, 65 and 66 (of course other sequences may be used). The cell lines derived from RAW cells transfected with plasmids encoding the three siRNAs pd2-hU6/0440.1, pd2-hU6/0440.2 and, pd2-hU6/0440.3 are designated hereafter as RAW-0440.1 (SEQ. ID. NO. :64), RAW-0440.2 (SEQ. ID. NO. :65), and RAW-0440.3 (SEQ. ID. NO. :66), respectively and collectively as RAW-0440. In addition, as a positive control for normal osteoclastogenesis, RAW cells were transfected with the empty vector (pd2-hU6) that does not contain a siRNA. Phenotypic analysis of all cell lines is shown in Fig. 4A. Panel a of Fig. 4A shows the control cell line, RAW-hU6, in the absence of RANK ligand where the presence of multinucleated osteoclasts is not observed and the undifferentiated RAW cells are completely devoid of TRAP staining. Upon treatment with RANK ligand, large, multinucleated, TRAP positive osteoclasts are seen demonstrating normal differentiation (panel b). The presence of the siRNA specific for SEQ. ID. NO:1 in RAW cells resulted in a greatly reduced ability of these cells to form large and mature osteoclasts in the presence of RANK ligand (panels c-e). In addition to a decreased number of osteoclasts per well, the RAW-0440 cells were smaller and most of exhibited a slight decrease in TRAP staining. Closer inspection revealed that these smaller osteoclasts were multinucleated suggesting normal cellular fusion of the RAW-0440 precursors. Analysis of another RAW cell line, RAW-0440.mix, transfected with an equivalent amount of all three siRNA expression vectors confirmed the previous phenotypic observations. As before, the control cell line transfected with the empty vector formed large multinucleated osteoclasts that stained for TRAP (Fig. 4B, panel b). As shown in panel c, the RAW-0440.mix osteoclasts were multinucleated but small and fewer in number.

The effect of each siRNA was assessed by isolating total RNA from the mature

osteoclasts after 3 and 4 days of RANK ligand treatment and probing with a fragment of the SEQ. ID. NO:1 cDNA to determine if knockdown of endogenous gene expression occurred. A representative experiment is shown in Fig. 5. When 10 µg of total RNA was probed with a fragment of the SEQ. ID. NO:1 cDNA, a single mRNA of 1.7 Kb was observed. A decrease, especially at day 4, in the amount of the SEQ. ID. NO1 mRNA was seen in the RNA isolated from the RAW-0440.1 cell line indicating RNA interference occurred in these cells (Fig. 5, top panel, compare lanes 3 and 6). Similarly, the expression of two known osteoclast marker genes, TRAP and Cathepsin K (Boyle et al., 2003), was significantly reduced in RAW-0440.1 cells (Fig. 5). The osteoclast-specific character of SEQ. ID. NO:1 was evident by the lack of expression in the precursor cells (see lanes 1 and 4). The difference in the expression of the SEQ. ID. NO:1 gene was not due to the difference in the amount of total RNA loaded on the gel as evidenced by the probing of the same membrane with a fragment of the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH, Fig. 5).

These results demonstrate that the absence of physiological levels of SEQ. ID. NO:1 in RAW cells impairs their ability to differentiate into osteoclasts properly and implies an important role for this gene in these cells.

SEQ. ID. NO:2:

The sequences used for RNA interference were derived from the polynucleotide SEQ. ID. NO:2 and have the SEQ. ID. NOs:67, 68 and 69. The cell lines derived from RAW cells transfected with plasmids encoding the three siRNAs pd2-hU6/0179.1, pd2-hU6/0179.2 and, pd2-hU6/0179.3 are hereby-designated RAW-0179.1 (SEQ. ID. NO. :67), RAW-0179.2 (SEQ. ID. NO. :68), and RAW-0179.3 (SEQ. ID. NO. :69), respectively. In addition, as a positive control for normal osteoclastogenesis, RAW cells were transfected with the empty vector (pd2-hU6) that does not contain any siRNA. Phenotypic analysis of all cell lines is shown in Fig. 6. Panel a of Fig. 6 shows the control cell line, RAW-hU6, in the absence of RANK ligand where the presence of multinucleated osteoclasts is not observed and the undifferentiated RAW cells are

completely devoid of TRAP staining. Upon treatment with RANK ligand, large and multinucleated, TRAP positive osteoclasts are seen demonstrating normal differentiation (panel b). Two of the siRNAs, namely those encoded by RAW-0179.1 and RAW-0179.2, resulted in a noticeable reduction in the ability of these cells to form large, mature osteoclasts in the presence of RANK ligand (panels c,d). A third siRNA sequence, RAW-0179.3, was not effective (see Fig. 6, panel e). In addition to a decreased number of osteoclasts per well, the RAW-0179.1 and RAW-0179.2 cells were generally smaller and contained less nuclei.

Isolating total RNA from the mature osteoclasts after 3 and 4 days of RANK ligand treatment and probing with a fragment of the SEQ. ID. NO2 cDNA to determine if knockdown of endogenous gene expression occurred assessed the effect of each siRNA. A representative experiment is shown in Fig. 7. When 10 µg of total RNA was probed with a fragment of the SEQ. ID. NO2 cDNA, two mRNAs of 2.3 Kb and 1.6 Kb were observed. A decrease, especially at day 4, in the amount of the SEQ. ID. NO2 mRNA was seen in the RNA isolated from the RAW-0179.1 cell line indicating RNA interference occurred in these cells (Fig. 7, top panel, compare lanes 3 and 6). Furthermore, although the RAW-hU6 precursor cells expressed detectable levels of SEQ. ID. NO2 in the absence of RANK ligand, expression was not seen in RNA from the RAW-0179.1 cells under similar conditions (compare lanes 1 and 4 in Fig. 7, top). Taken together, these results show that effective RNA interference occurred. Two known osteoclast marker genes were also significantly reduced, especially Cathepsin K, which was virtually undetectable in RAW-0179.1 cells compared to the control cell line. The difference in the expression of the SEQ. ID. NO2 gene was not due to the difference in the amount of total RNA loaded on the gel as evidenced by the probing of the same membrane with a fragment of the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH, Fig. 7).

These results demonstrate that SEQ. ID. NO2 is required for proper osteoclast differentiation in RAW cells suggesting an important role for this gene in these cells.

SEQ. ID. NO:3:

The sequences used for RNA interference were derived from the polynucleotide SEQ. ID. NO:3 and have the SEQ. ID. NOs:70, 71 and 72. The use of RNA interference as described in the invention for SEQ. ID. NOs1 and 2 was applied to SEQ. ID. NO:3.

- 5 The results obtained were similar showing that this gene is also required for proper differentiation of RAW osteoclasts. An illustration of this result is depicted in Fig. 8.

SEQ. ID. NO:4:

The sequences used for RNA interference were derived from the polynucleotide SEQ. ID. NO:4 and have the SEQ. ID. NOs:73 and 74. The use of RNA interference as

- 10 described in the invention for SEQ. ID. NOs1 and 2 was applied to SEQ. ID. NO:4. The results obtained were similar showing that this gene is required for proper differentiation of RAW osteoclasts. An illustration of this result is depicted in Fig. 9.

SEQ. ID. NO:5:

The sequences used for RNA interference were derived from the polynucleotide SEQ.

- 15 ID. NO:5 and have the SEQ. ID. NOs:75 and 76. The use of RNA interference as described in the invention for SEQ. ID. NOs1 and 2 was applied to SEQ. ID. NO:5. The results obtained were similar showing that this gene is required for proper differentiation of RAW osteoclasts. An illustration of this result is depicted in Fig. 10.

SEQ. ID. NO:6:

- 20 The sequences used for RNA interference were derived from the polynucleotide SEQ. ID. NO:6 and have the SEQ. ID. NOs:77 and 78. The same approach for RNA interference was applied for this sequence with the following modification. The siRNA expression plasmids pd2-hU6/1200.1 and pd2-hU6/1200.2 were transfected as a

mixture where equivalent amounts were used. As was observed for SEQ. ID. NO:1, pooling the siRNA expression plasmids produces similar results to those obtained from individual plasmid transfections. Thus, the cell line that was obtained from this transfection was termed RAW-1200.mix (see Fig. 11).

- 5 Treatment of this cell line with RANK ligand resulted in RAW cells that differentiated sooner than the control cell line, RAW-hU6. In addition, the osteoclasts were larger and contained more nuclei per cell (compare panels b and d in Fig. 11A). The experiment was repeated with TRAP staining conducted at days 3, 4 and 5 five to directly compare the RAW-1200.mix line with the control. As shown in Fig. 11B, the
- 10 osteoclasts from the RAW-1200.mix cells appeared much sooner and were mature by day 3, a point at which the control RAW cells are just starting to form small multinucleated cells. Furthermore, osteoclasts derived from the RAW-1200.mix cell line seem to have a reduced survival as a decrease in the number of remaining osteoclasts is observed starting at day 4. The control cells are mature by day 4 and
- 15 many osteoclasts are still present even on day 5.

This result demonstrates that RNA interference of osteoclast-specific genes using the approach of this invention not only identifies those genes that play a role in stimulating osteoclastogenesis, but also serves to validate those candidates that are negative regulators of this process.

- 20 To further substantiate the observations described above, Northern blot analysis was conducted on the total RNA isolated from the RAW-1220.mix cell line and compared to the control RAW-hU6. The blot was initially probed with a fragment of the SEQ. ID. NO:6 cDNA but the message was almost undetectable by this method. The same blot was probed for the osteoclast marker genes, TRAP and Cathepsin K, as before. As
- 25 shown in Fig.12, the expression of TRAP was significantly increased in the RAW-1200.mix cells in agreement with the phenotypic observation. Cathepsin K was also upregulated albeit to a lesser extent. Again, GAPDH demonstrated that equal amounts of RNA were loaded in each lane. These results, like those from the

osteoclastogenesis experiments, suggest that SEQ. ID. NO:6 is a negative regulator of osteoclast differentiation in RAW cells.

SEQ. ID. NO:7:

5 The sequences used for RNA interference were derived from the polynucleotide SEQ. ID. NO:7 and have the SEQ. ID. NOs:79 and 80. The use of RNA interference as described in the invention for SEQ. ID. NOs1 and 2 was applied to SEQ. ID. NO:7. The results obtained (data not shown) were similar to those of SEQ. ID. NO:6 showing that knock-down of this gene resulted in an increase in osteoclast differentiation suggesting that SEQ. ID. NO:7 is a negative regulator of this process in RAW cells.

10 **SEQ. ID. NO:57:**

The sequences used for RNA interference were derived from the polynucleotide SEQ. ID. NO:57 and have the SEQ. ID. NOs:81 and 82. The use of RNA interference as described in the invention for SEQ. ID. NOs1 and 2 was applied to SEQ. ID. NO:57. The results obtained were similar showing that this gene is required for proper
15 differentiation of RAW osteoclasts. An illustration of this result is depicted in Fig. 13.

L- Determination of knockdown effects on bone resorption

The functionality of the identified osteoclast-specific sequences was explored by seeding the cells on OsteologicTM (BD Biosciences, Mississauga, ON) discs to measure their bone resorptive activity. OsteologicTM discs are commercially available
20 and contain a synthetic calcium phosphate substrate and are well known to the skilled artisan as a model for bone degradation.

RAW cells were seeded in 24-well plates containing a calcium phosphate-coated disc (OsteologicTM) at a density of 35 000 cells/well. Treatment with differentiation medium

containing 100 ng/ml RANK ligand was carried out for 5 days where after the osteoclasts were stained for TRAP expression as described above to determine the position and number of multinucleated cells. Osteoclasts were removed with bleach and stained with 5% silver nitrate according to manufacturer's modified von Kossa method. Resorbed pits were observed microscopically. The percentage of resorbed surface area is determined by scanning the negative image of the disc and using Photoshop™ (Adobe) to calculate the percentage of black pixels at maximum contrast. The control, RAW-hU6, was set to the value of 1 and the maximal amount of resorption that was observed with the RAW-hU6 cell line in the presence of RANK ligand was set to 100%.

SEQ. ID. NO:1:

In order to determine if the function of the RAW-0440 cell lines were affected by knockdown of SEQ. ID. NO:1, the cells were cultured and differentiated on Osteologic™ discs. An equal number of RAW cells was seeded on each disc and treated with RANK ligand for a period of 4 days before being fixed and stained by the manufacturer's modified von Kossa method that stains the calcium phosphate substrate. White areas on the disc indicate osteoclast resorption. As shown in Fig. 14A, the control cell line, RAW-hU6, did not cause a large increase in the resorbed area on the disc (panel a) but treatment of RANK ligand to induce osteoclastogenesis resulted in a significant amount of substrate being degraded by the osteoclasts (panel b). All three RAW-0440 cell lines had a reduced ability to degrade the substrate and the discs had a larger area of unresorbed calcium phosphate substrate (panel c-e). The results are shown in Fig. 14B. The values (% black pixels) for the total resorbed area for osteoclasts from the RAW-0440.1, RAW-0440.2, and RAW-0440.3 cell lines were 8.7%, 45.9%, and 22.2%, respectively. These results indicate that targeting the SEQ. ID. NO:1 gene in osteoclasts has the effect of reducing their ability to resorb bone substrate.

SEQ. ID. NO:2:

The approach used for SEQ. ID. NO:1 was used to analyze the RAW-0179 cell lines. As illustrated in Fig. 15, the osteoclasts exhibited a reduced ability to resorb the substrate (Fig. 15A). Quantitative analysis of the remaining material on the discs
5 showed that total resorbed area was 36.1%, 29.4, and 51.2% for the RAW-0179.1, RAW-0179.2, and RAW-0179.3 cell lines, respectively (Fig. 15B). These results indicate that targeting the SEQ. ID. NO:2 gene in osteoclasts has the effect of reducing their ability to resorb bone substrate.

10 ***M- Differential expression of human orthologues of some of the murine osteoclast-specific sequences:***

The human orthologues for some of the murine osteoclast-specific genes have been isolated using gene specific primers for RT-PCR amplification and cloning of the corresponding double-stranded cDNA from mRNA of human osteoclasts and their differential expression pattern measured using RNA from human CD34+ precursor and
15 osteoclasts. Also, their tissue specificity was determined using RNA from 30 different human tissues (adrenal, breast, jejunum, trachea, liver, placenta, aorta, brain, lung, adrenal cortex, esophagus, colon, ovary, kidney, prostate, thymus, skeletal muscle, vena cava, stomach, small intestine, heart, fallopian tube, spleen, bladder, cervix, pancreas, ileum, duodenum, thyroid and testicle) purchased from Ambion (Austin,
20 TX). All RNA samples were amplified using RAMP and macroarrays were prepared as described in Section G. Each human orthologue cDNA was radiolabeled with α -³²P-dCTP using a random priming procedure as specified by the supplier (Amersham, Piscataway, NJ) and used as probe against the RNA present on the macroarrays. Hybridization and washing steps were performed following standard procedures well
25 known in the art. Fig. 16A shows examples of the differential expression of human orthologues for SEQ. ID. NO:2 and SEQ. ID. NO:4 in the various tissues and osteoclasts samples represented on the macroarrays. However, in the case of SEQ. ID. NO:1, the hybridization signal on the macroarray was undetectable due to the

relatively low abundance of this sequence. As such, standard RT-PCR with gene specific primers for human TSP50 was performed on human precursor and osteoclast samples in order to measure its expression (Fig. 16B). The 1.3 Kb TSP50 PCR amplicon was detected in the human osteoclast samples for both donor 1 and donor 4 (Fig. 16B, Lanes 2 and 4 respectively) but not the corresponding precursor samples (Fig. 16B, Lanes 1 and 3 respectively). The 1.3 Kb PCR amplicon was confirmed by sequence analysis as TSP50. It is evident from these results that the human orthologues of some of the murine selected osteoclast-specific sequences are similarly upregulated in the human CD34+ derived osteoclasts and are also highly specific. Thus, these results suggest that the use of the murine RAW264.7 model to identify osteoclast-specific genes involved in human osteoclastogenesis is a valid strategy.

N – Biological validation of the human orthologue for SEQ. ID. NO. 1 (SEQ. ID. NO. 88) in osteoclastogenesis.

In order to validate the biological significance of the human orthologue for SEQ. ID. NO. 1 (SEQ. ID. NO.88), it was important to demonstrate that the function observed in the mouse osteoclast model for SEQ. ID. NO. 1 was conserved in human osteoclasts. Unlike the mouse model where a cell line could be used for osteoclast differentiation, no equivalent model exists in humans. Thus, validation studies were conducted in human primary bone marrow cells using a commercial lentiviral short hairpin (sh) RNA delivery system as described by the manufacturer (Invitrogen, Burlington, ON) unless otherwise stated. The siRNA sequence, 5'-CTGCCTGATCTGGCGTGAT-3' (SEQ ID. NO. 90) was used to specifically target SEQ. ID. NO. 88, the coding sequence of which was cloned from a human osteoclast cDNA library in-house.

A template for the expression of the shRNA was cloned into the lentiviral expression vector and co-transfected in 293FT cells with expression vectors for the viral structural proteins. After two days, supernatants containing the lentivirus were collected and stored at -80°C. After titering, 20 MOIs (multiplicity of infection) were used to infect human osteoclast precursors purchased from Cambrex (East Rutherford, NJ). The

following day, the medium was replaced with fresh medium containing RANK ligand to initiate osteoclast differentiation. Approximately 7 days later, the cells were fixed and TRAP staining performed as described in section B - Preparation of osteoclast differentiated cells. In parallel, lentiviral particles containing a control shRNA against β -galactosidase were also used to infect the human osteoclast precursor cells.

Fig. 17 shows that infection of human bone marrow cells with lentiviruses expressing the specific shRNA for SEQ. ID. NO. 88 (AB0440 siRNA) resulted in a marked decrease of TRAP-positive multinucleated osteoclasts compared to human bone marrow cells infected with lentiviruses expressing the control shRNA (control siRNA) (see arrows in left panel of Fig. 17) in the presence of RANK ligand. These results were in agreement with the validation results obtained in the mouse model (section K- Results of RNA Interference studies) and thus, evidence that the human orthologue for SEQ. ID. NO. 1 (SEQ. ID. NO. 88) plays a similarly important role in differentiation of human osteoclasts.

O – A functional complementation assay for SEQ. ID. NO. 88 to screen for inhibitors of osteoclastogenesis.

A complementation assay was developed to test the function of SEQ. ID. NO. 88 in the differentiation of mouse osteoclasts from RAW264.7 cells devoid of the corresponding endogenous mouse protein. The RAW264.7 cell line containing the mouse-specific shRNA (RAW-AB0440si) for SEQ. ID. NO. 1, which showed greatly reduced ability to differentiate into mature osteoclasts, was transfected with an eukaryotic expression vector containing the entire coding sequence for SEQ. ID. NO. 88, termed lp200-hAB0440. This lp200 expression vector (SEQ. ID. NO. 91) was modified from a commercial vector, pd2-EGFP-N1 (Clontech, Mountain View, CA) where the NEO-KAN antibiotic cassette was replaced by a hygromycin resistance gene for selection in mammalian cells and an ampicillin resistance gene for propagation in prokaryotes. Expression of the inserted human gene sequence is under control of a strong CMV promoter in lp200. Approximately 2.5×10^5 RAW-0440si cells/well were seeded in 6-

well plates and transfected with either 1 μ g lp200 or lp200-hAB0440 using Eugene 6 (Roche, Laval, QC), and stable transfectants selected for 5 days in the presence of 50 μ g/ml hygromycin. Two RAW 264.7-0440si stable cell lines were selected - one that expressed SEQ. ID. NO. 88 (lp200-hAB0440) and the other containing only the vector (lp200). After expansion of these two cell lines, 4 000 cells/well for each were seeded in 96-well plates and left either untreated or treated for 4 days with 100 ng/ml RANK ligand. The cells were fixed and stained for TRAP expression in order to visualize mature osteoclasts.

Fig. 18 shows that the RAW-0440si cells transfected with only the empty lp200 vector were unable to efficiently form osteoclasts (left panels). Conversely, the cells transfected with lp200-hAB0440 (SEQ. ID. NO. 88) were rescued (complemented) and thus, differentiated in response to RANK ligand treatment into osteoclasts (right panels). These results confirm that the function for the mouse and human sequences corresponding to SEQ. ID. NO. 1 is conserved and essential for osteoclast differentiation.

Thus, it is anticipated that this type of complementation cell-based assay may serve as the basis for screening compounds capable of binding to and inhibiting the function of SEQ. ID. NO. 88. A compound library may be applied to this 'rescued' cell line in order to identify molecules (small molecule drugs, peptides, or antibodies) capable of inhibiting the complementation effect of SEQ. ID. NO. 88. Consequently, any measurable reduction in osteoclast differentiation would be indicative of compounds that attenuate the complementation activity of SEQ. ID. NO. 88 in the assay. It is further anticipated that this assay format may be applicable to any gene required for differentiation of RAW264.7 cells into osteoclast, which may be used for drug screening.

P – The human orthologue protein of SEQ. ID. NO. 1 (SEQ. ID. NO. 88) is membrane-bound and glycosylated.

It is contemplated in the literature that SEQ. ID. NO. 88 may encode a membrane-bound or secreted protease, termed Tsp50. In order to determine if the polypeptide for SEQ. ID. NO. 88 is truly membrane-bound or secreted, a plasmid (pCMX-HA-hAB0440) containing the entire coding sequence for SEQ. ID. NO. 88 was constructed. The expression vector, pCMX-HA (SEQ. ID. NO. 92) contains a strong CMV promoter for expression of the HA epitope and cDNA insert. Approximately, 2.5×10^5 Cos-7 cells/well were seeded in 6-well plates and transiently transfected with 1 μ g of the pCMX-HA-hAB0440 expression plasmid using Fugene 6 (Roche, Laval, QC). Cells in some wells were not treated (-) while others were treated with either 2 μ g/ml tunicamycin (T) for 24 hours or 0.5 units/ml phosphoinositol phospholipase C (P) for 1 hour. Tunicamycin blocks the reaction of UDP-GlcNAc and Dol-P in the first step of glycoprotein synthesis, thus inhibiting the synthesis of all N-linked glycoproteins. Phosphoinositol phospholipase C specifically cleaves glycosyl-phosphoinositol (GPI) linkages, which releases GPI anchored proteins into the surrounding medium. The expressed HA fused polypeptide for SEQ. ID. NO. 88 was detected by Western blot analysis with an anti-HA antibody (Sigma, St. Louis, MO). Following lysis of the pCMX-HA-hAB0440-Cos-7 cells, soluble fractions were prepared, separated on a SDS-polyacrylamide gel and transferred to a PVDF membrane. The protein blot was then incubated with anti-HA antibody for 1 hour and the bands visualized using the ECL kit from Roche (Laval, QC). The same Western blot was stripped and reacted with an anti-actin antibody to control for equal loading of protein samples.

Fig. 19 shows a polypeptide with a predicted size of 37 KDa corresponding to the full-length polypeptide for SEQ. ID. NO. 88. Interestingly, expression of this polypeptide was only observed when the transiently transfected cells were treated with tunicamycin in the presence of 10% FBS in the culture media compared to serum-starved cells (0% FBS) (Fig. 19, Lanes T). This finding suggested that inhibition of N-linked glycosylation resulted in trapping of the SEQ. ID. NO. 88 polypeptide within the cells, which is evidence that the protein is glycosylated. Following treatment with phosphoinositol phospholipase C, the SEQ. ID. NO. 88 polypeptide was no longer detected in the soluble fraction (Fig. 19, Lanes P), which suggested that it was released into the media likely due to cleavage of the proposed GPI linkage. As a

control for equal loading, the membrane was stripped and reacted with an antibody against the housekeeping protein, α -actin, which showed that the observed differences in expression of the SEQ. ID. NO. 88 polypeptide was not a result of unequal loading of the gel (Fig. 19, α -actin panel).

5 ***Q – Inhibition of RAW264.7 differentiation into osteoclast using a monoclonal anti-Tsp50 (SEQ. ID. NO. 1) antibody.***

In light of the results demonstrating that of the polypeptide for SEQ. ID. NO. 88 (depicted in SEQ ID NO.:153) is essential for osteoclast differentiation (see Example N) and it is localized at the cell surface (see Example P), then this protein represents
10 an excellent candidate for the development of an antibody therapeutic strategy for treating the symptoms of osteoporosis. A monoclonal antibody against mouse Tsp50 (R&D Systems, Minneapolis, MN) was purchased and used to test whether or not a specific antibody against the polypeptide for SEQ. ID. NO. 1 (depicted in SEQ ID NO.:93) would inhibit osteoclast differentiation in the RAW 264.7 model.
15 Approximately, 4 000 RAW264.7 cells/well were seeded in 96-well plates and treated with 100 ng/ml RANK ligand in the presence of increasing concentrations of either the mouse monoclonal antibody against Tsp50 or a control anti-HA antibody (Sigma, St. Louis, MO). Three days later, the cells were fixed and stained for TRAP expression and the multinucleated cells were scored.

20 Fig. 20A is a histogram showing that increasing concentrations of anti-Tsp50 antibody (anti-AB0440) resulted in a dose-dependent decrease in the number of multinucleated osteoclasts with maximal inhibition seen at 50 μ g/ml. Whereas, treatment of the RAW264.7 cells with equivalent concentrations of the anti-HA antibody resulted in no statistically significant effect. Fig. 20A represents an average of two experiments
25 conducted in triplicate. Treatment with the anti-AB0440 did not result in death of the RAW264.7 cells but rather, inhibition of differentiation as measured by the loss in mature osteoclasts seen after TRAP staining and no significant reduction in precursor cell numbers (Fig. 20B). These results indicate that antibodies which specifically target

osteoclast-specific cell surface or secreted proteins required for differentiation, as exemplified by anti-AB0440, have the potential to serve as therapeutic drugs for treating osteoporosis by reducing osteoclast numbers and consequently, bone resorption activity. It is contemplated that recombinant and/or monoclonal antibodies developed to the polypeptide for SEQ. ID. NO. 88 may function similarly to anti-AB0440 seen for the mouse model in this example.

R – Development of a functional interaction assay to screen for inhibitors of osteoclast activity using SEQ. ID. NO. 2 as a model.

SEQ. ID. NO. 2 (AB0179) belongs to an osteoclast-specific vacuolar (v)-ATPase, a large protein complex containing several subunits. The v-ATPase a subunit comprises four isoforms (a1 - a4), which constitutes the V₀ domain. This domain is important for the hydrolysis of ATP in order to provide the energy required for the secretion of protons across the plasma membrane into the pocket that is created between the ruffled membrane of the mature osteoclast and the bone surface. In osteoclasts, the a3 subunit interacts with the d subunit, which is important for the structural integrity of the ATPase complex (Nishi and Forgac, 2002). There are two d subunits in humans, d1 and d2, the latter found almost exclusively in osteoclasts and is coded for by the human orthologue of SEQ. ID. NO. 2 which corresponds to polynucleotide SEQ. ID. NO. 89 (encoding SEQ ID NO.:154). Validation studies using the RAW264.7 model have clearly demonstrated the importance of d2 in osteoclast function (section K - Results of RNA Interference studies) where in the presence of siRNAs against SEQ. ID. NO. 2, the bone resorbing activity of mature osteoclasts was markedly reduced. Additionally, it has been well documented that the a3 isoform is the major form of the v-ATPase a subunit in osteoclasts and bone in general (Smith et al., 2005). Thus, in order to identify molecules that are capable of inhibiting the function of the v-ATPase in osteoclasts, the specific interaction between the d2 and a3 subunits will be exploited.

The expression of the d isoforms in human osteoclast and precursor cells (HOPs) was

measured by Northern blot analysis. Approximately, 1.5×10^4 precursor cells/well were seeded in 96-well plates and a portion was treated with 33 $\mu\text{g/ml}$ M-CSF and 100 ng/ml RANK ligand for 7 days to form osteoclasts. Total RNA was prepared from the precursors and osteoclasts using Trizol™ (Invitrogen, Burlington, ON) and 10 $\mu\text{g/lane}$ was electrophoresed in a 1% agarose/TAE gel. The RNA was electrotransferred to a nylon membrane and hybridized sequentially to [^{32}P]dCTP labeled probes specific for the d2 (SEQ. ID. NO. 89) and d1 subunits, for the osteoclast-specific gene, Cathepsin K and for the housekeeping gene, β -actin. The washed membrane was exposed to film for the required amount of time to detect the corresponding mRNA bands.

Fig. 21A shows that SEQ. ID. NO. 89 (d2) was upregulated in response to RANK ligand (Panel 1; Lane RL) compared to precursors (Panel 1; Lane -). With the probe specific for v-ATPase d1, the opposite expression pattern was observed indicating that this d isoform was downregulated in osteoclasts (Panel 2; Lane RL) compared to precursors (Panel 2; Lane -). As expected, the osteoclast-specific gene, Cathepsin K was highly upregulated in response to RANK ligand and not present in the precursors (Panel 3). Equal loading of the RNA samples was evident by the non-differential expression pattern of the housekeeping gene, β -actin (Panel 4). Since a3 is predominantly found in the v-ATPase a subunit of osteoclasts, these results then suggests that the d2 subunit would most likely be complexed with the a3 subunit in human osteoclasts v-ATPase. Thus, isolation of a specific inhibitor of this interaction would preferentially reduce the osteoclast-specific v-ATPase activity and thus, bone resorption.

In order to experimentally demonstrate the interaction between d2 and a3, the coding sequence corresponding to SEQ. ID. NO. 89 (d2) (SEQ ID NO.:154) was cloned into the prokaryotic expression vector, pGEX-2T (Pharmacia, GE Healthcare), expressed as a GST fusion protein in *E. coli* and purified with glutathione beads. In parallel, cDNA fragments of mouse v-ATPase-a3 (amino acids 1-385) and v-ATPase a4 (amino acids 1-388) were cloned into the eukaryotic expression vector, pCMX-Flag in order to express a Flag-tagged a3 subunit or a4 subunit in mammalian cells. The pCMX-

Flag/v-ATPase-a3 and pCMX-Flag/v-ATPase-a4 recombinant plasmids were transfected in 293FT cells and cell lysates were generated in which, the v-ATPase-a3 and v-ATPase-a4 FLAG-tagged polypeptides were readily detected with an anti-Flag antibody (Fig. 21B, II, upper panel).

- 5 In order to measure the interaction between d2 (SEQ. ID. NO. 89) and a3 or a4, equal amounts of 293FT lysates containing either Flag-tagged a3 or a4 were incubated with purified GST or GST-d2 at 4°C for 90 minutes under mild agitation. After washing, the protein mixes were separated on a SDS-PAGE and transferred to PVDF membrane. The membrane was then incubated with anti-Flag antibody (Sigma, St. Louis, MO) and
- 10 the bands visualized using the ECL kit from Roche (Laval, QC). Clearly, only the a3 fragment could be detected in the GST-d2 reactions compared to the GST reactions indicating a specific interaction between d2 and a3 (Fig. 21B, I-a3, upper panel) but not between d2 and a4 (Fig. 21B, I-a4, upper panel). The membrane was then re-probed with anti-GST antibody, which showed that equal amounts of GST fusion
- 15 protein were used in each reaction (Fig. 21B, I, lower panel). Additionally, the use of an anti-Flag antibody showed that equal quantities of a3 and a4 were present in the binding reactions (Fig. 21B, II, upper panel) and the same membrane re-probed with an anti-actin antibody, demonstrated that equal amounts of the corresponding cell lysate was used (Fig. 21B, II, lower panel). Thus, this observed specific interaction
- 20 between d2 and a3 forms the basis for developing a screening assay to interrogate compound libraries (small molecule drugs, peptides, or antibodies) in order to identify those compounds capable of inhibiting this interaction. Such a screening assay may be developed as a FRET (fluorescence resonance energy transfer) method or any similar methods, which are highly sensitive and easily upscalable for high throughput
- 25 screening in multiwell plates. These compounds may be useful as therapeutics for modulating the bone resorption activity of osteoclasts by inhibiting the function of the osteoclast-specific v-ATPases.

- v-ATPases present in other tissues, most notably the kidney (Nishi and Forgac, 2002) where the d2 gene is expressed at low levels as shown by us and others (Nishi et al.,
- 30 2003; Smith et al., 2005) do not appear to contain the a3 subunit but rather, the a4

subunit (Stehberger et al., 2003; Smith et al., 2000). Therefore, an inhibitor of the interaction between $\alpha 2$ and $\alpha 3$ would preferentially be effective in human osteoclasts and would not interfere with v-ATPases in other tissues.

5 One of skill in the art will readily recognize that orthologues for all mammals maybe identified and verified using well-established techniques in the art, and that this disclosure is in no way limited to one mammal. The term "mammal(s)" for purposes of this disclosure refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

10 The sequences in the experiments discussed above are representative of the NSEQ being claimed and in no way limit the scope of the invention. The disclosure of the roles of the NSEQs in osteoclastogenesis and osteoclast function satisfies a need in the art to better understand the bone remodeling process, providing new compositions that are useful for the diagnosis, prognosis, treatment, prevention and evaluation of
15 therapies for bone remodeling and associated disorders.

The art of genetic manipulation, molecular biology and pharmaceutical target development have advanced considerably in the last two decades. It will be readily apparent to those skilled in the art that newly identified functions for genetic sequences and corresponding protein sequences allows those sequences, variants
20 and derivatives to be used directly or indirectly in real world applications for the development of research tools, diagnostic tools, therapies and treatments for disorders or disease states in which the genetic sequences have been implicated.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it maybe modified, without departing from the spirit and nature
25 of the subject invention as defined in the appended claims.

TABLE 1 – Differentially expressed sequences found in osteoclasts and demonstrated to have an effect on osteoclastogenesis following inhibition with specific siRNAs.

Nucleotide Sequence No.	NCBI Unigene #/Gene Symbol/Gene ID	Accession Number	ORF Nucleotide Positions/ Polypeptide sequence No.	Function
SEQ ID NO. 1	Mm .102265 /Tsp50 /235631	NM_146227	26-1345 encoding SEQ IDNO.:93	peptidase activity
SEQ ID NO. 2	Mm .19298 / Atp6v0d2 / 242341	NM_175406	70-1122 encoding SEQ ID NO.: 94	hydrogen-transporting ATPase activity, rotational mechanism
SEQ ID NO. 3	Mm .20904 / Crtap / 56693	NM_019922	72-1274 encoding SEQ ID NO.: 95	extracellular space protein; function unknown
SEQ ID NO. 4	Mm .12654 /A230106M15 Rik/ 231717	NM_175474	314-1114 encoding SEQ ID NO.: 96	hypothetical protein LOC231717; function unknown
SEQ ID NO. 5	Mm.181860 / Tubb6 / 67951	NM_026473	28-1371 encoding SEQ ID NO.: 97	GTPase activity; structural molecule activity
SEQ ID NO. 6	Mm .323393 / Josd1 / 74158	NM_028792	905-1513 encoding SEQ ID NO.: 98	hypothetical protein LOC74158; function unknown
SEQ ID NO. 7	Mm.332739 / Lat2 / 56743	NM_022964	162-737 encoding SEQ ID NO.: 99	extracellular space; function unknown
SEQ ID NO. 57	Mm .103560 / Jundm2 / 81703	NM_030887	232-723 encoding SEQ ID NO.: 100	transcriptional repressor activity; shown to play a role in RANK-mediated signal transduction, especially in osteoclast differentiation

TABLE 2 – Differentially expressed sequences found in osteoclasts with putative roles in bone remodeling.

Nucleotide Sequence No.	NCBI Unigene #/Gene Symbol/Gene ID	Accession Number	ORF Nucleotide Positions/ Polypeptide sequence No.	Function
SEQ ID NO. 8	Mm.10154 / Tesk1 / 21754	NM_011571	1497-3380 encoding SEQ ID NO.: 101	Protein kinase activity
SEQ ID NO. 9	Mm.142827 / Otud5 / 54644	NM_138604	287-1987 encoding SEQ ID NO.: 102	hypothetical protein LOC54644
SEQ ID NO. 10	Mm.146001 / Rassf8 / 71323	BC004678	1-311 encoding SEQ ID NO.: 103	Ras association possibly involved in signal transduction
SEQ ID NO. 11	Mm.153014 / Gcn111 / 231659	BC068244	251-1246 encoding SEQ ID NO.: 104	possibly involved in amino acid biosynthesis with exact function unknown
SEQ ID NO. 12	Mm.153159 / Cct6a / 12466	NM_009838	55-1650 encoding SEQ ID NO.: 105	chaperonin containing TCP-1 possibly involved in protein folding and binding
SEQ ID NO. 13	Mm.157103 / Hsd3b7 / 101502	NM_133943	53-487 encoding SEQ ID NO.: 106	involved in steroid biosynthesis
SEQ ID NO. 14	Mm.169234 / 2310005014 Rik / 67914	NM_026452	6-947 encoding SEQ ID NO.: 107	hypothetical protein LOC67914
SEQ ID NO. 15	Mm.266341 / Nrp2 / 18187	NM_010939	537-3281 encoding SEQ ID NO.: 108	receptor activity and cell adhesion

Nucleotide Sequence No.	NCBI Unigene #/Gene Symbol/Gene ID	Accession Number	ORF Nucleotide Positions/ Polypeptide sequence No.	Function
SEQ ID NO. 16	Mm.17917 / Efhd2 / 27984	NM_025994	55-777 encoding SEQ ID NO.: 109	calcium ion binding
SEQ ID NO. 17	Mm.200499 / Eif2ak1 / 15467	NM_146165	116-958 encoding SEQ ID NO.: 110	protein kinase or transferase activity
SEQ ID NO. 18	Mm.20845 / Abcc5 / 27416	NM_013790	200-4510 encoding SEQ ID NO.: 111	ATPase activity, coupled to transmembrane movement of substances
SEQ ID NO. 19	Mm.21880 / Htra2 / 64704	NM_019752	146-1522 encoding SEQ ID NO.: 112	proteolysis
SEQ ID NO. 20	Mm.2271 / Ccl9 / 20308	NM_011338	154-522 encoding SEQ ID NO.: 113	chemokine activity
SEQ ID NO. 21	Mm.24684 / Fosl2 / 14284	NM_008037	171-1151 encoding SEQ ID NO.: 114	regulation of transcription, DNA- dependent
SEQ ID NO. 22	Mm.251199 / Arrdc4 / 66412	NM_025549	139-1029 encoding SEQ ID NO.: 115	molecular function unknown
SEQ ID NO. 23	Mm.2534 / Pstpip1 / 19200	NM_011193	242-1489 encoding SEQ ID NO.: 116	cell adhesion
SEQ ID NO. 24	Mm.266592 / C030034I22Ri k / 77533	XM_488832	1-987 encoding SEQ ID NO.: 117	molecular function unknown

Nucleotide Sequence No.	NCBI Unigene #/Gene Symbol/Gene ID	Accession Number	ORF Nucleotide Positions/ Polypeptide sequence No.	Function
SEQ ID NO. 25	Mm.268165 / Cflar / 12633	BC029223	475-1920 encoding SEQ ID NO.: 118	caspase activity
SEQ ID NO. 26	Mm.272047 / Helz / 78455	BC060114	246-1286 encoding SEQ ID NO.: 119	helicase activity
SEQ ID NO. 27	Mm.278726 / Mak3 / 72117	NM_028108	296-802 encoding SEQ ID NO.: 120	N-acetyltransferase activity
SEQ ID NO. 28	Mm.279861 / Polr2f / 69833	BC024419	49-432 encoding SEQ ID NO.: 121	regulation of transcription
SEQ ID NO. 29	Mm.280895 / Uck2; AI481316 / 80914 ;98383	BC023789/ AI481316	218-1003 encoding SEQ ID NO.: 122	kinase activity/ hypothetical protein LOC98383
SEQ ID NO. 30	Mm.217216 / Magi1 /14924	BC095943	574-3920 encoding SEQ ID NO.: 123	intracellular signaling cascade
SEQ ID NO. 31	Mm.286536 / Fblim1 /74202	NM_133754	137-1264 encoding SEQ ID NO.: 124	cell adhesion
SEQ ID NO. 32	Mm.286753 / Rgs3 /50780	NM_019492	236-2068 encoding SEQ ID NO.: 125	signal transducer activity
SEQ ID NO. 33	Mm.298728 / Nisch / 64652	NM_022656	335-4399 encoding SEQ ID NO.: 126	receptor activity; integrin binding
SEQ ID NO. 34	Mm.129840 / 9430063L05Rik/ 229622	BC050783	371-3727 encoding SEQ ID NO.: 127	hypothetical protein LOC229622; function unknown

Nucleotide Sequence No.	NCBI Unigene #/Gene Symbol/Gene ID	Accession Number	ORF Nucleotide Positions/ Polypeptide sequence No.	Function
SEQ ID NO. 35	Mm.31672 / Cdk6 / 12571	NM_009873	56-1036 encoding SEQ ID NO.: 128	cyclin-dependent protein kinase activity
SEQ ID NO. 36	Mm.331198 / Tdrkh / 72634	BC057030	94-1776 encoding SEQ ID NO.: 129	transcription factor
SEQ ID NO. 37	Mm.44901 / 2610510H03Rik / 68215	NM_026620	30-1319 encoding SEQ ID NO.: 130	function unknown
SEQ ID NO. 38	Mm.348047 / Usmg4 / 83679	BC046620	329-610 encoding SEQ ID NO.: 131	function unknown
SEQ ID NO. 39	Mm.37803 / Specc1 / 432572	BC030438		No significant predicted ORF at present/ function unknown
SEQ ID NO. 40	Mm.295306 / BC025076 / 216829	BC025076	123-494 encoding SEQ ID NO.: 132	hypothetical protein LOC216829; function unknown
SEQ ID NO. 41	Mm.45815 / Bcar3 / 29815	BC023930	405-2867 encoding SEQ ID NO.: 133	guanyl-nucleotide exchange factor activity
SEQ ID NO. 42	Mm.4615 / Dlgh3 / 53310	NM_016747	325-2874 encoding SEQ ID NO.: 134	function unknown
SEQ ID NO. 43	Mm.86572 / BC017612 / 170748	BC017612	192-371 encoding SEQ ID NO.: 135	function unknown
SEQ ID NO. 44	Mm.354736 / Gas2l3 / 237436	XM_137276	730-2781 encoding SEQ ID NO.: 136	function unknown

Nucleotide Sequence No.	NCBI Unigene #/Gene Symbol/Gene ID	Accession Number	ORF Nucleotide Positions/ Polypeptide sequence No.	Function
SEQ ID NO. 45	Mm.240265 / 5830415L20Rik/ 68152	BC027051	81-428 encoding SEQ ID NO.: 137	hypothetical protein LOC68152 ; function unknown
SEQ ID NO. 46	Mm.27545 / Hrmt1l2 / 15469	BC002249	25-1056 encoding SEQ ID NO.: 138	S-adenosylmethionine-dependent methyltransferase activity
SEQ ID NO. 47	Mm.28071 / 1810030N24Rik/ 66291	BC027508	65-358 encoding SEQ ID NO.: 139	integral to membrane; function unknown
SEQ ID NO. 48	Mm.293761 / Pofut1 / 140484	BC046295	56-1237 encoding SEQ ID NO.: 140	transferase activity, transferring glycosyl groups
SEQ ID NO. 49	Mm.341204 / Itsn2 / 20403	NM_011365	258-5234 encoding SEQ ID NO.: 141	calcium ion binding
SEQ ID NO. 50	Mm.347964 / Fahd1 / 68636	BC026949	189-872 encoding SEQ ID NO.: 142	hydrolase activity; calcium ion binding activity
SEQ ID NO. 51	Mm.46513 / 2610200G18Rik/ 67149	NM_025998	87-710 encoding SEQ ID NO.: 143	hypothetical protein LOC67149; integral to membrane; function unknown
SEQ ID NO. 52	Mm.6743 / Nfe2l1 / 18023	NM_008686	249-2474 encoding SEQ ID NO.: 144	regulation of transcription, DNA-dependent
SEQ ID NO. 53	Mm.78861 / Nolc1 / 70769	NM_053086	30-1229 encoding SEQ ID NO.: 145	nucleolus organization and biogenesis

Nucleotide Sequence No.	NCBI Unigene #/Gene Symbol/Gene ID	Accession Number	ORF Nucleotide Positions/ Polypeptide sequence No.	Function
SEQ ID NO. 54	Mm.86437 /Spcs3 / 76687	BC054817	59-601 encoding SEQ ID NO.: 146	hydrolase activity; receptor activity
SEQ ID NO. 55	Mm.296902 / Tapbp1 / 213233	BC017613	264-1619 encoding SEQ ID NO.: 147	function unknown
SEQ ID NO. 56	Mm.159563 / Tm7sf4 / 75766	XM_128030	50-1294 encoding SEQ ID NO.: 148	transmembrane 7 superfamily member 4 ; function unknown

TABLE 3 – List of mRNA spliced variants for some Sequence IDs isolated thus far from mouse and human osteoclast RNA samples

Nucleotide Sequence No.	Spliced Variant Identification	ORF Nucleotide Positions	Polypeptide sequence No.
SEQ ID NO. 83	0440-TO4-22-mFL_15	21-1259	SEQ ID NO.:149
SEQ ID NO. 84	0179-SL22-hFL_36 (human orthologue variant #1)	40-1092	SEQ ID NO.:150
SEQ ID NO. 85	0179-SL22-hFL_1 (human orthologue variant #2)	40-978	SEQ ID NO.:155
SEQ ID NO. 86	0799-SL22-mFL_3_(TAG1-3'UTR)	40-978	SEQ ID NO.:151
SEQ ID NO. 87	0799-SL22-mFL_4_(TAG1-3'UTR)	124-750	SEQ ID NO.:152

TABLE 4 –List of some human orthologue

Sequence Identification	NCBI Unigene Cluster	Accession Number	ORF Nucleotide Positions	Polypeptide sequence No.
SEQ ID NO. 88	Hs.120365	NM_013270	51-1208	SEQ ID NO.:153
SEQ ID NO. 89	Hs.436360	NM_152565	70-1122	SEQ ID NO.:154

- 5 **TABLE 5** – list of additional sequences identification of plasmids and siRNA oligonucleotides

Sequence Identification	name	Description
SEQ. ID. NO. 58	p14	Vector for STAR
SEQ. ID. NO. 59	p17+	Vector for STAR
SEQ. ID. NO. 60	pCATRMAN	Vector for STAR
SEQ. ID. NO. 61	p20	Vector for STAR
SEQ. ID. NO. 62	OGS 77	Primer used for STAR p14 vector
SEQ. ID. NO. 63	OGS 302	Primer used for STAR p17+ vector
SEQ. ID. NO: 64	0440.1	siRNA sequence for SEQ. ID. NO. 1
SEQ. ID. NO: 65	0440.2	siRNA sequence for SEQ. ID. NO. 1
SEQ. ID. NO: 66	0440.3	siRNA sequence for SEQ. ID. NO. 1
SEQ. ID. NO: 67	0.179.1	siRNA sequence for

Sequence Identification	name	Description
		SEQ ID NO.:2
SEQ. ID. NO: 68	0.179.2	siRNA sequence for SEQ ID NO.:2
SEQ. ID. NO: 69	0.179.3	siRNA sequence for SEQ ID NO.:2
SEQ. ID. NO: 70	0799.1	siRNA sequence for SEQ ID NO.:3
SEQ. ID. NO: 71	0799.2	siRNA sequence for SEQ ID NO.:3
SEQ. ID. NO: 72	0799.3	siRNA sequence for SEQ ID NO.:3
SEQ. ID. NO: 73	0351.1	siRNA sequence for SEQ ID NO.:4
SEQ. ID. NO: 74	0351.2	siRNA sequence for SEQ ID NO.:4
SEQ. ID. NO: 75	1035.1	siRNA sequence for SEQ ID NO.:5
SEQ. ID. NO: 76	1035.2	siRNA sequence for SEQ ID NO.:5
SEQ. ID. NO: 77	1200.1	siRNA sequence for SEQ ID NO.:6
SEQ. ID. NO: 78	1200.2	siRNA sequence for SEQ ID NO.:6
SEQ. ID. NO: 79	0233A.1	siRNA sequence for SEQ ID NO.:7
SEQ. ID. NO: 80	0233A.2	siRNA sequence for SEQ ID NO.:7

Sequence Identification	name	Description
SEQ. ID. NO: 81	0682.1	siRNA sequence for SEQ ID NO.:57
SEQ. ID. NO: 82	0682.2	siRNA sequence for SEQ ID NO.:57
SEQ. ID. NO. 90		siRNA sequence for SEQ. ID. NO.88
SEQ. ID. NO. 91		lp200 expression vector
SEQ. ID. NO. 92		pCMX-HA expression vector

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U.S. Patent No. 6,498,024, Malek et al., December 24, 2002
(U.S. Patent Application No. 11/000,958 filed on December 2, 2003 published under
No. US 2005/0153333A1 on July 14, 2005 and entitled "Selective Terminal Tagging of
Nucleic Acids"
- 10 US Patent 6,617,434 Duffy, September 9, 2003
US Patent 6,451,555 Duffy, September 17, 2002

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5 Throughout this specification the word "comprise", or variations such as
"comprises" or "comprising", will be understood to imply the inclusion of a stated
element, integer or step, or group of elements, integers or steps, but not the
exclusion of any other element, integer or step, or group of elements, integers or
steps.

10 Any description of prior art documents herein is not an admission that the
documents form part of the common general knowledge of the relevant art in
Australia.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated or recombinant antibody or antigen binding fragment which binds to a polypeptide having at least 67% similarity with SEQ ID NO: 153 when used to inhibit osteoclast differentiation, bone resorption or bone remodeling by impairing an activity of the polypeptide in osteoclast precursor cells or in osteoclasts or to diagnose bone disease or detect bone remodeling.
2. The isolated or recombinant antibody or antigen binding fragment of claim 1, wherein the polypeptide has a sequence at least 80% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 90% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 95% identical to SEQ ID NO.:153 or SEQ ID NO.:93 or identical to SEQ ID NO.:153 or SEQ ID NO.:93.
3. The isolated or recombinant antibody or antigen binding fragment of claim 1 or 2, wherein the activity is osteoclastogenesis.
4. The isolated or recombinant antibody or antigen binding fragment of claim 1 or 2, wherein the antibody or antigen binding fragment reduces differentiation of osteoclast precursor cells into osteoclasts.
5. The isolated or recombinant antibody or antigen binding fragment of any one of claims 1 to 4, wherein the antibody is a polyclonal antibody.
6. The isolated or recombinant antibody or antigen binding fragment of any one of claims 1 to 4, wherein the antibody is a monoclonal antibody or an antigen binding fragment thereof.
7. The isolated or recombinant antibody or antigen binding fragment of any one of claims 1 to 4, wherein the antibody is a chimeric antibody.
8. The isolated or recombinant antibody or antigen binding fragment of any one of claims 1 to 4, wherein the antigen binding fragment is a FV, a Fab, a Fab' or a (Fab')₂.

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9. An antibody or antigen binding fragment which impairs osteoclastogenesis, the antibody or antigen binding fragment being isolated by the method of:
- providing a candidate antibody or antigen binding fragment which binds to a polypeptide having at least 67% similarity with SEQ ID NO.: 153 to an osteoclast precursor cell;
 - testing osteoclastogenesis, whereby reduced osteoclastogenesis positively identifies an antibody or antigen binding fragment capable of impairing the activity of the polypeptide in osteoclast precursor cells or in osteoclasts;
 - isolating the antibody and;
 - optionally producing antigen binding fragments of the isolated antibody.
10. The antibody or antigen binding fragment of claim 9, wherein the candidate antibody or antigen binding fragment binds to polypeptide having a sequence at least 80% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 90% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 95% identical to SEQ ID NO.:153 or SEQ ID NO.:93 or identical to SEQ ID NO.:153 or SEQ ID NO.:93.
11. The antibody or antigen binding fragment of claim 9 or 10, wherein the antibody is a polyclonal antibody.
12. The antibody or antigen binding fragment of claim 9 or 10, wherein the antibody is a monoclonal antibody or an antigen binding fragment thereof.
13. The antibody or antigen binding fragment of claim 9 or 10, wherein the antibody is a chimeric antibody.
14. The antibody or antigen binding fragment of claim 9 or 10, wherein the antigen binding fragment is a FV, a Fab, a Fab' or a (Fab')₂.
15. A conjugate comprising the antibody or antigen binding fragment of any one of claims 1 to 14 conjugated with a therapeutic agent.
16. A pharmaceutical composition comprising the antibody or antigen binding fragment of any one of claims 1 to 14 or the conjugate of claim 15 and a pharmaceutically acceptable carrier.

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17. A method for treating or preventing bone remodeling or bone disease comprising administering an antibody or antigen binding fragment which binds to a polypeptide having at least 67% similarity with SEQ ID NO.:153 or a conjugate comprising the antibody or antigen binding fragment thereof to a subject in need.
18. The method of claim 17, wherein the antibody or antigen binding fragment is as defined in any one of claims 1 to 14 or wherein the conjugate is as defined in claim 15.
19. The method of claim 17 or 18, wherein the subject in need suffers from a condition selected from the group consisting of bone loss, osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Turner syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets, fibrogenesis imperfecta ossium, osteosclerotic disorders, pycnodysostosis and damage caused by macrophage-mediated inflammatory processes.
20. A method for identifying a compound able to inhibit osteoclast differentiation, the method comprising:
 - a. contacting a candidate compound with a polypeptide having at least 67% similarity with SEQ ID NO.:153 or a cell expressing the polypeptide, wherein said polypeptide is capable of inducing osteoclast differentiation;
 - b. measuring activity or expression of the polypeptide,
 wherein a reduction in the activity or expression of the polypeptide positively identifies a suitable inhibitory compound.
21. The method of claim 20, wherein the polypeptide has a sequence at least 80% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 90% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 95% identical to SEQ ID NO.:153 or SEQ ID NO.:93 or identical to SEQ ID NO.:153 or SEQ ID NO.:93.

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22. The method of claim 20, wherein the step of measuring the activity or expression of the polypeptide comprises determining osteoclast differentiation.
23. The method of claim 20, wherein the method further comprises a step of inducing osteoclast differentiation.
24. The method of claim 20, wherein the reduction of the activity or expression is associated with a reduction of osteoclast differentiation.
25. The method of any one of claims 20 to 24, wherein the candidate compound is capable of binding to the polypeptide.
26. The method of any one of claims 20 to 24, wherein the candidate compound is an antibody or an antigen binding fragment thereof.
27. The method of any one of claims 20 to 24, wherein the candidate compound is an siRNA or a shRNA.
28. A method of purifying an inhibitor of osteoclast formation, said method comprising:
- (a) contacting a library of candidate compounds with a polypeptide having at least 67% identity to SEQ ID NO: 153 or a cell expressing said polypeptide;
 - (b) measuring the expression or activity of the polypeptide; and
 - (c) purifying from the library of compounds a compound that reduces the expression or activity of the polypeptide.
29. A purified inhibitor of osteoclast formation when purified by performing the method of claim 28, wherein the purified compound was not known before performing said method to be in a purified form or to inhibit osteoclast formation.
30. A pharmaceutical composition comprising the purified inhibitor of claim 29 and a pharmaceutically acceptable carrier.

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31. Use of the antibody or antigen binding fragment of any one of claims 1 to 14, conjugate of claim 15, pharmaceutical composition of claim 16 or claim 30 or purified inhibitor of claim 29 in modulating osteoclast differentiation or in treating or preventing bone remodeling or bone disease.

32. Use of the antibody or antigen binding fragment of any one of claims 1 to 14, conjugate of claim 15, pharmaceutical composition of claim 16 or claim 30 or purified inhibitor of claim 29 in the preparation of a medicament for modulating osteoclast differentiation or in treating or preventing bone remodeling or bone disease.

33. Use of an isolated or recombinant polypeptide in modulating osteoclast differentiation or in treating or preventing bone disease or bone remodeling, said isolated polypeptide comprising a sequence selected from the group consisting of polypeptides having at least 80% identity with SEQ ID NO.:153 or SEQ ID NO.:93 and fragments thereof.

34. Use of an isolated or recombinant polynucleotide in modulating osteoclast differentiation or in treating or preventing bone disease or bone remodeling, said isolated polynucleotide being selected from the group consisting of:

- a. A polynucleotide comprising SEQ ID NO.:1 or SEQ ID NO.:88,
- b. A polynucleotide comprising nucleotides 26-1345 of SEQ ID NO.: 1 or nucleotides 51-1208 of SEQ ID NO.: 88,
- c. A polynucleotide comprising a sequence at least 80% identical to a. or b.,
- d. A fragment of any one of a. to c., and
- e. A complement of any one of a. to d.

35. The use of claim 34, characterized in that the polynucleotide comprises a shRNA or siRNA.

36. Use of a compound which interferes with the activity or expression of a polypeptide having at least 80% identity with SEQ ID NO.:153 or in SEQ ID NO.:93 or a polypeptide encoded by SEQ ID NO.:1 or SEQ ID NO.:88 in modulating osteoclast differentiation or in treating or preventing bone disease or bone remodeling, wherein

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said compound is selected from the group consisting of antibodies and antigen binding fragments thereof binding specifically to the polypeptide or to a fragment thereof and siRNAs or shRNAs specifically inhibiting activity or expression of a polypeptide encoded by SEQ ID NO.:1 or by SEQ ID NO.:88.

37. Use of a pharmaceutical composition in modulating osteoclast differentiation or in treating or preventing bone disease or bone remodeling comprising a) an isolated or recombinant polypeptide having at least 67% similarity with SEQ ID NO.:153 or a fragment thereof and b) a pharmaceutically acceptable carrier.

38. The use of claim 37, wherein the polypeptide has a sequence at least 80% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 90% identical to SEQ ID NO.:153 or SEQ ID NO.:93, at least 95% identical to SEQ ID NO.:153 or SEQ ID NO.:93 or identical to SEQ ID NO.:153 or SEQ ID NO.:93 or a fragment thereof.

39. Use of a pharmaceutical composition in modulating osteoclast differentiation or in treating or preventing bone disease or bone remodeling, the pharmaceutical composition comprising an isolated polynucleotide selected from the group consisting of:

- a. A polynucleotide comprising SEQ ID NO.:1 or SEQ ID NO.:88,
 - b. A polynucleotide comprising nucleotides 26-1345 of SEQ ID NO.: 1 or nucleotides 51-1208 of SEQ ID NO.: 88,
 - c. A polynucleotide comprising a sequence at least 80% identical to a. or b.,
 - d. A fragment of any one of a. to c., and
 - e. A complement of any one of a. to d.
- and a pharmaceutically acceptable carrier.

40. Use of an isolated or recombinant polypeptide in the manufacture of a medicament for modulating osteoclast differentiation or for treating or preventing bone disease or bone remodeling, said isolated or recombinant polypeptide comprising a sequence selected from the group consisting of polypeptides having at least 80% identity with SEQ ID NO.:153 or SEQ ID NO.:93 and fragments thereof.

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41. Use of an isolated or recombinant polynucleotide in the manufacture of a medicament for modulating osteoclast differentiation or for treating or preventing bone disease or bone remodeling, said isolated or recombinant polynucleotide being selected from the group consisting of:

- a. A polynucleotide comprising SEQ ID NO.:1 or SEQ ID NO.:88,
- b. A polynucleotide comprising nucleotides 26-1345 of SEQ ID NO.: 1 or nucleotides 51-1208 of SEQ ID NO.: 88,
- c. A polynucleotide comprising a sequence at least 80% identical to a. or b.,
- d. A fragment of any one of a. to c., and
- e. A complement of any one of a. to d.

42. The use of claim 41, characterized in that the polynucleotide comprises a shRNA or siRNA.

43. Use of a compound which interferes with the activity or expression of a polypeptide having at least 80% identity with SEQ ID NO.:153 or in SEQ ID NO.:93 or a polypeptide encoded by SEQ ID NO.:1 or SEQ ID NO.:88 in the manufacture of a medicament for modulating osteoclast differentiation or for treating or preventing bone disease or bone remodeling, wherein said compound is selected from the group consisting of antibodies and antigen binding fragments thereof binding specifically to the polypeptide or to a fragment thereof and siRNAs or shRNAs specifically inhibiting activity or expression of a polypeptide encoded by SEQ ID NO.:1 or by SEQ ID NO.:88.

44. Use of a) at least one polypeptide selected from the group consisting of polypeptides having at least 80% identity with SEQ ID NO.: 153 or SEQ ID NO.:93 and fragments thereof, b) the antibody or antigen binding fragment of any one of claims 9 to 14 or c) the purified inhibitor of claim 29 in the diagnosis of bone disease or detection of bone remodeling.

45. Use of at least one polynucleotide in the diagnosis of bone disease, the polynucleotide being selected from the group consisting of:

- a. A polynucleotide comprising SEQ ID NO.:1 or SEQ ID NO.:88,

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- b. A polynucleotide comprising nucleotides 26-1345 of SEQ ID NO.: 1 or nucleotides 51-1208 of SEQ ID NO.: 88,
- c. A polynucleotide comprising a sequence at least 80% identical to a. or b.
- d. A fragment of any one of a. to c.
- e. A complement of any one of a. to d., and
- f. A library comprising any one of a. to e.

46. A method of modulating osteoclast differentiation or for treating or preventing bone disease or bone remodeling comprising administering a pharmaceutical composition comprising a) an isolated polypeptide selected from the group consisting of polypeptides having at least 80% identity with SEQ ID NO.: 153 or SEQ ID NO.:93 or fragments thereof and b) a pharmaceutically acceptable carrier.

47. A method of modulating osteoclast differentiation or for treating or preventing bone disease or bone remodeling comprising administering a pharmaceutical composition comprising a polynucleotide selected from the group consisting of:

- a. A polynucleotide comprising SEQ ID NO.:1 or SEQ ID NO.:88,
- b. A polynucleotide comprising nucleotides 26-1345 of SEQ ID NO.: 1 or nucleotides 51-1208 of SEQ ID NO.: 88,
- c. A polynucleotide comprising a sequence at least 80% identical to a. or b.,
- d. A fragment of any one of a. to c.
- e. A complement of any one of a. to d., and
- f. Any two or more of a. to e.

and a pharmaceutically acceptable carrier.

48. The use according to any one of claims 31 to 45, or the method of claim 46 or 47 wherein the bone disease is selected from the group consisting of bone loss, osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Turner syndrome, Gaucher disease, Ehlers-Danlos syndrome,

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Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets, fibrogenesis imperfecta ossium, osteosclerotic disorders, pycnodysostosis and damage caused by macrophage-mediated inflammatory processes.

49. The antibody or antigen binding fragment according to any one of claims 1 to 14, the conjugate of claim 15, the pharmaceutical composition of claim 16 or 30, the purified inhibitor of claim 29, the use of any one of claims 31 to 45 or the method of any one of claims 17 to 28, 46 or 47 substantially as herein before described with reference to any one or more of the Examples and/or Drawings.

Dated this TWENTY FOURTH day of October 2011

Alethia Biotherapeutics Inc.

Patent Attorneys for the Applicant:

F B RICE

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FIG - 1

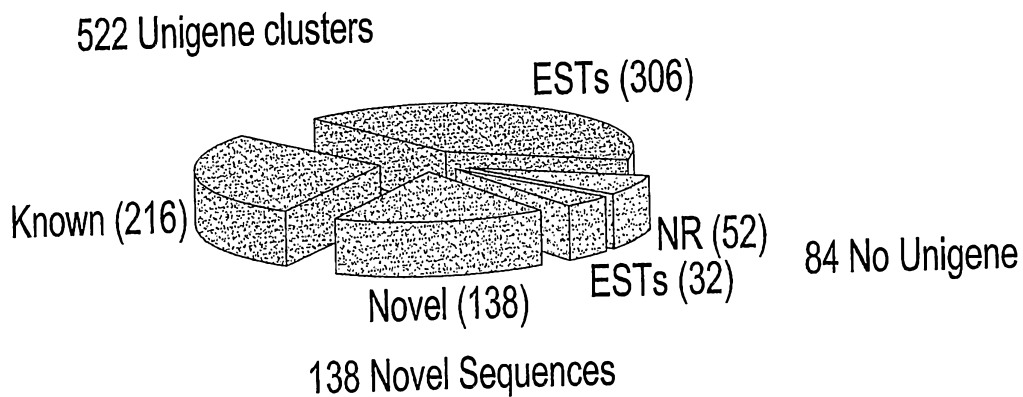
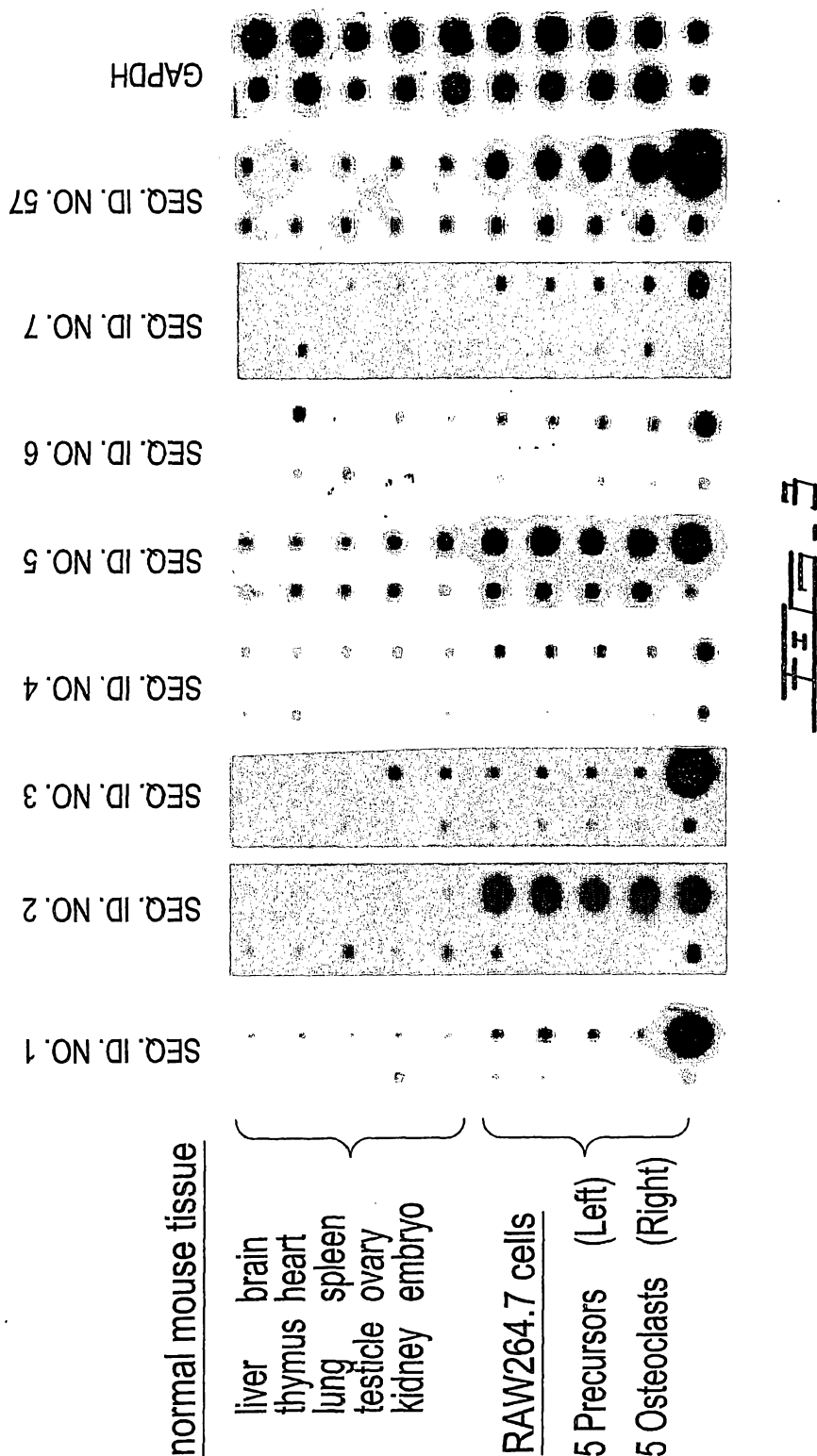


FIG - 2

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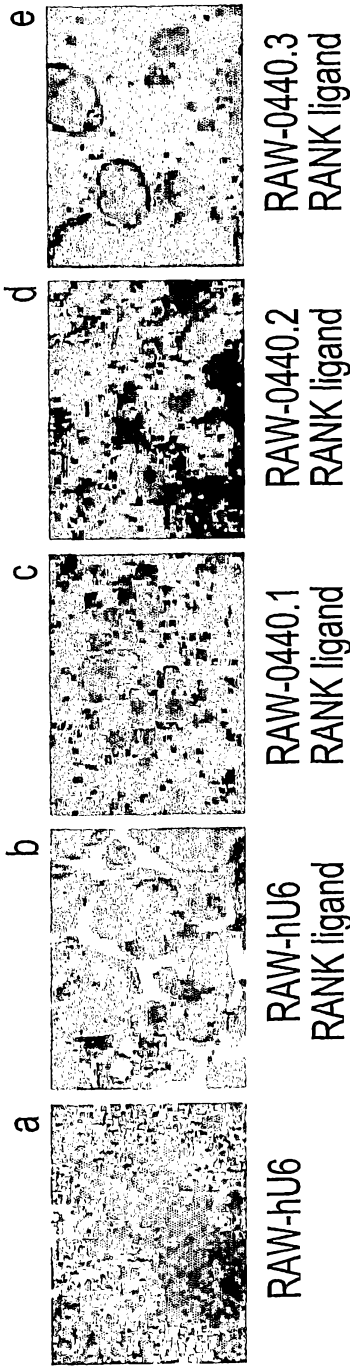


FIG. 4A

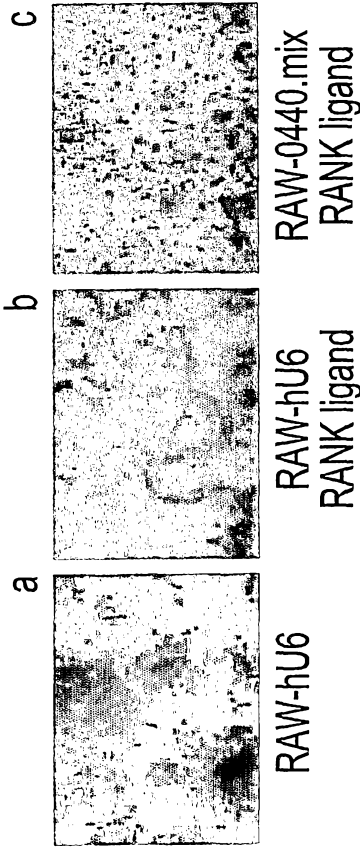


FIG. 4B

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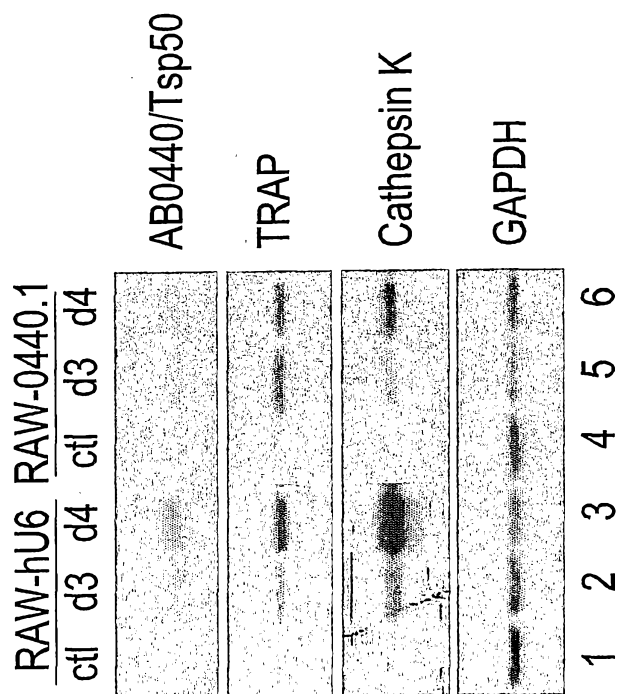


FIG. 5

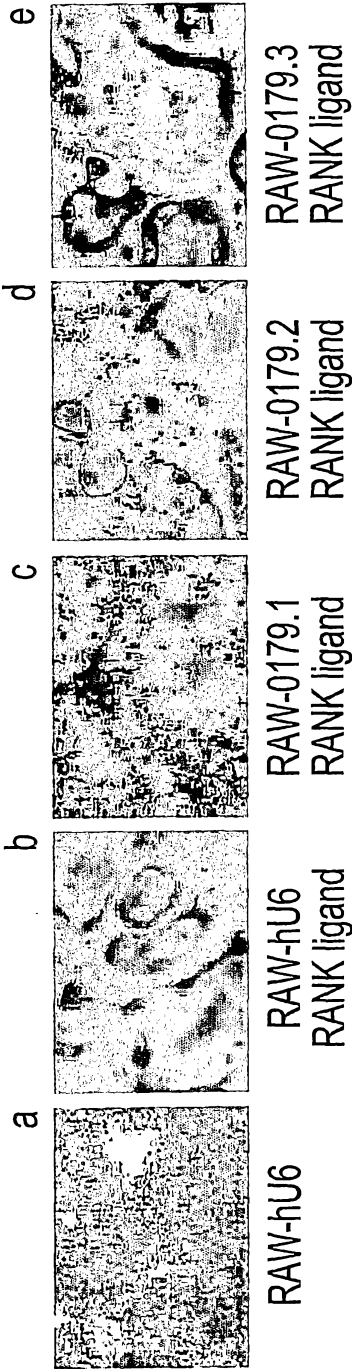
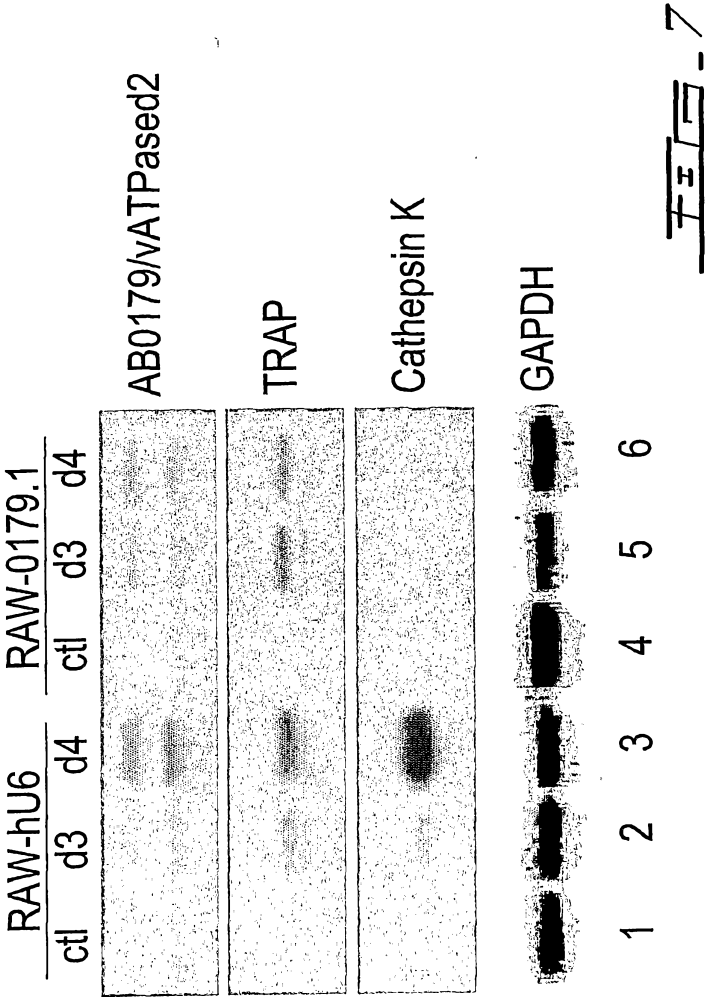


Figure 5



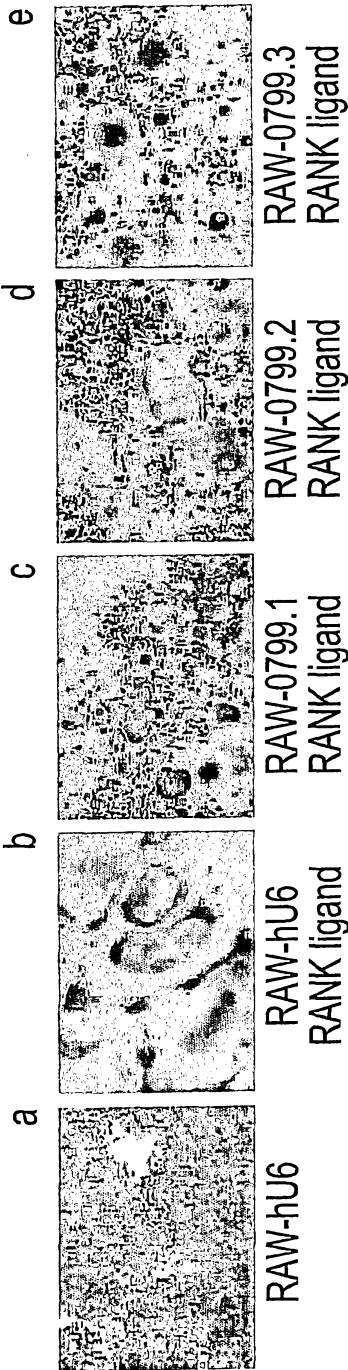


Figure 9

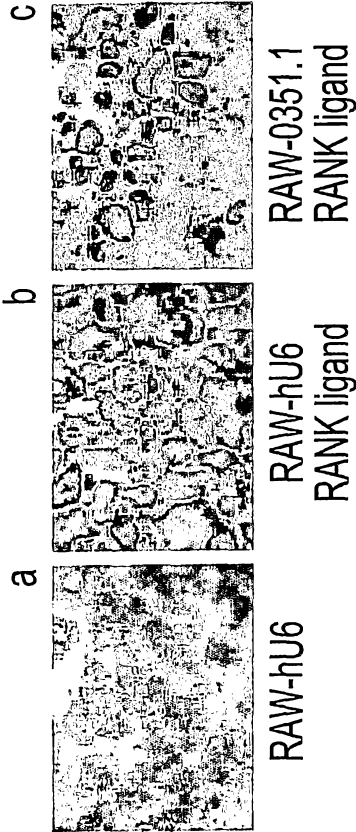


Figure 10

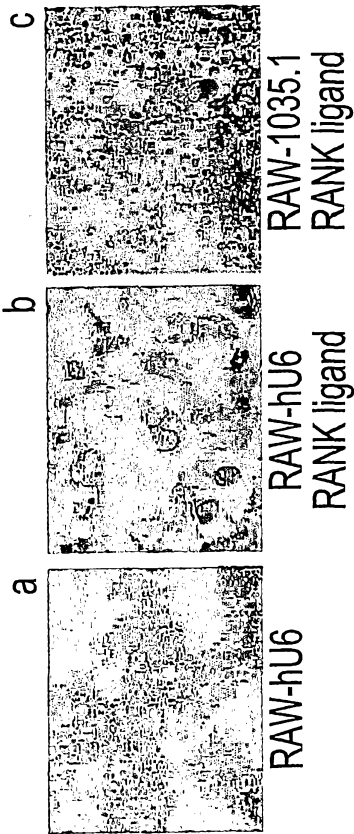


FIG - 10

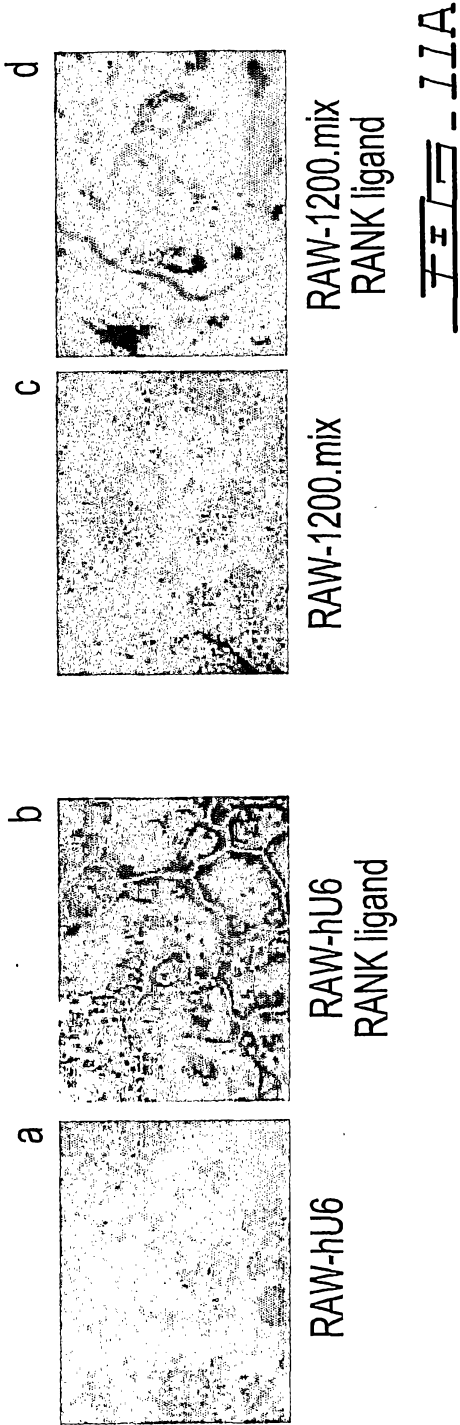
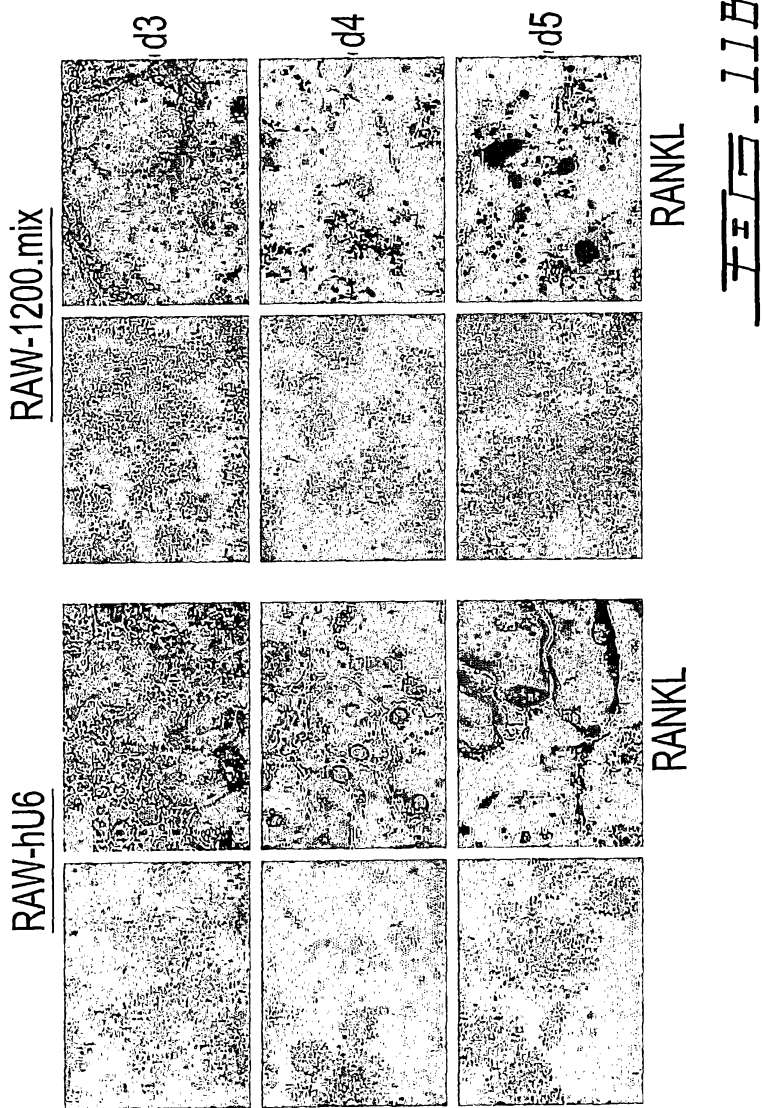
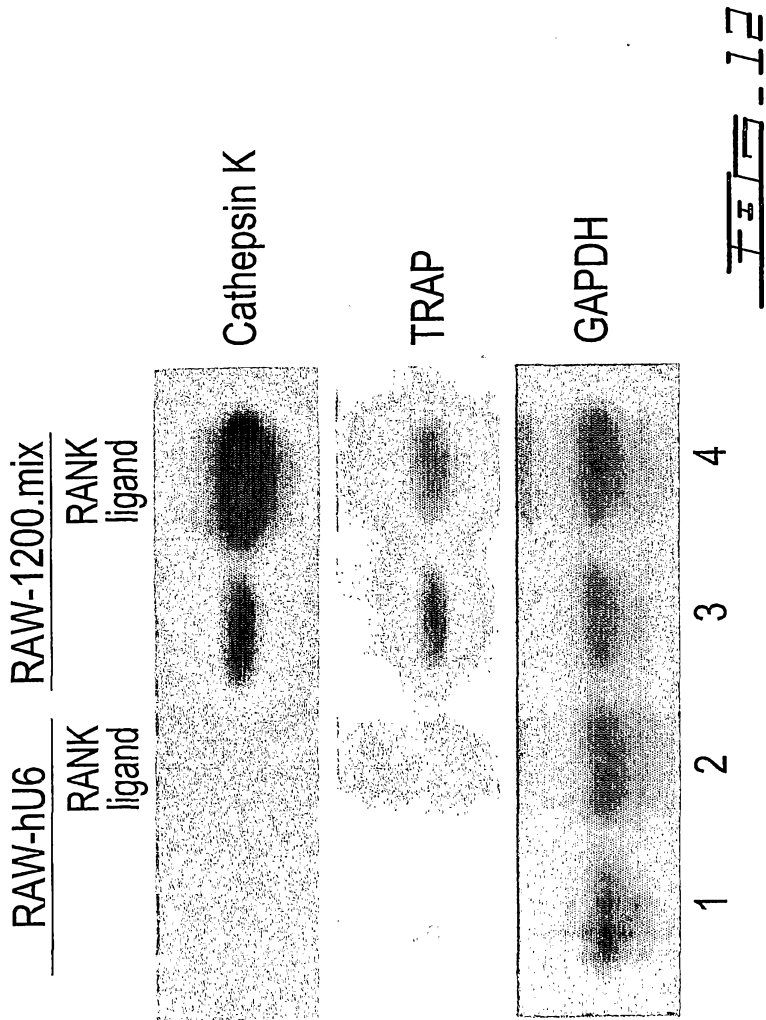


FIG - 11A





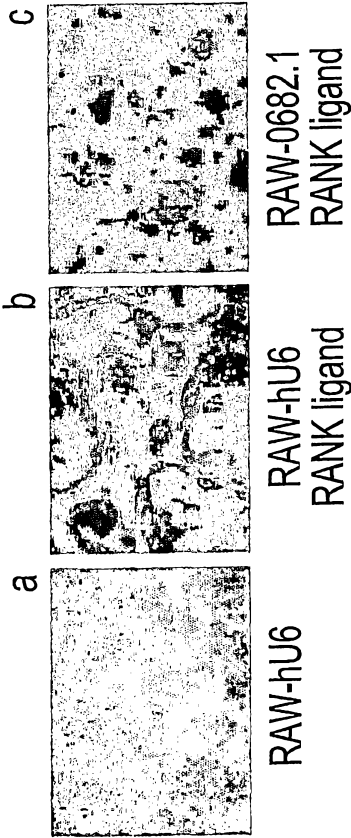


FIG - 13

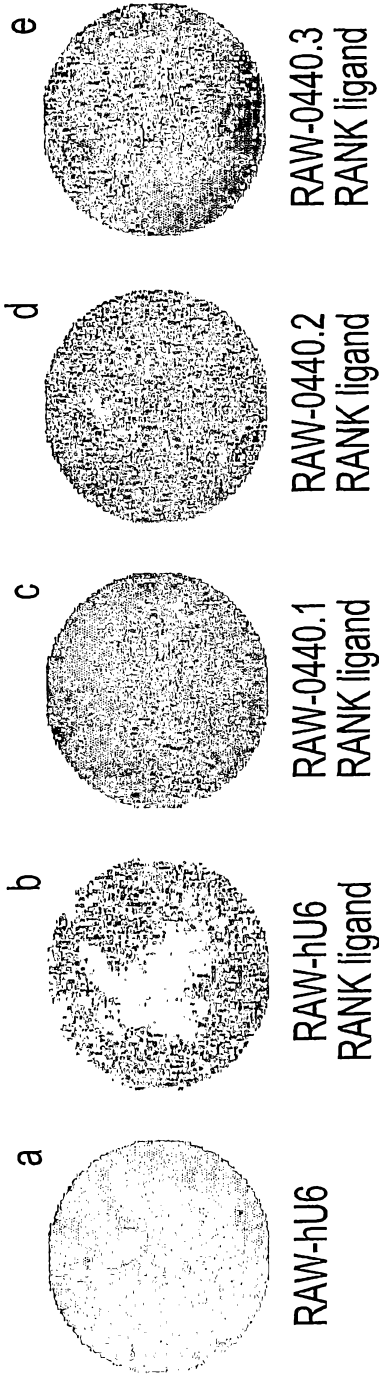


FIG - 14A

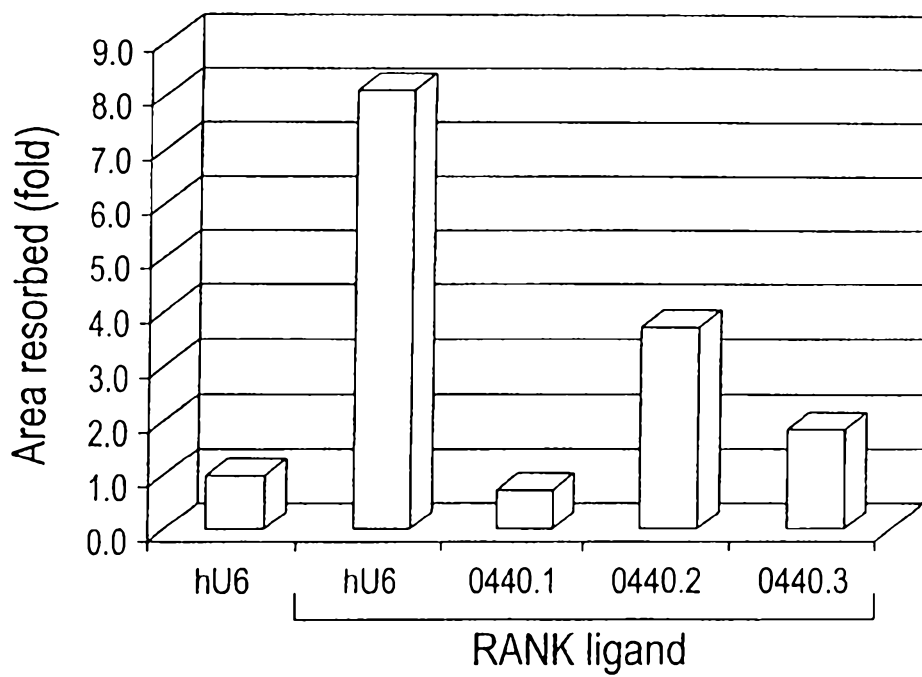
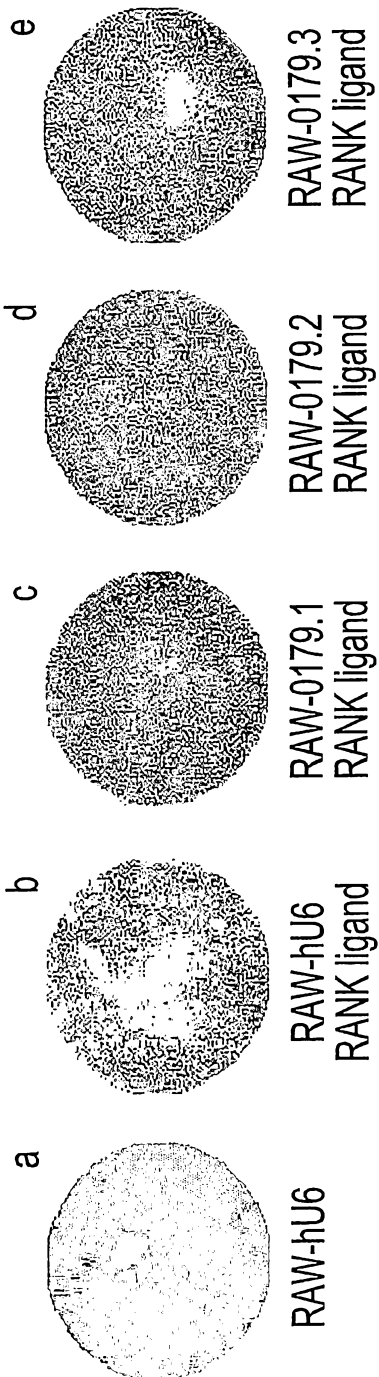
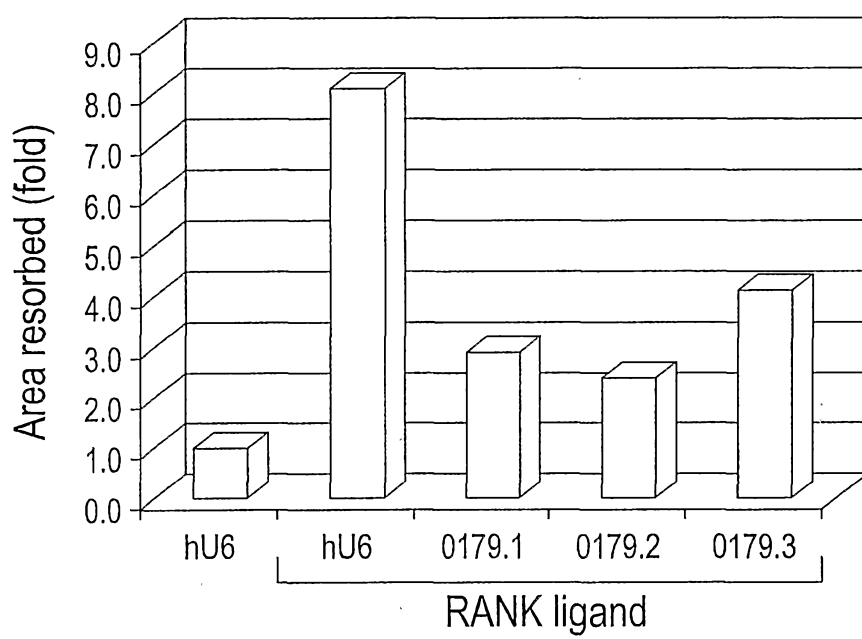


FIG. 14B

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FIG. 15A

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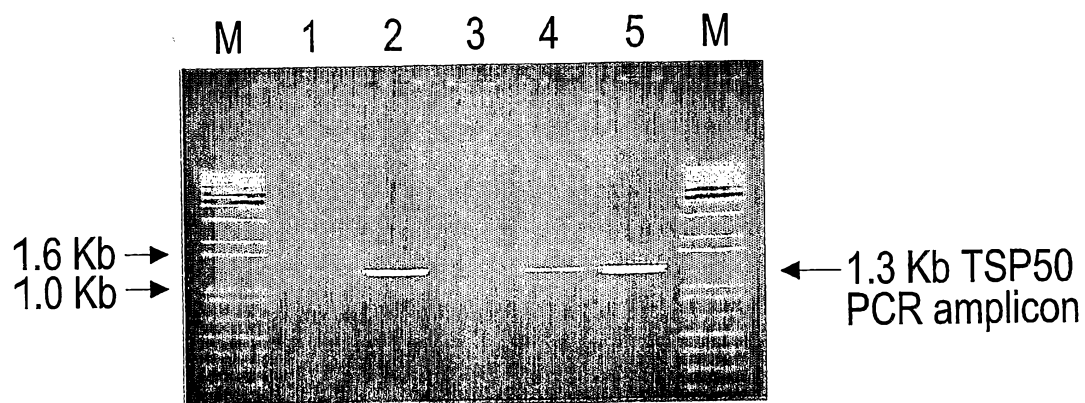
FIG. 15B

		Precursors & Osteoclasts								Human Tissues									
		1	2	3	4	5	6	7	8			1	2	3	4	5	6	7	8
Donor 1 - Exp 1	A																		
- Exp 2	B																		
Donor 2 - Exp 1	C																		
- Exp 2	D																		
Donor 3 - Exp 1	E																		
Donor 4 - Exp 1	F																		
Mouse Bone Marrow	G																		
RAW264.7 model	H																		
		A B C D E F G H								A B C D E F G H									
		P - Precursor OC - Osteoclast								P - Precursor OC - Osteoclast									

A1 - P	A2 - d3 OC	A3 - d7 OC	A4 - d13 OC	A5 - Adrenal	A6 - Breast	A7 - Jejunum	A8 - Trachea
B1 - P	B2 - d3 OC	B3 - d7 OC	B4 - d14 OC	B5 - Liver	B6 - Placenta	B7 - Aorta	B8 - Brain
C1 - P	C2 - d3 OC	C3 - d7 OC	C4 - d14 OC	C5 - Lung	C6 - Ad Cortex	C7 - Esophagus	C8 - Colon
D1 - P	D2 - d3 OC	D3 - d7 OC	D4 - d11 OC	D5 - Ovary	D6 - Kidney	D7 - Prostate	D8 - Thymus
E1 - P	E2 - d3 OC	E3 - d5 OC	E4 - d7 OC	E5 - Sk Muscle	E6 - Vena Cava	E7 - Stomach	E8 - Sm Intestine
F1 - P	F2 - d3 OC	F3 - d5 OC	F4 - d7 OC	F5 - Heart	F6 - Fa Tube	F7 - Spleen	F8 - Blader
G1 - P	G2 - d2 OC	G3 - d4 OC	G4 - d7 OC	G5 - Cervix	G6 - Pancreas	G7 - Ileum	G8 - Duodenum
H1 - P	H2 - d5 OC	H3 - P	H4 - d5 OC	H5 - Thyroid	H6 - Testicle		

SEQ. ID. NO. 2		SEQ. ID. NO. 4	
FEB-16A			

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M - DNA ladder
 1 - Precursor CD34+ cells } Donor 1
 2 - Osteoclasts }
 3 - Precursor CD34+ cells } Donor 4
 4 - Osteoclasts }
 5 - Positive control (human breast cancer cell line - MDA231)

FIG. 16B

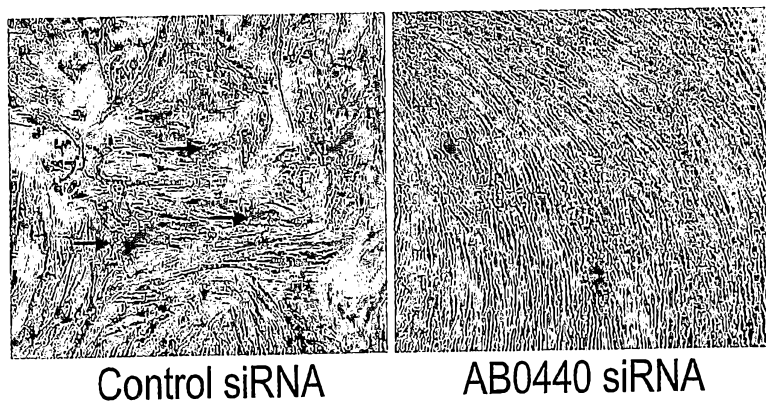
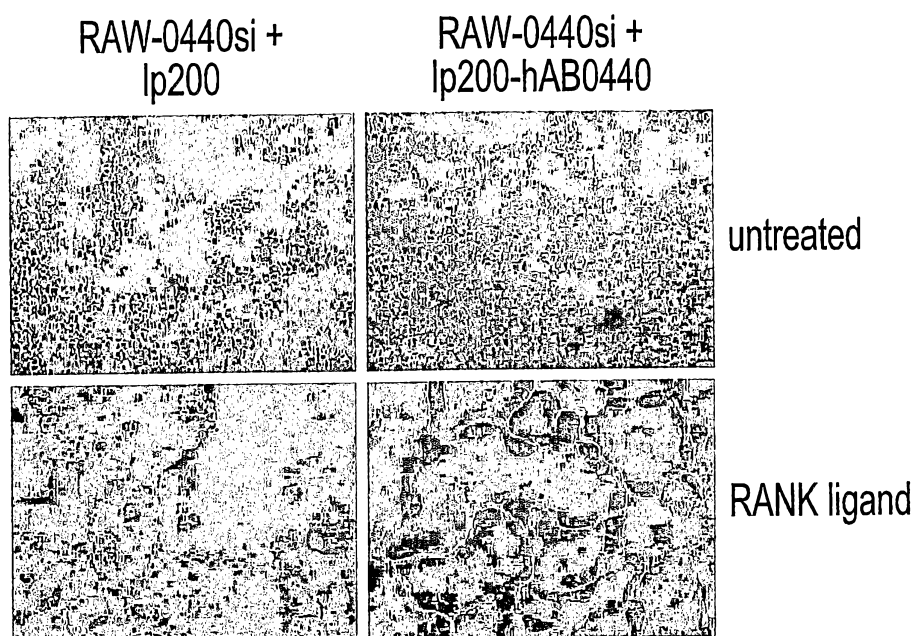
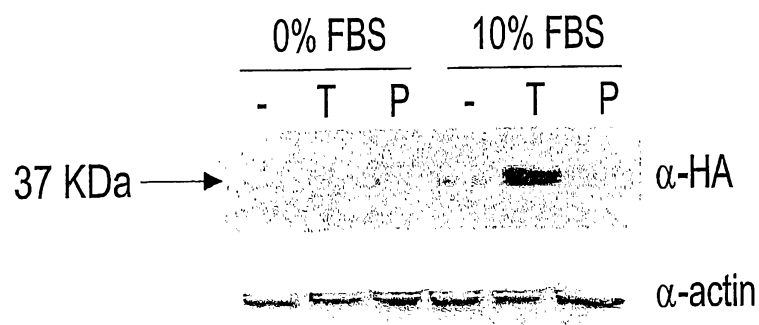
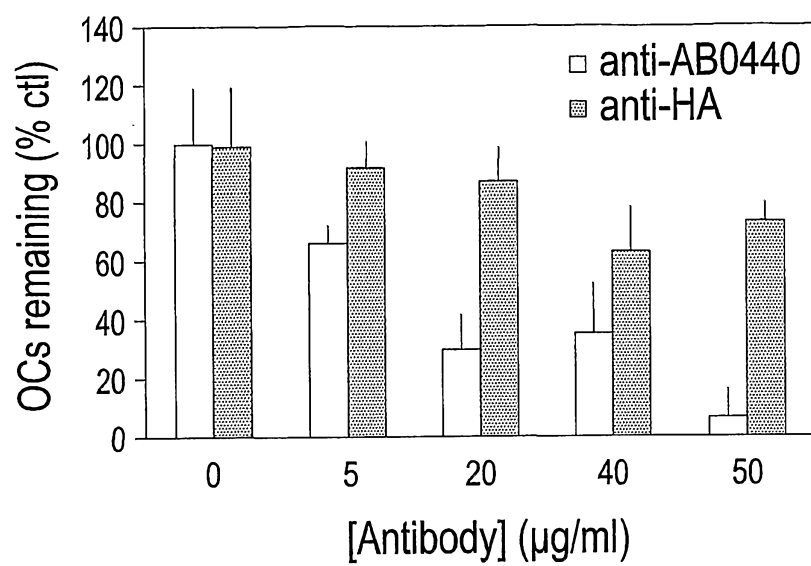
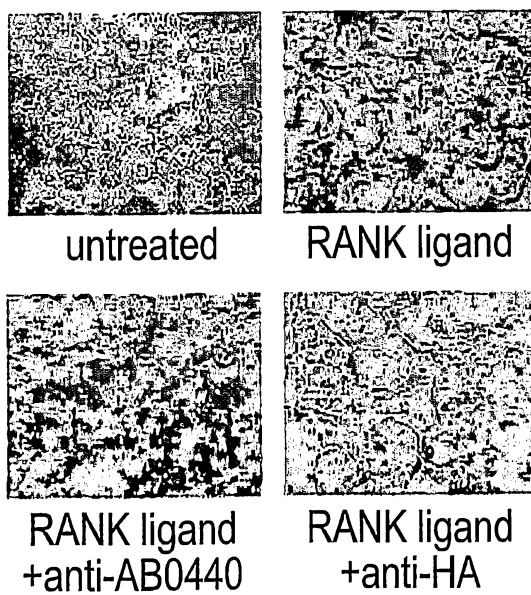


FIG. 17

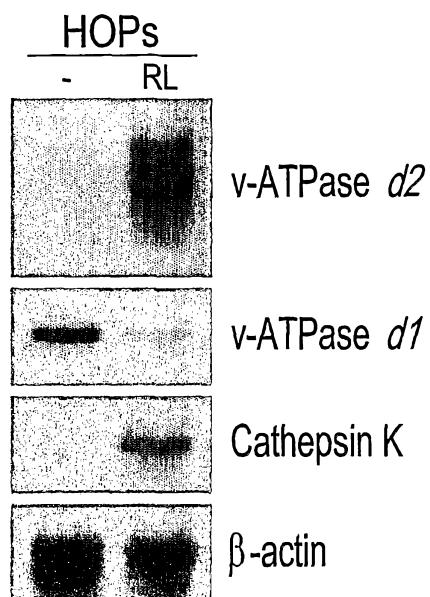
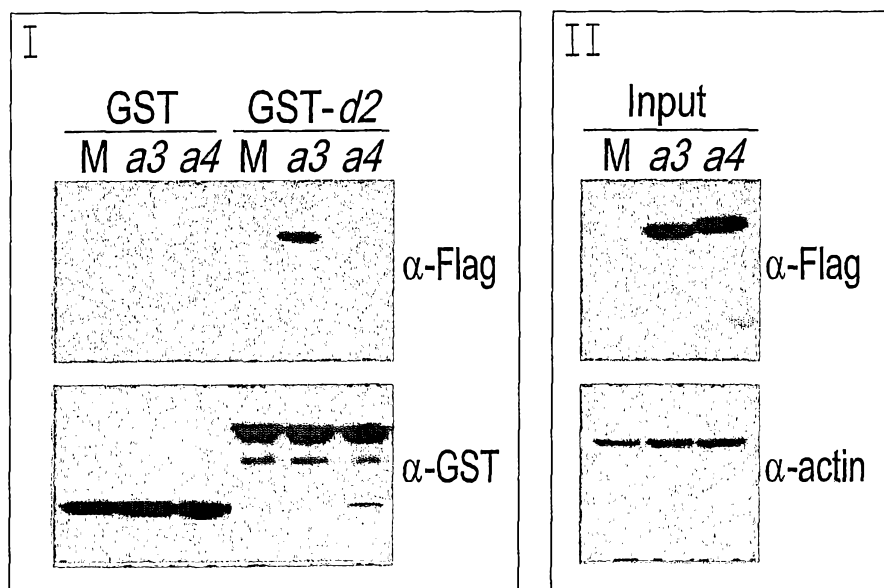
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FIG. 18FIG. 19

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FIG. 20AFIG. 20B

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FIG. 21AFIG. 21B

SUBSTITUTE SHEET (RULE 26)

SUBSTITUTE SHEET (RULE 26)

NucleotideSequence (5' - 3')		ORFs
GCCTGGAGCGGAGGACACATTAAAGACTTGGAAACCAAGTCGTACGAGAGCCCTGTTTGTCCGTGCGGTGCGGGCCCTACA ACGGGGAGAACTGGAGAACTGTCATTTCCGACATGAGAGCTCGCGCTTCCGACTTCCCTCAAGCCCTTCTACGAGTGCCTG GCTGCTCGAGGGGTCGCGGAGATCAAGGACTTCAAGGACTTCTACCTCATAGCAGATCACTATGTGGAAGTTCT GGATGTAAGATTGTTGTGAGGAGACCCCTCACCCAGTCATAGAGGCTATCCGCTGGAGAAATTTGTGGCGACCATGT ACCACATATTACAGTTTGCCTATTACAAATTGAATGATCTGAAGAAATGACGCCCGTGTGCTCAGCTACCTGCTCTTT GACCAGTGAACAGGGTCATGCAACAGAACCTGGTGTACTATCAGTACCACCGGACAAAGTGGGCTCTCGATGAGCA CTTCCAGCCAGACCCGAAAGCAGTTTCTTCTTAAATGTACAGCCTCCAGAGGAACTGTACGACTTTCGCTCAGGAAC ACCTAATGGATGACGATGAGGAGAGTTGTGGAGTATGTGGACGACTTGTGGAGACGGAGAGTCTGCCTAGTCCACA GGGCTAAGGAACCTCTCTCCGAGTCTCTTCTTCAAGTCCCTGGTGTGTATACCTCACAGCCTTTCTTCTTAA AGTAAGAAAGAACCCATCTCTCCCTACCAAGTCAAGCCTGACTTCCCTTGTTCACACTCAGTATTCACGCTTGT TTTATGTTTACAGCTCTTCAATGCTTCTTCCCTTCAACATGTTTCCGCTCATCTAGTCTCTCTCCTCAAGTCCAC GTTCGCTCCTCCTGATCCCATGCTCTCCCCATGTTTCAAGAAACAGCTCTTGTGTGCTGCTTTTCTCATCCCCGGA AGAAAAATCAGTATTATTTTAAAGTAAGAAAAACACTAAAGATGATAAATATATTGGAGAAATTAATAAAAAA AAAA	SEQIDNO. 4	EYKSLPGAEDHIKDLETKEYES LFVRVRAVYNGENWRTSISDMEL ALPDFLKAFYECLAACEGSRKIK DFKDFYLSIADHYVEVLECKIRC EETLTPVIGGYPVEKFAVATWYHY LQFAYYKLNLDLNAAPCAVSYLL FDQSDRVMQONLVVYQYHRDKWG LSDEHFQPRPEAVQFFFNVTTLQK ELYDFAQEHLMDDDEGEVVEYVD DLLETEESA
GACTCGGCTCCGGGAGACAAAGGGCCCTGTCTGTCGCGGCCCCCGAGCTGTTCCGGGCCATGGGCAGGACAGACCCGTCG CGCCGCTCCAGAGCCAGGCTCCCCAGCACAGGCTACACACTGGACACTCAAGCCAGACAGAGCCCCACACACCCCTC TCTGGACTGACGAGATGAAGCTAGAGTCCAGAGAGACTGACTGTGTGCCCTGAAGTGAAGCCAGCCTGGAGACTGT GAGCTGACCTTCAAAGTGTAGCAGAACTGGGTGGGCGCCCTGTGGGACAGGTTGCAGTCTCTCGTGACCATGAAGC TCAACGAGCGCAGCTTGGCTTCTACGCAACCTGCGATGCCCGGTGGACAAACGCGGCTTCTGTACAAAGCTGTGTGC CGTGGGACCGGCTCGACCGGCGCTGTTTGTCTCGGGGCAATATCTCTTTTACTTCGAGGCGAGAGGAGCCGCGCA GCCGTGGGCGTCACTCTGCTGGAGGCTGACCGTGGAGCTGTGTGGATGCCCGGAGGAGTTCGCCCTTCGAGTGCCT TTGCCGGGGCCGATCCCGGCCGTACGTCTGGCCGTGACAGCCAGGCGAGCCCTGGAGGCTGGGTGAAGGACACTGTCC CGGCCAGCTTCCACTATCTGCGCTTGGTGGTGGGAGCTGGAAACAGCAACTGGCTGCCATGCGCGAGGAAGCCCGC CAACGCTTACCCGCCAACCCGAGCCCGGTTTGTACCCAGAGACCCAGAGAAACGCGTGGTGTGTGGAGCACGCTGC CCGAGCAGCCCTCGGTAGCCCTCAGCGGCCCGCCACTGCCCCCGCGGAGGCTCAGCGGCCAACCGGCCCTTG GCATCTTCGCGCCAGCTGCGGATATGACTAGAGGTGAGGCTTACGAGTCCCTTAGGACCCAGTGGCGGAGGCGAGGCTGG CTAGCAGCTTAGAGTCCCTTGGATCTTGTGCTGTGACTCAGCCAGGACCCAGGACCCAGGACCCCTAAGGGGACATA GTGGGTAAAGGTATTACATGTATTCGTTCCGTAGAAATGGCTGTGTGCTGAGTCCAGCTCCAGGGGACATAGGACATA TGACTCAGGAGACCTGTGCCCTGGGTGAGAGGCACTTACTCTGAGAGAAATCTGGAACCTGAAACCTGAGGTGCTTC TAGAGCCCAAGGAGCTGGTTCTAGAGAACTCCGCGCCAGGCTGTGTGACCTTGACAGCCCGGAGCTGGCCACA GGCCCATGGGGCCAGGGTTTACCTGGTGCCTCTCAAGGATCTAAAGCTTGAACCTTGAAAGCTGTCTGCGGCTGCTGT	SEQIDNO.: 96	MKLNERSLAFYATCDAPVDNAGF LYKRGGRGTGSHRRWFVLRGNIL FYFEAEGRREPLGVILLEGCTVE LVDAREEFAFAVRFAGGRSRPYV LAADSOAALEGGWVKALSASFHY LRLVRELEQQILAAMREGSPANA LPANPSPVLTQRPKENGWVWST LPEQPSVAPQRPPLPPRRRASA ANGPLASFQQLHARYGLEVQALR DQWRGGQAGLASLEVPWHPGSAE TQTQDQPALRGHSGCKVLHVFRS VWVPVCPNPGSQGT

NucleotideSequence (5'-3')	ORFs
GGGCTACACACAGTAGGTGGGAATTGAACTGGATAGGTCCTCCACAGGCTCTCTGGCCTGGAAACACAGCTAAGTCAG GACTGTGCAGCTTTGTAGGTAGCCCGGGCAGAAAGAGGCTCCCTTGACCTCGTCCCTGGCTGGGACCCAGCTTC CTCCAGTTTACCTGGAGAGACAGGCTCCGACTGATTCATCTGCTGACGACGAGGAGCCAGGCACATGTCCTAGC CAGTCAGGTGACAGTGGGCTCAGGACTGGGCTACTTCTCTCACACACAGTGTGGCTGTCTCCAGAGGTTGGG CAGGACAGCGGCCCCACCTGGGTTCTTTTACAGTCTCTCAGTGCCTGCCCTGAGGGGACACTCCAATCGCTGCA TCCATAGAACAGATTTCACCTGGCCCCCTCTCTCTGGGGGTGGGTGGTCCCATGGTCTCTCTGTCTGTCTGT TCGCCAGGCTCTTTGGCTCTCTGTGGCTCAGGGCCAGGGCACATTGGCTGTGGGTTTTCTTTGAAAGTACAGAGGCTA CTGTCTTCCACCAAGTGAAGTAAAGTAGTCCAGTCTACCCCTGCCATTTTGTACTTGTGGCTGCAAGGGGTGGCATTG TCTCCAGGGAGCCAGGCCCTCGCAGGAGACACACGGGCCCTAGTCACTTGGCCTGACTTGGCCCTCTGTCTCTCTGAG CTCAGCTGTCTGCACAGGTGTGGCTCTGGGGACTTGGTCTGTCTCTCAACTCTCCACTGGAGTCATACGGCTGAGGT GTAGACTTGTAGTGTGGGACGGGCTTACAACTCTAAAGTACGGGACGAGGTTGGGGAGACAAGGCGACAGTTGTTCC CTCTCCCAAGCACAAAGTGAACACACAGCTGATTTCTGGGCTAGGAGATTATCAATCATGACAGGCTATGAGGGCCA AAATAAAGCGGGTGC	SEQIDNO.: 97
CAGCGCCCGAGCGCAGACGGCGCCGCCATGAGGGAGATTGTGCACATCCAGCGGGCGCAGTGCGGGAACACAGATCGGTAC CAAGTTTTGGGAAGTGATCAGTGTAGACACGGCATCGACAGCGGAGGCTACGTGGCGACTCAGCGCTGACAGCTGG AGAGGATCAGCGTCTACTACATAGATGATCACTCTAAGAACTACGTACCCAGGGTGCCTGTGGACTGTGGACCCCGG ACCATGGACAGTGTAGGTGTGGGCTTTTGGGCACTCTCCGGCTGACAACTTCATCTTCGACAGACGCGGTGCGG AAACAACTGGCCCAAGGCTCATACACGAGGGCGGAGCTGTGGATTCGGTGTGGATGTGTGTCGCAAGAGAGTGTG AGCATTTGCACTGTCTTACGGCTTCCAGTCAACCATCTCGTGGCGGTGGCAACGGCTCAGGCATGGGCAACATGCTC ATCAGCAAGATCCGAGAGGATACCCGACCGCATCATGAACACCTTCAGCGTTCATGCCGTCAACCAAGTCTCAGACAC CGTGTGGAGCCCTACAACGCCACATTCAGTGCACAGCTGGTAGAAGAACACCGACGAGACTTACTGCATCCACAACG AGGCCCTCTATGACATCTGCTTCGCAACGCTCAAGCTGACACACCACTTACGGGACCTCAACCACTTGGTATCCCGCC ACCATGAGCGGTGTACCACTTCGCTTCCCTGGCCAACTCAACGCCGCTCTGGCCAGCTGGCTGTGAACATGGT GCCATTCACACGCTCTCCACTTCTCATGCGCGGCTTTGCCCCCTCAGCAGCCGGGCGAGTCAGGACTACCGTCCCTGA CAGTGCTGAGCTCACACAGCAGATGTTTGATGCCAAGAACATGATGGCTGCTGTGACCCACGCGCATGGCCGTACCTG ACCGTCGCCACTGTCTTCGGGGGCCCATGTCCATGAAGAGGTGAGACGAGCATGTCTGGCCATTCAGAACACAGAACAG CAGCTACTTTGTGGAGTGGATCCCCAACAAATGTCAAGTAGTCTGTGTGGACATCCCAACACGGGCCCTGAAGTGGCCT CCACCTTCATTTGGCAATAGCACTGCCATCCAGGAGCTATTCAAGCGCATCTCCGAGCAGTTCTCGGCCATGTTTCGCGCGC AAGGCTTCTCTGCACTGTTTACCGGTGAGGGCATGGACGAGATGGAGTTTCAACGAGCGCGGAGAGTAAACATGAATGACCT GTGTCTCCAGTACCGAGTACAGGACGCCACGGTCAATGATGGGGAAGAGGCAATTTGAAGACGAGGATGAAGAGAGA TCAACGAATAAGGAGGCCATAAGTGTCTACAGTGAACCTCTGCTCTTTCTTTAGCTTGTGAGCTGTGGCAATGCTGCGCTG	SEQIDNO.: 97 MREIVHIQAGQCGNQIGTKFWEV ISDEHGIDQAGGYVGDSSALQLER ISVYVNESSKKYVPRALVDLE PGTMDSVRSRSPFGQLFRPDNFI GQTGAGNNWAKGHYTEGAELVDS VLDVVRKECEHDCCLQGFQLTHS LGGGTGSGMGTLLISKIREEYPD RIMNTFSVMPSPKVSPTVVEPYN ATLSVHQLVENTDETFTYCIDNEAL YDI CFRILKLTTPTYGDLNHLVS ATMSGVTLSLRFPMGQNLADRLK AVNMVPPRLHFFMPGFAPLTLAR AVNMVPPRLHFFMPGFAPLTLAR GSQQYRALTVPELTQOMFDKNNM MAACDPRHGRYLTVATVFRGPM MKEVDEQMLAIQNKNSSYFVEWI PNNVKVAVCDIPPRGLKMASTFI GNSTATQELFKRI SEQFSAMFRR KAFET HGTTCGMDMTEETAEFSN

Nucleotide Sequence (5' - 3')		ORFs	
GTCTAAGCATGTCACTGGCGCCCTCTCAAAACCAATGACACACACACTGTTCTCCAGGTTACCTGGAAACAGTCCAGCAGACC AGGAGATCTCATATAGGAACCTTGAAGCAAGTAGGGGGCTCACACAGGGCTAAAGAAAGTGACCAACCTTTTGTTAAG CCCCCTTCCACCCCATCAGAGTTAGAAAGGATTGTTTTCATCTCGGTGATAAAACCTAAAGCCACACAGTGTCTG CCTTAAGTGAATGCACACTATGGAACTTTATGACAATTCATTCATAATAAAATGCTAAACCTGTAACCAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	MNDLVSEYQYQYQDATVNDGEEAF EDEDEEELINE		
SEQIDNO. 6	SEQIDNO. : 98	MSCVPWKGDKAKAESDLPQAAAP PQIYHEKQRRRELALHALNNVFQ DSNAFTRETLOEIFQLSPNTMV TPHKKSMLGNGNDYVNVIMAAALQ TKGYEAVVWMDKRRDVGIVIALTNV MGFIMNLPSSLCSWGPDLKPLKRPQ HWICVREVGGAYYNLDSKLKMP WIGGESELRKFLKYHLRGKNC LLVVPVEEVAHQSMRADV	
GGCCTGCTTTGTCGCGCGCTGGGCCAGGTGCGCGGCCCGCAAGCTCCAGGTGGCGGCTCGGGGAGACGAACAGTCCCCCGCC GGCAGGACAGCGGGAAGGAGCCGGGATCGGCCCTCACGTGACACAGGAGGTGCTGCGGGGACGGTCAGCCCGGTGGGC CAAGGCTGCACTCGGGCGAGGCAAGCGTCCGGCGCACCTTCGCGGGCAGCGGGAACCTCCCCCGCGCGGCCCGGGC TGCCGTCCCTTCCCTTCGCGGCTCTCCCGCGCAGGGAAGCGGCTCTCCGTGGGCCGAGCTCCGCCAGTCCCGCTGGC GGTCAATGAGCGCTATCCCGAGCGCCCGCGCGGCTCAGCGACCTCAGCCCTCCGATCTCGCTAGCTCTTGGCATTTGG GCCCTTTCTCGGCCACCCACCCCGTCTTCGGAGCCTGTGTGTTGTAATTCGAGCAAAATGGAAGAAAGGAGCGATGT GACCCCTTCGGTTCGCTCTGCAATGAGGCCCTAGTTGGCATCTGACAGAGAGGAACACACGCCCAGGAAAGCGTGGTG TTTCTTTTTTCCAAAGGGGCTGGAGGGGAAGGGGGAGCCAAAGGAGGAATCCTACGTTTATATGTTTTTTTTTTC TTTGTAAATCTACACTTTGAAAGTTGGCTAAATNAACTAATCCAAAAGTTATTTTCTCTATCGAAGACAGAGAAAA AGGTAGATTTTTTTTTTTGTCCTTTTGATTTCCAACTTTCTCCAGTGACAAAGCATAAATCATGAACACACAGAGAA TAAATAGTGAATCTCAGGAATCCGAACAGGAACTTAGACTTTCTCAGGAGGAAGGACGGAGTGTTTAGCGGCTC TGCTTGAACTTAAATCGAAAAACATAGATTGGTGCCATGGAAGGAGACAGGCAAGGCAAGCTGAATCTTCGGACCTTC CCAAGCAGCGCCCCCAAAATCTACCATGAGAAGCAGCGCAGGAGCTCTGTGCTCTTCATGCTCTCAACCAACGCTCTCC AGGACAGCAACGCTTCAACGGGGAAACGCTGCAGAGATTTTCCAGAGGCTGTCTCCGAAACACTATGGTGAACGCCAC AAGAAGACATGCTGGGAATGGGAACATATGATGTGAATGTCACTATGGCAGCACTTCAACCCAAAGGCTATGAGACTGT TTGGTGGGAACGGAAGGACGTGGGTGTCATTGCTCTTACTAATGTGATGGCTTTCATCATGAACCTGCCCTCCAGCC CTGTGTGGGTCCACTCAAGTTGCCCTCTCAAAAGACAGCACTGGATGTGTTCGTAGGTGGGAGGGCCCTACTACAAC TCTGACTCCAAACTCAAGATGCCAGATGGATTGGAGCGGAGATGAGCTCAGGAATTTCTAAATACCATTTTCGGAGG TAAAAACTGTGAACCTCTACTGTTGTACCGGAAGAGTGAAGCCCATCAGAGCTGGAGGCCGCGTGTGACAGTTGT TTGACCCCTTTGTCTCAACCTCCAGACCTCTTTGATGTGCTGTGGCTCTACAGTCCACTTCCCAAAACATCTCATTTG GGTTTTCCCTTCAGATTTGCCAGTGCAATAGGACAGATGTGTGGACTGTACAGAGCACCCAGCAGTCTGTGCTGGGG GAAGAAGGTAGGAGCTCTGAACACTTAGGCCAAGCCATTGAACCCCTTGTCTATTCAGAGAGGGAGCCAAAGAGGCGTCT CTTTAGGGGGCTGGGTTATTTCTCCCTTTCCATAAGGTCTTGATACAGGCTCTGCTGGTAGTGTCACTGATGCTTCAGG CTTAGCGGAAGCGCCCTTCTCTCTGTGGTCAATAGGCTCTTCTGGTCCCTTTTAAACCCCAAGCCAGCTGT CAAGACTCCAGAGGCTCACTGTGATCAGCTGCACTTATAGGCTCTTCTGGTCCCTTTTAAACCCCAAGCCAGCTGT GGGTTTTTATAGAGGGCTCTGCTATTTCCAAATAAGGTGAATAAGCACTCTCTTACTCTTCTGCTGAAGACATGCTG			MSCVPWKGDKAKAESDLPQAAAP PQIYHEKQRRRELALHALNNVFQ DSNAFTRETLOEIFQLSPNTMV TPHKKSMLGNGNDYVNVIMAAALQ TKGYEAVVWMDKRRDVGIVIALTNV MGFIMNLPSSLCSWGPDLKPLKRPQ HWICVREVGGAYYNLDSKLKMP WIGGESELRKFLKYHLRGKNC LLVVPVEEVAHQSMRADV

Nucleotide sequence (5'-3')		ORFs
TAATACACACGTGGGTAAAGCCAGAGTAGGTAGTCACTGGTGGCTCTTCACTCAATCGTGTCCCTATCATTTCACTACA TTGACTGGGGAGCTTTGGGACAAGACAATCAACAGGAGAGTACTCAAGTTGGCCATTTTAGCAAAATCAAAACACA TTACACAGCCTAAATTCATAGTTTGGACAGAGTTGGCGAGGAATGCCATGAAGTAAGTTCAGGGTTGAGC CCGTAGGCACGCTCCTGAGCTCCAGAGCTGGCAGCAATCTCAGTTGGCTGTATGCATCAAGCTAGAGCCTCTGAGTT TGGCGTCTGTAGTTTCTTTGACAAACAGGGTTGGCTGCCCACTTCAACTAGTTCTAGATCATTTTCTTGTAAAT TTTGGAAAATGAGGGGAAATATATACCATACCCCACTGCAATGTGTGTGGCTTCAAGCAGGTGACCTGGCCA GCCCTTACCGATCCATGCTCTGAGAGCTGAGAGCTGCCCACTGGCTGTCTTCTCCCTTGGCAGCAGACTACC TGGGCTTGCATGTTAATCCTGAGCAAGCTTTTGGGTGAAGGGGGTGTCTCCCACTGTGACTGGAGTGCATGTTT ACACAGCACTTTTCTGACATGTATCTCAATCCAACAGGCCCTTTTATTCAAGTGGCAGAGCCTCGAGTGGCT ACTGCACTGGCTCAGCCATGGTCACTGTGCACTTTCTACCAAGATCTGTGGCACTATGGGAACTCTGCCCTG CACAATGACATTCCAATCACTACCAAGAGTTTACAGCCGACCTTGTGATTTGTACCAAGCAGGACCTTGGCTCCAT GGCATGTGCGTGATAGTAAAGCATTTCTTGGGAAGAGAGACTCTTCCCTACAGATCTGCTTGGCTGTGCAATGGC ACTGCAACAGAGCCACACACGTGGAGTCCATGAGCTAGTGGATGTACAAAGACGTTAAGCATTTCAAGGCTGGTTT TGTTTATATCCAAATCTGGTGTAGGAACAGGACCCATGTAAATGCCCCAGGGCAAGCCCACTCTGTGAGGAAG GGCAGCCTGACCTGACGCCAGCAAGGGCAGCCCTAGCTTTGTTTCTTGTCTTATTCCTTCTTCTGTGGCCTT GTGCTGGGTTTGTGTACAAAGATGTATTTTGTTTAACCAATATTAATAAGAAAGCCG	SEQIDNO. 7	MSAELELLWVPVSGLLLLLLGATA WLCVHCSRPGVKRNEKIYEQRNR QENAQSSAAAQTYSLARQVWPGP QMDTAPNKSFERKNKMLFSLLEG SNQEPDAAAYVDPIPTNYNWCFF OKPSEDDDDNSYENVLVCKPSTP ESGVEDEFDYQNSVSIHQWRESK RTMGAPMSLSGSPDEPDDYVNGD VAAAEINI
GGCATCAGCTTGGGCAGGTGTGGGCACAAGATGAAGGGCCATGGTGAAGAGCCCTCACCCCTCAGCCTTACAGCCTCTT CCCCAAGCCACAATGAGTCCGAGCTGGAGTGTGTGGCCGCTGTGGGATATTGCTGTGCTGTGGGGGCCACAGC CTGGTGTGTCCACTGTCCGTCAGGAGTGAAGAGAAATGAGAAATCTACGAGCAGAGGAGACCGGCAAGAAAATG CACAGAGCTAGCTGCGGCTCAGACATCTCCCTGGCCAGGAGGTGTGGCCAGGACCCAGATGGACACAGCTCCAAAC AAGTCATTTGAAGGAAGAACAGATGCTGTCTCCACTTGAGGGAAGTAACAGGAGCCTGATGCTGCCTATGTAGA CCCCATCCCTACAAAACCTACTACAACTGGGATGTTTCCAGAAAGCCCTCAGAAAGACGACGATTCCAACTCTACGAGAAATG TGCTCGTCTGCAAGCCACAGACCCCGAGTCAGGTGTCCAGGACTTTTGAAGATTAACAGAACTCAGTATCCATCCATCAG TGGCGAGAGTCCAAGAGGACTATGGGTGCACCAATGTCCCTATCAGGAAGCCAGATGAGGAGCCAGACTATGTGAATGG GGATGTGGCCGAGCAGAGAACATCTAGGAGAACCAATCAATCGGAAGGAAGAGGGCCGAGGATGGGGATCTGAG CGGAACTGAAGCCTTACTGCTGTGAATAAAGCCTGTCTCCAGGATGCTCAAGTTTACACCTGGCCGTGGCTG CTCCACAGCTGGGAGACATGGGCACTGCCAGAGCCCAACCTCAAGTATGCCCTGGACTTCTTTGGGGGCAAGCA AGTGCCAGAGGATATAGACTGTGCTGACTGGAAGCCCAAGACCTGAGGCAAGATGTGTCCCACTCTCACAATCAAAAT GAGGCAACAACAGTGGCATTTGTGGGTTTGTGTTTGTGGCTGACGATCTCACTAAGTTACTCAGGCTGATCTCAAA CTTGTAAACCTCAGTCCATGTTTGGGATGGGGCATAACAGTTTTTTTTTTTCTTCTTCTTGTGGACCTCAGATTA CTTATGTGCACTCTAGGACTGTGCTATGACTCTTTTGTGGTTAACTGAAGTTGCTGGAGTCTGATTTAATATGTCA	SEQIDNO. 99	

FIG. 27

Nucleotide sequence (5' - 3')	ORFs
ATGTACGGGGTTCCTCTGCTCAGAGCATATATGTACTAACTGTAGCAGAGGAATGGGTGTGGGTAACCTGGGATCG CTTTGGTTTCTTAGTGGCTCAGTTTGTGTGATCTTTTCATTCTCGGGGACCTTGTGCGTGCATAGGGAATAA AACTGCCCTCACCAACACCAATAAACCCCTGTGAGTGTGAGAAAAA	
SEQIDNO. 57	SEQIDNO.:100 MMPGQIPDPSPVITAGSLPGLPLT GLPSSALTTTELKYADIRNIGAM IAPHLFLEVLKGRPOPVKSELD EEEEERPKRRREKNKYAAACRNK KKERTFELQRESERLELMNAELK TQIEELKLERQQQLILMLNRHPT CIVRTDSVRTPESEGNPLLEQLD KK
GCGGAGGGAACACTCGGGGGCCGACGCGGGGGCGCTGCGCGGACGCGGACGCTGCAGCGGGCGGGCGGGCTTGGCGCG CGCGGCTCCGGCGCGGACGGGCTTGGCAGCGGGCGGACGACGCGGAGTGGGCACCGCGCTGCAGCAGGGTTCT GGGCCGGGGCCCGCTTCTGCCAGCGGCTTCTGACGCCCTCCAGCGCGGCTGCCACTCTCTCTGCTATGATGCCT GGGCAGATCCAGACCCCTTTCAGTGACCGCAGGCTCTCTGCCAGGCTCGGCCCTCACCGGACTTCCAGCTCTGCTCT GACCACAGAGAGCTGAATATACGTGACATCCGCAACATGGGGCGATGATTGGCCCTTGCACTTCTCGAGGTGAAC TGGGCAAGAGGCCCCAAACCGTGAAGTGAAGTGAAGTGAAGAGCAGAGGAAAGGCGCGGGAAGAAACAAA GTCGCTGCAGCCAGATGCCGGAACAAGAAAGGAACCGACAGATTTCTGCAGAGGAGTCAGACGGCTGGAGCTCAT GAACGACAGAGTGAAGACGACATAGAGAGCTGAAGTGGAGCGGCAACAGCTTATCTGTATGCTCAACCGCCACCGCC CCACTGCAATCGTGCACACAGATAGCGTCCAGGACGCCAGTCCGAAGGCCAACCCACTGCTGGAGCAGCTGGACAAGAA TGACTGAAGGCTGGAGGAGCATCAGAGGAAGAGGAGGAGGAGCATAAAGAGAAAGAGGACGAGCAAGTGA CAGAGGGCCCTCCAGGCACGTGACAACTATGATGAGGCTTAGCATAACTAGCTCCAGCTGGCTCTCTTTTGAAA CTCAGCCCTGCGCGCAAGACAAAGCGGACTGAAGAAACAGAGGGAACAGTGCTGAGACCAAGGTTGACCCGCAGA TAGGGGCTGTCCACTCCAGGGCCAGCTTGAAGAGCACCTGAGCCAAGAGGTGCCAACCCAGGTAGTAGCCTCAGGCA TCTCTTTGGCTCTCTGCAAGACCCACCCAGGGGACTACTGAGCAGCCAAGAAAGCCATGCATGCAACACACAGTG TGGCCCGGAGTGGAACTCAGCATAGACTCAACTCCACCTCCCGCTCCCAAGCCAGTGGAAAGGGGTGCACCTGT GGGGTGCATGGCCAGCTGGAGTTGGCTGCGGCACAGAGCGCGGGCGCCCTTCCAAAGCAGTACTTAATCAATGAA TGTTTACAGACTGGCTGTCTGCGGGGCTTCCAACTGCACACGGTTTATATCTTTTCTTTTCTTTCTTTCTTTT TTTAATATTTTTTACAAAAGATTTTATACAAGCAAT TAATCACTCGATGTGACACAGTACAAATATGCTATGGTCTGTTATGGACATCCACCCAGTTAAGGCCATTTGTAATTC CTAAGTACTGTAGGCTCTGGGTGTTGGGGGTGGCCAGCGGGTGAAGTACATTTCCATCTCTGTAACCCCTTCCCTAGTA CCGAGTCTCTGATCGTTACGTAAACATTGCTCTTAATACCCCAAAAAA	

[illegible]

Nucleotide Sequence (5' - 3')	ORFs
CCGCTCAGACCTCTTCTGCCACCTTCGCCAGAAATCACCCCCAGCTGGGGGGACAATCTAAACAGATCAACCCCTTCT CACTCGGGAAGACCTCAGGGGTGCAAGATCAAGCTGTGTGACACACACCTTGCAAGCCGGCCACTCCACTGCCCTGGTT CCACATCACCACTTACTCCAGCTGCCCTTATGTACCACTCCAGACATCTCTGGTCAGCCTGAGACCCCTGTCCG CCGTGTCTGCTCACTACCTTTCATCCCTTGAGCTTCCCGACGGATGGAGATGCTATGCCAGGTCTGTGGCCCTTCCCCCA TGGGCCCGACTGAGGAGAGGATGGAATCGGAGGGCAGCAGCCCTGAGCAGAGCCCCCAGGCCCTGGCTCCCCAGCTGCCCT CTGGCTGTGGCCACTGACAACTTCATCTAGTACTTGTCTCAGCCTCGCAGCCCTGGTCTCTTAGATCAGAGCACTCCCT CAACAATAATCCCCCTGCTGTGGTGTGAATTCCCCACAAGGGTGGGTAGGAGCCCTGGAACCGGGCACAGCATAGCC TTCCCCGGGACAGACCCCTGAGACAGACAGCCCTCACCCGCCCATCAGCTCCCCGGGAGCCGAGGAGGGGTGCC TGCCCTGGCTGCTGCCCTTGGCCCGTTACGCTTGGCTTCTATCCATGTGCCCGCCCTACCCCACTGTTGCCGCTA CGCCAACTTGAACCTGTAGCGGGCAGTCTTCTGCCACCGAGGCATCATGCCAAGCCACCCACCCAGCCCTGCAGC TGCTGGGGCACGCTCTTAGCAGTGAGCCTGTGAGCTTCCAACTTGGCCTTCCGGATACCTGTAGGACAG TGCACTTGTGTGACAAATGCCAGCCCCAGATGGGCTGACTAGTCTTCTCCCCGTATAGGGAGCCTCAGCATGGTCTCAA TGGACAGAGCACTCTTAGCGGACCCCTGGGTTCACTTCCCATTTGGGATCACCGAATAGACACAGCATTTGTGACACA CAGGACTAACACAGTGTAAAGTATTTAAATAATTTCAAATAAACTGCTGGTGGTCCGGGCCATCCATCCACTCAGCG GAGCGCCCTCCCTGACCCATCTCTAGTTTGGGAAGTTCTTAAGGAAGTCAAGTCTTTCTGGAGGCTTCTTTACTCTT CCCAAGAGAAGTCCAGTTTCTGGAGCAGCTTCAAGCAAGCAGCAGGTCACTCCCTTAGCTGGGCAATGCCCGAGAGTGAGG GAGTGTGGAGGAATAGACTCTTTAAATAATTGGCAGGCCGTAGGTTAAGGATGTAGGTCAAGAGTCTTGTTCAGTGTCT TGGAAAATAAAGCATCAGTGAGT	SEQIDNO. : 102
CTGAAGCCGAATCCCGGAACCAAGTAGCAGAGAGCTCGSCCGGCTTGGAGGGAGACAAGGCTGCGACCAATCCGCTCTCC GTACCGTCCCATCGACTTCACATCCGGATCTCCTCTGGGCGTGACCCGCGTCCGCTCTGCGGTCTCGAACCCGGTGT CTGATCTTTTATCCAGGCTTGTCTTCCGTGTGCTCTCGCGACACCGTAGCCCTCATCCGGGTTCTTCTCCCG CGTCTCTCGGTTTGTCTGTGTGGGTACTTGTGGGCTGCGGCATGACTATTTCTCCCCAAAAGAACCGCCACCTC CCGACGCCACCCGGCCAAAGAACCGCCGCCGCTGCCCCCGGCGCTCGGCCGCTGCGGGGTAGGCGCT GGTGGCGGCGCACGGGTGTGGGCGGAGAGACGACCGTACTCCGGCGTGTGGGGCGGCTCCCGGGCTTCGCC GCCACTCAGGGCCGCTCCCGGGCCGCTGTGTCTTTCATCGTTGGGCACTGGCCGTGCCCTGGCGAGTCCGCG GCCCAACTCGCGGGGTGGCGGGCAGGGGTGTGTGGGCGTGGTGGTACCCTGGGCGTGGGCGCTGCTGCTCGG GCCCGGCACAGCAAGCGCGCGCTCAAGCTCCCGGCTGTGGCGAGTTGGCGGGCAGTCCGGAACTGTAAGAGGTCG CAGGAACTATGGTTTGAAGGCTTCCGGGACAAGAAAGGCTTCATCATCAAGCATGAAGGAGCAGCGTGCCTGTCT ATTTCGGGCTGTAGCTGACACAGGTGTATGAGACCCAGCATGATGAGGTTGTTCCAAAGCATTCGACTGCACTATCTGA DFTTNNRKRKNKNHNIEMO	SEQIDNO. : 103

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NucleotideSequence (5' - 3')		ORFS
TGAAGAACGGTGAATTACTTCTCCAACTATGTCACAGAGACTTCAACCTATATCAACCGGAAGCGGAAAAACAACCTGC CATGGCAACCAATTGAAATGCGAGCTATGGCAGAGATGTACAAACCGTCTGTGGAGGTGTATCAATATAGCACAGAAAC TATCAACACATTCATGGGATCCATCAAAATGAAGATGAACCCATCCGTGTAGCTACCAACCGGAATATCCACTATAATT CAGTGTGAATCTTAACAAGGCCACTATTGGTGTGGGCTGGGCTTACCGTCACTTAAGCCAGGCTTTGCAGAGCAGCTCC CTGATGAAGAAATGCCATAAAGACATCAGAAGAGTCAATGGATTGAACAGCAAAATGCTGGAAGACAAGAAACAGAGCTACAGA CTGGAGGCCACAAATGAGGCCATAGAGGACAGGTGGCTCGAGAACTTCTACCTTCAGTGGCTGAGGATCAAGAGAAAC AGGCCCGCCAGGTCCGGGACCCAGCAGCCCGGAAAGCCAGTGCACATGACGTTTCAGCACAGCAGCAGCAGCCTCCAGT GGCTTGGAGGAATGGAATAGTCGGTCCCGCACGGCAACGAAGTTTCAGCCCTGCTCAGCTGAGCACCTTGAATCTGCATGCCGA GCTAGGCATTAAGCCCTTCCCGAGGCACTGTGTAGTCTTTGGCAAAACCTCTTCCCTGTGACCCAGGTACAAGCA GTGAGTCTCAGCAGGGGTGATCGGGCCACTTCTCCTCTTGTGTCCCTCTACCTCTGCTGTGAGTCCCGGGCCCTCATC CAGCAGATGTCCCCCTCTGCTTGTGTTGAATGATGGGACGATGATGAGATCTAGCATCGGTGCTGGCAGTGTCCCA ACAGGAATACCTAGACAGATGAAGAAAAACAAAGTGACACAGAGAGCCACCCAGACAAAGATTGATGGACACCCAGGG ACTGGACATCATTCCCGATCCCCACTCTGCCCTTGTATGTCACCCAAACTTCTTTGGCTTTCTTCCCTTTGGCTTCC TTCCTTTGTTTCTCTTTTCTTTTTCCTTCTCCCTCTGGCCGGCCACCCATGCGCTCCATCCATCTCATCTCCCT GCCACCACCATTTGCTCTGCCAGCTGAAGTGCCTATTGCCCCGCGCACAGCACCATCTCAGCATTCACACAGGGGACTCT GGAAAGGGTGGGAAGGTAGGCAAGAGGCCACAGAGACAGACCATCTGGCAGCCAGGACGCCCAAGAGAGACATTC AGACAAAGGAAGTCTTGTCTCACCTTCCCTTAAAGATCAGATAAACTTGTCTATCCCTTCCAGCAATGATGACAGGAAA ATGGAAGTGGCAAGTTTCTCTTAGTATCCGAAGAAATCTGAGCCTTCAATGTTAAAAATTTTCTTAAATTAATAATGTGCT TTATTTTCAAAAAA		AMAEMYNRPVEVYQYSTEPINT FHGIHQNEDEPIRVSYHRNIHY NSVVPNKATIGVGLGPSF KPGFAEQSLMKNAIKTSEESWI EQQMLEDKKRAIDWEATNEAIE EQVARESYLQWLRDQBKQARQV RGPSPRKASATCSSATAAASS GLEWTSRSPRQRSSASSPEHP ELHAELGIKPPSPGTVLALAKP PSPCAPGTSSQFSAGGDRATSP LVSLYPALECRALIQMSPSAF GLNDWDDDEILASVLAVSQOEY LDSMKKNKVHREPPPKDS
SEQIDNO. 10		SEQIDNO. :103
ATTTTATATGTGAGGCTTCAGTTGGTGTGAAGAGTTGCCCTCTGACTGTGCAAAATTGACATAACTATCAGGGGCGAG TTGGCATAGCTCCGCCAGCAGAGCCTGCACAGTGAAGATGCAGCTCATGGTACTCGTGTGGAGTGTGGCAGCACGGA CCGACAGATCAGCACTCTCCACAGCTAAGACAGCCCAAGTCTCGGCAACACAGCTGCTGTAAAGTCAAAAAGGCTCTG CAGACAAGAAAGTCTTACCTAGAGCAACATCTGGGAACATCTTTGCAAGTAAGGACCTTGTATAGATTGAGGAAATCAT GTGAAAAGACAAAGGCTGATGGCAGCGGGCACAGGAAGACAGGCAATTGACATTTGCCCTTTGACAGGTTAG GCCTTAATGATATATAAACGATGCTCTGTGTCTTCCCAACACAGCCTGCTTGAATCGGTAGATACTGTGGCGAGGCT AGCTCGTGAGTATTCCTTTTGTATCACACCAGTGTGTTAAAGTTGTGTCTGTATGCTGTCTGTGTTATTTTAAAGTTC TGGGAAGACCTGTGCGCGTGTAGCTACGGCCATCAGTAGTTACTCAGTATTTGCTGTCTCCACGTTTCCAGTGCAAC TTTCATGCCAGGCGATGGCTGGTGGTCAAGCCGGGAGCCCTTCCCGCTCATTTATATATATATATATATATATATAT AAATGACCGCAGATGGCTATATGTTGTAGTGTAAACCAAGTGGAACCTTAATGGCAATAAATAATATATATATATAT GAGGGGAAAAGTGGAAATACAGGTTTACAGCCAGACATGGTGGGTGATAGCCCTTCAGTGTATTTCTGTCTCCCTCACT GACCTAGAAGGATTTGAGCTGCTGACGCTTTAGACAGAAAATGTCCACATTTGCTGACTGTGGGCCATAAATATGCTTTT		FICEASVGVDRSCPLTVQIDIT IRGQLGIAPPSRACTVMQLMV LAVECGSTDRQISTPPLRQPS PAATQLLVSAKRSAETRSLHLE QHLGTSLOVRTLID

Fig. 31

NucleotideSequence (5'-3')		ORFs
AGTACTGCTTTGCTGATGATATAAATAAGAAATCTGTAATAATGTAATAATGTAATAATTTCTTTTGACTTTATTTCAAA ATGTATATTTTCTGATTTATATCATGAGCTATAAAGCAAAAGATCAATATCTGATATTTCTCCCAATAATAAATTTTCA AGATTCAATTGGAATAAAAAAAAAAAAAA	SEQIDNO. 1.1	SEQIDNO. : 104 MKSTSRDAVLFFSESILVPTARK ALCDPLEEVREAAAKTFEQLHS TIGHQALELILPFLKQLDDEE VSEFALDGLKQVMVAKSRVLP YLVPKLTTPPVNTRVLAFLSSV AGDALTRHLGVILPAVWLALKE KLGTDPDEQLEMANCOAVILSVE DDTGHRIIIEEDLLEATRSPEVG MRQAAAIILNMYCSRSKADYSS HLRSILVSGILIRLFDNDSSPVLE ESWDALNAITKKLDAGNQLALI EELHKEIRFIGNECKGEHVPGF CLPKRGVTSILPVLREGVLIGS PEQKEEAAKGLGLVIRLTSADA LRPSVVSITGTLIRILGTGTG L

FIG. 32

NucleotideSequence (5' - 3')		ORFs
CTGCCAGGACACTCGGTGAGCAGGTGAGACACACCATCTGACGTGACAGCTGGTCCCGCCAGCCACCGCAGCGTCC CCTCGTCTGTGTTTCACTGTTTCACTTTTGAAATACCTTTTATTCGAAGGGGAGCTCAGGAGATGGCATTTCCAGAA AGTATTTAGTACATCAAGCACAGAGCCAAAGCTTAAATCCACCCACACACAACTGAAGATCGCCTCTCCCTCTC TTGCCCTTATCTCCAGAGAGAGAAAGAGAGCGTGCACACCCCTCAGCAGCGGAGCAAGGGGAGCCGACACTCGG TCAGCCCGGATGAGCAACTCGGGCCCTCTCTTATCTGGAGGCCCTGTCTGAGGCAATGAGCGGGCATCAGTGTCTG CCTGATGCTGCGCTTGGCTTCTGGCGGCCCTGACTCTACCTGGCTTGTCTGGAGAGAGGCTGCCAGTCCCTCCTC CTCAGCTCCGGGCTTGGGGTACAGGCCATTCGAAGGAGTTTATAAAGGCTTTGATTTTCATTTGAAAAA AAAAA	SEQIDNO. 12	SEQIDNO.: 105 MAAVKTLNPKAEVAPAAALAV NISAARGLQDVLRTNLGPKGTM KMLVSGAGDIKLTQDGNVLLHE MQIQHPTASLIAKVATAQDDIT GDGTTTNNVLIIGELIKQADLYI SEGLHPRIITEGFEAAKEKALQ FLEQVKVSKEMDRETLIDVART SLRTKVHAEALADVLTEAVVDSI LAIRKDEPIDLFMVEIMEMKH KSETDTSIRGLVLDHGARHPD MKRVENAYILTCNVLSLEYKT EVNSGFYKSAEEREKLVKAER KFIEDRVKKIIELKKKVCSDS KGFVVINQKIDPFSLDALAKE GIVALRRARRNNMERLTACGG IALNSFDDLPDCLGHAGLV YEYTLGEEKFTFIEKCNNPRSV TLNVKGNPKHTLTQIKDAIRDG LRVKNALDDGCVVPAGAVEV ALAEALIKYKPSVKRAQLGVQ AFADALLIIIPKVLQNSGFDLQ ETLVKQAEHSESGQLVGVDS TGEPMVAEMGVWDNYCVKKQL

Page 33

Nucleotide sequence (5' - 3')		ORFs
TTTCAACCCACTGAACAAGATGTTTATAGTACACCGATACAAAATACATAATAGATAAGCATGTTGTCTACCCCTTGT TCCATAAGTGTCTTTTGAAGTGTGTAATGTTTCTCCTAAATAAGCATGTTGACACATGCTGTAAAGCTAGCCCTT TGGAAATAGTCCGGAAATTTCTATGCCAACTCAGGCTCAGGAGACCCAGGTCGAAAGAAATAATTTGTTGGATGTATT TGAAATTTACAGCCAACTCCCTGTGTAACATGTAAATCTTCCAGTGTAAACACATCTGGGTAAATTTATGGGTTGC ATAATGTCTAATAAATACTTAAAAAGTG	SEQIDNO.13	LHSCIVTIATNILLVDEIMRAGM SSLKG
CAACCTCCTCAGTGGCCAGTTTGTGCGCCCTGGGACTTACTACAGCTGGGCATGGCAGACTCTGCACAGGTGCCAACAC TGGTATACCTGGTACAGGTGGCTGCGGCTTCTGGGGAACATAATGTTTCGGATGCTGCTGGAACGGGAGCCAGGCTC CGGAGCTGCTGCTTTGACCTGCACCTGAGTTCTTGGCTGGAGGACTGAAAGCAGGGCTTGTGCAGGTGACTGCCAT CCAGGGGATGTACTCAGGCCATGAGTGGCAGCAGCATGTCTGGATCACTGTGTCATCCATACAGCTGGGTTGG TGGATGTTTGGGAAGGCAGTCCAAAGACCATCCAAAGTCAACGTGCAGGGCACACAGAAATGTGATGCTGTTGT GTGAGACTGGCACTCAGTACTGTTCTACAGAGCAGATGGAAGTGGTGGGCTTAACATCAAGGGCCACCCCTTCTA CAGGTGAGCTCAGCCCCACTTAATCTTAGAGCCCATTTCCCTCCAGCACTCAGTCTTCTTCTCCCTCTCCAGGGCAA TGAAGATACCCATATAGGCAGTCCACAGCCATCCCTACCATGCTAAAGCCCTTGTGAGCAGCTGGTCTCGAGG CCAAATGAAGGAAGTCAATGGAGGGTACCCCTGGTGACATGTCCCTTCGATGAGCTTCTGTTGAGGTGAT CAGGTCAATGAGACTTCTACTACAGGACTGGCTTTGGAGGTGCTTATTTTCGGGCCCTCCAGACTTCTGTTGAGCA CGGTGCGGTCTATGTTGTAAGGACAGGACAGAGGCTCGAGGAGTGGCTCTGATGTTGGCAGACTCACGCTGTACG CTGGCTCCAGCGAGCTCAGGACAGAGTGGCATTTTCTGATGAGTTGAAACCGGGGAAAGCATCCAAG CAGTTGGAGGGCTGACATAAGAACATGGCTAGTTTATGATGACCAAGAGGAGCAGCTCTCCAGAGAAAGGAGAA AGCATCTACACGGGATCCAGTAGTGCAGGATGCCAGGAGGCTGGTGGCTACGGGCCCTTGGAGAAAGGCAACTTTG ATTAATCAGACAGTAGAGGTGGGCAAGATCTACAGGGGCCAAGGCCAGCTTCTCTCCCTCCCTCCCTGCTG GCAGGCAATGTTGCTTGGATGCACATACTGGTGGCCGGAGCTGGAGCAGCGGGCAGCACTCATGGGTGGCCAGGTGA TTTCTGCTATGATAAGTCACTTATAAAGCTACGAGACTTCAACATGGAGTTTCTGAGTCCCTGTTGCTTCTGACTGA TAGGCGCCACCCACTGCTGCCCTACTGGCTGCTAGTGTGCTAGTACCTCAATGCCCTGTGCTGAGTGGCTGCCG CCACTGGTGTGTACACACCCCTGTGATCCCTACAGCTGGCTATGGCCAAACACCACTTTTACTGTCAGTACCAACAA GGCACAGCGGCATTTGGCTACAAGCCCTTCTCTCATGGGAAGAGAGCAGGACCCGACCACTTCACTGGGTGGCAGGCGA TGGAGGTTTCAAGCTCGGTGATGGCAGGCGAGGACCTTGGACACTTCCAGGTCCTGAGCCCCCAAT CTGAGTGAAGAGAAATGGCTGCCCTTTTGAAGATGAAGACTGTCTGCTACATCATGACTCCGTAAGTGGACCCCTGCCA CATCTTAACACACAGATCTCTGAGACTGTTCTATTTCCAGTCTCTAGTCTAGGATAGGTTTGGGGAAAGGCCATC TTTGGTGCCAACTCAGGCTGCGAGGTAGTGGCAAAATGATTTCTGAATGGTCTCACTACCTCTCTCTGTTTCCAGT TTCTCAAGCAGGAGGAAACAGAGACTCCAGAGATCTTACGCTGGTCTGCTTACTTCAGCTACCAATTTTCAGACCTGGCTC CTGCCACATCTGGCTCTCCTTAAGGGTTATAGTTTCCACCATTTTTTAAAGTGTATCTCTTTTAGACATTTATCTTTTAAAT	SEQIDNO.:106	MADSAQVPTLVYLVGTGGCGFLG EHIVRMLLEPRRLRELRFDL HLSSWLEELKAGPVQVTAIQGD VTQAEVAAAMSGSHVVIHTAG LVDVFKASPKTIHKVNVQGTQ NVIDACVQTGTQYLVYTSSMEV VGPNIKGHPFYR

FILE.34

7575

NucleotideSequence (5'-3')		ORFs
TGGCAAGAGAGAGCTGGCTGTACACCTAGATCCCATCTGATCACCATCATGCCATGAGTCGCTGGGGTCTCTGC TGGGGCCACCTGTGGGGCTCCTCTTTACTGCACTGCTCCTATTGGGTCTGAGTTCGAGAGCTGCACCACTG GAGAACTACAACCTTGAGCTTACGATGGCTCAAGCAAGGTCAAGATCAATCATCAGAACTGCTCGGAGGCAATG ACCGATTGCTGTGGATCGCTTCTGGCGTTTCAATCCAGTGAGAGGGCTAGCGAAGATTACAGTTTGTCTGTCTTGT TTGTCTTCCCTTTGGAAACTGAATGCCATAATCTGGATCAAAAGTTCCAGAACTGAAGGTATGGACAGACAGACA GGCCAGCTTAGGGAGAAAGGAGATGCAGCTGTGAAGGGATCGTTGCCCAACAGGACTGTGGTGGCCAAAGTGAATGCAG GAACCGGGCCGGAATTCGGCTCTCGGCTAAATCTCAGCTGCTCGGAAAGGCTCAACCATACTCAGTGCCAACTCA GACTCTGTGTGTGTCACCATGGATGGATCATCTGTACCTTGTATTTTAGCAGAAATTCATGTCTCAGATTCTTTG TTCTGAATCCTTGTCTTGTCTAGACACAAAGCATACATGTCTCTTAAATTAATATGATCACTATAATCTCTGTGTG CAGAAATTCAGAAATAGACCTTTGAAACCAATTTGCAATGTGAGTGCAGATCCATGCTGGGCTAGTGCAGCAATGAAACA GAATCCAGAAACAGTGTCTTTTATATGGGAAATACAGATAAAATGGCCACTGATGAACATGAAGTTAGCAC TTTCCCAACACAGTGTACACTTGCACCTTGTTTTGGATTTCTCATACCAAGACTGTGAACACAAATTTCAAGAAATG TGTTCAAATGT TGTGAGT TATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGTATGT GTGGTATGTGTGTATGCAATTTGTCTATATGTGTATCTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT CATGTGTATGTATGT CTGT GTTAGTATGTTTATAGAAAAGACAGTCTGAGATGCTTCTCCTCAATACCTCTCCACTTATATCTTGGATAGACAAAAG TAATGACAAAAAATGCTGTGTGTATATGGAAGAGGGGACACATATCCATGGATGGTAGAAGTGTAAACTGTGCAGTC ACTGTGGACATCAATATGCAGGTTCTTTCACAAATGTAGATATAAAGCTACTATAGTTATACCC		KEKSWLYTLDPILLITIIAMSSL GVLLGATCAGLLLYCTCSYSGL SSRSCTTLENYFELYDGLKHK VKINHQKCCSEA
SEQIDNO.16	GGGAGCGCGGCGCAGAGAGGGGCGCGGCGAGGCGGCTGCCGGGGCCACCATGGCCACCGACGAGTTGGCCAGCAA GCTGAGCCGAGGCTGCAGATGAGGGCGGGAAGGCGGCGAGGCGACGAGCAGCGCGGCTCAACGGGCGCGCGCGCGG CGCGGCGGAGGCTCCCGACGAGACTGCCAGGCGTTGGGCGACGCGGCGACGACGAGCTGAGCGCCAAAGCTGTCGCGCGC GGGACCTCAACAGGGCATCGGCGAGCCACAGTCGCCACGCGCGCGGTCTTCAACCCCTACACCGAGTTCAAGGAGTT CTCCAGGAAGCAGATCAAGACATGGAGAAGATGTTCAAGCAGTATGATGCCGCGAGGATGGCTTCACTCGACCTGATGG AGCTGAACCTCATGATGGAGAAGCTGGGGCCCCCAGACACACTTGGGCTTCAAGAGTATGATCCAGGAGTGGACGAG GATTTCAAGACGAACTCAGCTCCGGAGTTCCTTCTGTATCTTCGCAAGGACGACGAGGAGTTCAGGAAGACAG CGGCTTGACGCTCCTGGCCCGCTGTCCGAGATCGATGCTCTCCAGAGGCGCTTAAGGGTCCCAAGAACTTCTTCGAGG CCAAGGTACAGGCCATCAACGTGTCCAGCGCTTTGAGGAAGAGATCAAGCTGAGCAAGAGGAAGGAAGCAGGCT GAGGAGGTGAAGCAGCGGAAAGCGGCTTTAAGGAGCTGCAGTCCAGTCCAGTCCAGAGCCAGCCAGGCGCAGACCTGG	SEQIDNO.:109 MATDELASKLSRRLOMEGEGGE ATEQPGLNGAAAAAAEAPDET AQALGSADDELAKLLRRADLN QIGIEPQSPSRRVFNPTFEKE FSRQIKDMEKMFQYDAGRDG FIDLMELKLMMEKILGAPQTHLG LKSMIQEVEDDFDCKLSFREFL LIIFRKAAGELQEDSGLHVLAR LSEIDVSTEGVKAKNFFFAKV QAINVSSRFEETKAEQEERKK

FIG. 37

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Nucleotide sequence (5'-3')	ORFs
AGCCTTGACAGTGATAGAAAGCATCTACATCTCTGGATGACCCCTCAGTGCCTTAGATGCCATGTGGGCAACACATCT TCAACAGTGTATCCGGAAGCGCCTCAAGCTCAAGACGGTTCTGTTGTTACACACAGTTCAGATATCTGTCGATTGT GATGAGGTGATCTTCAAGAAGGAGGCTGATACAGAGAGGTAAGTCCATGAGAGCTGATGAACCTTAATATGGGATTA CGCTACGATTTTAATAACCTGTTGCTGGAGAGACCCCTCAGTTCAGATTAATGTGAAAGAAAGTACTGTTTAC AAAAATCAGAGAACAGGCGCTTAAGCCAGGCTCAGTGAAGAGGAGGCGGTGAAGTCCGAGAGAGGAGGAGGCTG CAGGTGGAGAGAAAGGCAAGGTTCTGTCCTTGGTTCAGTCTACTGGTCTACATCCAGGCTCAGGGGGCCCTTGGC TTTCTGTCATCATGTCCTTTCATGCTGAATGTGGGAGCACTGCTTTCAGCACCTGGTGGCTTAGCTACTGGATCA AGCAAGGAAGGGGAAACAGCAGTGTATCAAGGAAACAGAAAGTTCGTGATGACAGCATGAAGCAACCCCTTCATG CAGTACTACGCCAGCATCTACGCCCTCTCCATGGCAGTCACTGCTGATCTTGAAGCCATTCGAGAGTGTCTTCGTCAA GGGCACACTGAGAGCCTCCTCCGGCTCCATGATGAGTATTCGGAAGGATCCTTAGGAGCCCATGAAGTTTCTTGATA CTACCCCAACAGGAAGGATCTCAACAGGTTTCCAAAGACATGAAGTGAAGTGGATGTGGCTGCCCTCCAGGCTGAG ATGTTTATTCAGAAATGTAATCTTGGTGTCTTCTGTTGGAAATGATGCTGGAGTCTCCCATGGTTCCTCGTGGCGGT GGGGCTCTCCTCATCTCTCTCACTTCTCCACATTTCTCCAGGCTCCTGATTCGTGAGCTAAAGCGGTTGACAAATA TCACGAGTCTCCTTCCACATCAGCTCAGCATTCAGGCTGGCCACCATCCATGCCATCAACAAAGGCGAG GAGTTTTCACAGGATCAGGAGCTCCTGGATGACACAGGCTCCTCTTCTGTTTCCCTGTTTCACTGTGCAATGAGTGGCT GCCAGTGGCTGGACATCATCAGCATTCGCTTGAATACAGCATTCGCTGATGATGCTCAGGCTAGGCTGAGGCTGAG TTTCAGCCTATGCGGGCTTGCATTTCCAGCTGTCAGTGAATGAGTGAATGCTCAGTTCACCTGCTCAGGCTGAGGCTG GAGAGAGAGCAGGTTCACTTCGTGGAGAGGATCAACCATATATCAAGACTCTCTCTTTTGGAAAGCACCTGCCAGAA CAAGAACAGGCTCCTCCCATGACTGGCCCGAGGAGGAGAACTAACCTTTGAGAAATGAGAAATGAGATACCGGGA ATCTCCCTGCTTGAAGAAAGTCTCTTCAACCAAGCCCAAGGAAAGATGAGCATTTGGGAGCGAACAGGGTCA GGGAAGTCTTTTGGGATGGCCCTCTCCGTCTGGTGGAGCTATCTGGAGGCTGATCAAGATTGATGGAATAAGAA CAGTGACATCGGCTGGCCGACCTCCGAAGCAACTGGCCATCATCTCTCAGGAGCAGTCTGTTTCACTGAGTGGCTGCA GATCAACCTGGACCTTTCAACACAGTACACGGAAGACAGATCTGGATGCTTAGAGAGAGCAGCATGAGGAATGT ATTGCCAGCTACCTCTGAACCTTGAAGTGAAGTGAAGAACGGGACAACTTCTCTGTTGGGGAACCGGAGCTGTT GTGCATAGCAAGAGCCCTGCTGCTCACTGTAAGATTCTGATTTTAGATGAAGTACAGCCGCTATGGACACAGAGACAG ACTTACTGATCCAGGAGACCATCCGGGAGACATTTGGGAGTGCACCATGCTGACCATTTGCCATCGCCTGCACACAGTT CTGGGCTCTGACAGGATCATGGTGTGGCCCGAGGACAGGTGGTGGAGTTTGACACCCCATCGTCTCTCTGCTTAATGA CAGTTCAAGATTCTATGCCATGTTTGTGCTGACAGAAACAGGTTGGCTGTCAAGGCTGAGTCTCCCTCCCTCGAAGT CTCTTCTCAGAGCATTTGCCATCTCTCTGTTTGGGCCCCCTCATCTCTGCTGTAACCTCGCCCTTTCCAGTTT TATCTCTCACAAACCATTCAGGATTAGCTGTGTTTCACTTTAAGGAAAGTATATTTTATGATTTATTTATTTAT CTATTCTTAATGAATTTAGTTTGTCTTAATGCACTTTAAGAGGCTTCAAGGAGTCAAGGAAACCATTAATAATGTTAT CAGTGGCTTAATGAAGCTTTATATGTAGTACTATATATAATTTCTGTACATGAGCTATATTTACAGATAAATG TAAGCGGCCCGGAATTTCTAGGGCTCTCTGCTTTCTGTTGCTGAGTCTGCTTTATGTTAGAGCAGTGGGCAAGC CAGCCCCACCCAGTCTGCTCCAGTGTTCATGCTTCAGGTTCTCTGAGGCTGGTGGCCACAGAGTTGTGAGTTCCCTG	LEGSIASVGTFAVVAQQAWILN ATLRDNLFGKEFDEERYNSVL NSCCLRPDLAILPNSDLTEIGE RGANLSSGQQRQISLARALY SDRSIYILDDPLSALDAHVGNH IFNSAIRKRLKSKTVLFTVTHQL QYLVDCDEVIFMKEGCITERGT HEELMNLNGDYATIFNNLLIGE TPPVEINSKKEATGSKQSDKG PKPGSVKKEKAVKEEGQLVQV EEKGQGSVPWSVYVWYIQAAGG PLAFIVIMVLFMLNVGSTAFST WMLS YWIKQGGSGNSTVYQGNRS FVSDSMKDNPFMOYYASIIYALS MAYMLLILKAIIRGVVFKGTLRA SSRLHDELFRILRSPMKFFDT TPTGRILNRFSDMDEVDVRLP FOAEMFIQNVILVFFCVGMIA VFPWFLVAVGPLLILFSLHLIV SRVLIRELKRLDNTTQSPFL SHITSSIQGLATTHAYNKRQEF LHRYQELDDNQAPFFLFTCAM RWLA VRLLDLISIALITTTGLMI VLMHGQIPSA YAGLAISYAVQL TGLFQFTVRLASETEARFTSVE RINH YIKTLSLEAPARIKNKAP PHDWPQEGEVTFENAE MRYREN LPLVLKKVSFTIKPEKIGIVG RTGSGKSSGLMALFRLVELSGG CIKIDGIRISIDIGLADLRSLA IIPQEPVLFSGIVRSNLDPFNQ YTEDQIWDALERTHMKECIAQL PLKLESEVMENGDNFVSGERQL LCIARALLRHCKILLIDEATAA

723 - 40

[illegible]

Nucleotide sequence (5' - 3')		ORFs
GGAATTCTAGCATGTTGGTGTATTAGTAGTCAAGAGGAGGCAATTAGAGCTGTACCCAGGGAATTCCTGATCCTCTTA CATGTATAATAGCAAGACCGGGCCAGGAACAGCAAGCAGTCTGAAGCCAGCTGGGTCTGCCACTAAGAAGATGAAGC CTTTTCATACTGCCCCCTCTCCTTCTCACTTCTTCAACTGCTCTTGGAACTCTGGGCCAGATCACACATGCAACAGAGACA AAAGAAAGTCCAGAGCAGTCTGAAGGCACAGCAAGGCTTGAATGAAATGAAATGTTTCAATGGCTTCAAGACTCTTCAGA TTGCTGCCCTGCTATAACTCAAGGATTCAGTGTCAAGATTTATAGTTATTTTCCACCAAGTGGTGGTGTACACAGG CGGGCATCATCTTTATCAGCAAGAGGGGTTCCAGGTTGTGCCAACCCTAGTATCGGAGTTCAGAGATGCATTTGAA AGATTGGAGCAAAACTCAACAACCGGACCTACAACAATAAATTTGCTTGAAGAGAGGGTGTGAACCTGCCAGCTACT TTCTTTGGTCTTCCCCAGTGACCACTAAGTGGCTCTAAGTGTATTATTTTATAGTATATAAACAATTTTCTTTCTGT TCCACTTTAAGTGGCATATCTGGCTTTGTCAAGAGGGAACTTGTCTGTGCCAACCCCACTCATCTGAAACTCAGAT GCTTGAAGGTCTGAAGCTGACCTCAATGACTACACATAATATTTGATTGAGATAAATGGCAAGCTCTGGAGAGATGGC TTGGTGGTTAAGAGCAGTCTCAACAGAGAGCCTGGGTCAATTTCCACTAGATGGCAGCTCAAACTATCTATAA TTCCAAATCCAAAGAAACTGATTTGCCCTTATTTGCTTATAGTAGTATTTACAGTATTTCTTTATAAATCACTT GACATGACCATCTTGTAGCTACAGCCATCTTAACCTGCCTCAGAACTCACTCAAGTTCTTGCACTTTTCGGTTTCCACGGAT TTTAAAGTGGATAAACTGTGAGAGTGGTCTGTGGGACTTTGGAATGTCTGTCTGATAGTCACTATATGGCAACCCAGG TACATTCACTAGGATGAATAAATTTCTGCCCTTAGCCAGTAGTATGTCTGTGTGTAAAGGACCCAGCTGATTTTCCCA CCACCCCTCCCATCTGTAAAGCCACTAATAAAGTGCACTATATGCAGCCACAAAAA		MKPFHTALSFLLITLGIWAQ ITHATETKEVQSSSLKAQQGLEI EMFHMGFQDSSDCCLSYNSRIQ SKRFIGYFPTSGGCTRPGLIFI SKRGFQVCANPSDRRVQRCIER LEQNSQPRTYKQ
SEQIDNO. 21		SEQIDNO. : 114
CCCGAGTGTGCTGCCCTCCTGTCTGCTTGGTTAGGGACATCCCGGGAGCGAAAGCCAGCCGCTGGCCGGGCCCGGTG GACCAGCGAGCGCAGACATGTGCGCGCCCGCGGCGAGGGGGAAGAAACCACTGTTTCTCTCGGCCCCCC ACCGGGATCATGTACAGGATATATCCCGGAACTTTGACACCTCGTCCCGGGCAGCAGCGGCTCTCTGCGCACGCGG AGTCTACTCAGCGGTGGCGGGCCAGCAGAAGTTCCGGGTAGATATGCCCTGGGCTGGGCTCTCTCAATCCCTATCC ATCAACGCCATCACCAACAGCCAGGACCTGAGTGGTGGTACAGCCACAGTATCACCTCCTCAATCCCTATCC ACGCTCATCTCCCTACAGTCCCTGCCAGGCTGGCTTCACTCCCTGGGCAATGGCTCTCCCAAGACCTGGAGTATCA AGCCATCGGTACACCCGTGGCCCGCAGAGGAGATGAGCAGCTGTCTCCTGAGGAGGAGAAAGCTCGAATCCCG AGGGAGAGAAACAAGCTAGTCAGCCAAAGTGTGGAACCGTCCCGGGAGCTCACAGAGAAGCTGAGCGGAGACCGA GGAGCTGGAAGAGGAGAGTGTGGCTGCAGAAAGAGATTGTAGCTGCAGAGAGAGAGAGCTAGAGTTATGT TGGTGGCTCAGGCCCCGTGTGCAAAATCAGCCCCGAGAAAGCTCCGATCGCCCCCACTCCGGGCTGCAGTCTTGGC GGTACGGGCAAGTCCGTTGGCCCCGTGTGAGAGGAGGAGCTCCGAGAGAGAGACAGCCCTCTTCTCAGCAGGAT GGACAAGCCAGCTCTGTATCAAGCCCATCAGGAGCTCGCGGGGTGGTGTACGGGAGAGAGCTCTGACACACC CCATCGTGGTGAACCTCCAGCTGCCATCACTCCGCACTTCAAACTGTCTTACCTACCTACCTACCTACCTACCTACCT GAGTCGCTTCGTGCGCCCTCAGAGTCTCTGCTCCAGGCTCACCGCAAGAGCAGTAGCAGTGGGACCACTCATCAGACTC CTTGAACCTCCCCACACATTTCTAGCCCTGTAAACCTGTCTCTGCGCCAGCTCTGGAGGAATCTCTCATCCATCATACC		MYQDYPGNFDTSRGSSGSPAH AESYSSGGGGQQKFRVDMPSG SAFIPTINAIITTSQDLQWVQP TVITSMNPNYPYRSHPSPLPGL ASVPGHMLPRPGVIKTI GTTV GRRRDEQLSPREEKRRIRRE RNKLAACACRNRRELTEKLOA ETEELEEEKSLQKEIAELQKE KEKLEFMLVAHGPVCKISPEER RSPPTSLGLSLRGTGSAVGPV VKQEPPEEDSPSSSAGMDKTQR SVIKPISIAAGGFYGEELHTP IVVTSTPAITPGTSLNLFVTPN VLEQESPPSPSESKAHRSS

FIG. 42

Nucleotide Sequence (5' - 3')	ORFs
TGTTTTGGAACGACCCCAAGTTCCAGATCAGAGCGTCAAGACGAGCTCCAGGTTGTCACTCAGTGGATGTCAACACAC CGCCCTATTGACTCCTATGCTGAAGACGACGAGAGAAATGGTTGGCTTGGCTTTTACCTCTGGTCTGTGTCACTG AGCGTCAAGATCGAGAGAAAGGCTACTGTAAACGGAGAGCTATCCCTATCTATGCAGAAATAGAAAAATTGTTTCATCTCG TTGGTTGTTTCCCAAGCGAGCCATATTCCAAACCCAGACGTACTTGGCTAGTGTGAAACAAAGACAGTCCGGCAGCATGG GTGCCAATGTTTCGAGGAAACCACTATTGGTTCTGGAGTAGCGGACACCTTGGAAATGGGAAGATGCTTAAGATCCCACTGTCTC ACCCCATCCATCCTTGGATTGCTGCA TCATCAGAGTGGACTACTCTTAGCTGTAATCCAAGCTTCTTGAATCATTAATAAA TACAT	GSIOYCVRAVLERPQVPDDQSVR RELQVSHVDVNTPLLTPLMLK TOEKMVGWLFTSGPVSLSVKI ERKGYCNGEAIPIYAEIENCSS RLVVPKAAIFQQTLYLASGKTK TVRHMVANVRGNHIGSGSDTTW NGKMLKIPPVTPSILDDCCIIRV DYSLAVIQAS
SEQIDNO. 23 GCTCCTTCCATCTTGGCTGCTGATTCTAGACCCCAACAAACAGGTTGAGCCCTTTTCTCCTCCGGCAGTTGCTCTCTG GCTTGTGGTGCCTTCTGAGCGTTTCAGACGGCGCCGCTGGAGTGGAGGGAGGSCCTGGCTAGCCGCGCTGGGACT GGGACGTGCTCTGGCTCTGGCCCATGCTCAGCCCTGCTTGAAGCAGGAGTGTCTAGCATTTGACAAACGCCCTTGGAG GATGATGCCCCAGCTGCAGTTCGAGATGCTTCTGGTGCAGGACCTTACGCCCCACACAGGGTATGAGGTGCTACTGC AGAGGCTGTGGACGGCAGGAAGATGTGCAAGGATGTGGAGGAGCTGCTCAGACAGAGGGCCCGAGCGGAGGAGGTAC GGGAAGGAGCTGTGCAGATTGCACGCAAGGCTGGTGGCCAGACAGAGATGAATCCCTGAGGACCTCCTTTGACTCCCT GAAGCAGAAACAGAGAAATGTGGGACGTGCACATCCAGCTGGCCCTGGCTGAGGAGTGCAGGAGCCCTGGAGG AGTTCCGAGAGACAGAAAGAGCAGCGGAAGAAATGAGGCCATCATGGACCCGTCTCCAGACAGACGATGTTGCTGCTC TACAAGAGACCATGAGTCAAGAGGCAATATGACAGAAAGTGCAGGATGCAGATGATGTGACAGGCGCTTCGACGG TGTGAGTGCATGGCCACAGAAACAGTAGAAAGACCCAGAACCAAGCAGTGCAGAGTGCAGCCACAGAGG CAGAAAGAGTGTACAGGCAAAATATCGAAACAACTGGAGAGAGCGAGACCCGAGTGGGAGCAGGACACCGGACTACCTGT GAGGCCCTCCAGTTGACGAGTTTGAACGGCTCACCATCTCCGCAATGCCCTGTGGTGCATCTGTAACCCAGCTCCCAT GCAGTGTCAAGGATGATGAGCTCTATGAGGAAGTGGCGTACCCTTGAAGGCTGTGATGGAAGGTGACATCAATG CTTCAATCCAGTCCAAAGCATGGACAGACCCAGCTCCGGTGCCTTATCAAGACTATGATGACAGGAGGTGAC CCACTGATTGGCAGCCCTAGCATCCAGCCCTCTGCGGTGTGATAAGAGGTTCTTGGGCTGCTACATGGAAGTCCCA GACCACCTTCTGCTCTCCACAGAGACTCTGACTCCACCCCTGAGCGGAAATGAGTTGGTCTACGCATCCA TCGAAGTGCAGGCGACCCAGGAAAACCTTAACCTATCAGCCCAAGACTACCGGCACTCTACGACTACATGCAAGAAAT TCTGATGAGTGGACATTTCCGGGGGAGACATCTCTGGGGTTCATCTCTGGAAAGGGGAGGATGGCTGGTGGACTGTGGAGCG GAAACGACAAACGTGGCTTTTCTCCCTGGTGTGACTTGGAGAAGCTCTGAGGAAAGGCTAGCAGTCTCCACATACCTCCG CCTGACTGTGAGGTGAGGACTGTTTCTTTCATCACCGCCAGGCTCTACGGGGCCAGAACCAAGCCCGTGGTGTCTGGG CATGGGCTGGGTGCTGGCTACTCTCATATAATGTCTCCAGAAAGGAAAAA	SEQIDNO. : 116 MMAQLQFRDAFWCRDFTAHTGY EVLLQRLIDGRKMKDVEELLR QRAQEBRYGKELVQIARKAGG QTEMNSLRTSFDLSLKQTEENVG SAHIQLALALEERLSLEEFRE RQEBQRKKYEAIMDRVQSKLS LYKTMESKKAYDQKCRDADLDA EQAFERSVANGHQKQVEKSONK AKQCKESATEAERVVRQNIQL ERARTEWQEHRHTTCTEAFQLQE FDRLTILRNALVWHCQNQLSMQC VKDDELYEEVRLTLEGCDVEGD INGFIQSKSTREPPAPVPYQN YVDREVPLIGSPSTQPCGVI KRFSGLLHSGSPKTTSPAASAT ETLTPPTERNELVYASIEVQ ATQGNLSSAQDYRALDYDTAQ NSDELDISAGDILAVLLEGEDG WWTVERNQRGFVPGSYLEKL
SEQIDNO. 24	SEQIDNO. : 117

FF-45

715-46

NucleotideSequence (5'-3')		ORFs
ACCGTGGAGGACCACTGCGCAGAAAACCTCACCTGGTTCTGATTAAGGGTCTGCTGATGGAGATTTGGTGAGAGCTT AGATCAGAACGATGTATCCTCCTTAGTTTCTTACAGGGATTACACAGGCAGAGCAAGATACCAAGGACAAAGAGTT TCTTGGATCTGGTGATTTGAATGGAGAAACTGAATCTAATTTGCTTCAGACCAATGAATTTGTAGAAAAATGCTGTAAG AACTCCACGAATAGACTTGAACACAAAGATCCAGATACACCCCTCAGCCAGGAGCAAGATCAATATGAATATC TCTCAGGCTTCGCTCCAAAATGAGTATCAAGTAACTCAAGCTCCAGATCCAGATGGGCGAAGAAAGAGCCAAAGATTG TGGAATACCGTGACAGTCAAAAGAACACTGTGTAAGACATCCATCCAGGAATCAGGAGCTTTTACCTCCGACATCCGT GAAGAGACTTACAGGATGCAGAGCAAGCCCTAGGAATCTGCTTGATCATTTGATTTGGACACGACACAAATATCT TCAAGAGACCTTCACTTCCCTGGGCTATCATATCCAGCTTTCTTGTTCCTCAAGTACATGATCAATCAACCCAGATTGTTT GCCGATATGCAAGTATGGCCCAACATCAAGACTATGACAGCTTTGCTGCTGCTTCTGCTGAGCCTAGGAGCTCCCAAGC ATGATGGCAGAGATCAAGTTCACCTCAGGTTCTCCTTGGATCATGTCAAGAACATGTTTACGGGGACACGTGCCCTTC TCTCAGAGGGAAGCCAAAGCTCTTTTATTCAGAACTATGAGTCTGTTAGGTAGCCAGTTGGAGATAGCAGCTGGAGG TAGATGGGCCATCAATAAAAATGTGGACTTAAGCCCTGCAACCCAGACACTGCAAACTCAGCAAGAGCTGATATC TTTTGGAGCCTGTGCACAGACAGTATCTCACTTGGAGAGCCCTCCAGCTCATCTCTGTGTATCTGCAGAGCTCTC CCAGCAGCTGAAGCAAGGAGAGAGCCCACTCGTGGACCTCCAGTTGAACCTATGGACAAAGTGTATGCGTGGAAACA GTGGTGTCTTCTTAAAGAGAAATACAGCCTCAGCCTGCAGCACACTGTGAGGAAGAAACTCATCTGGCTCCTACGTGA GAAACCCAGACCGTTGGTGTCTTGGTATATCATCCAGGTTGGGCTTGGAGCAGAGCTTGGCGGTACGGCTGCTTCT GGCTGCTTCTGGCTCTGCCGTGAGTCTGCCCTAGGCTTCTCTGTGCAAGGATGAGCCGTAACTGCTGCTGGGAA ACGCTCACTCCGCGCCGCTTACCTCTCTAACTTCCCTACTTACCTTCTAGTCGATGTTTGGCCAGAGTG TGGAGAACAGTAAGACATAAACCTATTGTTTGTGTTTGTGTTTGGGGGGAGGTTATCAACCAAGTTATAT GTATGGGTGATAGTGTAGTGTCAAGATTGACATGAATGAATTTGAGACTTACCTGAGTTTGTCTGCTGCTGCTG GGTAAATTTGTTCTATGGACATCTAATCAATTAATGAATTAACCTATTAAGTACCCATTGCTTCAAGACTTTCACA TTGGCCACCAATTTCTGTGACCCAGCTCCATTTATTTCTTCTTCTGCAAAACCAAAATTTCAATATGCTGTTTAAATA TCTACAGTCTAATGCTTTGTAAGACATCTAGATAGAAAATAGTTACCATGAGCAGAGGCTGGCTGACCTCAC CAGCTGTGCAGTGGCTTCGGTGAAGAGAAATGAGCCCTACTCTTGAAGGTTGTAGTCTGGAGAGCAGTGTACCT TGCTGGGCAGCAGTAGAGCCAGCCCAAGAACACACAGTGTGAGGGAGCTTGGCTGGTGGCTCAGGATCAGG AACAGAGGGATGACCAACTTGGGGCTTTGAGGTGGCCACCCAGCATCCATCATCTGTGAACCTGCCAGAGCTGTG AAGGGCGGGTCTGTAGAACTAAGGCTGCAGGATCTCCATGACACAGGGCAACACAGGGTATCTGAGAAAGGTCCTCG TGAGGGTCCAGTATTATAGTGCAACAGAGCCAGAGGCTCGGATCAGACAAATGACCCATTGCACTGAGTAAAGATGTA AGTGAATGAGTGAAGATGTGTGGGCACACGGAAATCTGAGGGACACACAAAGCTTTTATGAGAGATGTTTGTGTTG TTGTTTGTGTTTGTGTTTGTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTGTTG TTGGGTGCATGATATAGAAATTCACAAAGATCAAAAAA		TQSSQARSNNMTLQASLPKLS IKYNSRLQNGRSKEPRFVEYRD SQRTLVKTSIQESGAFPLPPHIR EETVRMQSKPLGICLIIDICIGN DTKYLQETFTSLGYHIOFLFP KSHDITQIVRRYASMAHQDQYD SFACVLVSLGGSQSMGRDQVH SGFSLDHVKNMFTGDTCPSL RGKPKLFFIQNYESLSQLEDS SLEVDGPSIKNVDSKPLQPRHC TTHPEADIFWSLCTADVSHLEK PSSSSSVYLOKLSQQLKQRRR PLVDLHVELMDKVYAWNVSQVSS KEKYSLSLQHTLRLKKLILAPT
SEQIDNO. 26	SEQIDNO.: 119	

713 - 47

NucleotideSequence (5'-3')	ORFs
CCTTTGAAACAACCTTTGTTGATGAGAGCTCTCCAGGATTCGCTATAGAAAGACTTTGGATGGATGCATGGAAGCGTAGC TCTGGAGACGCTGAGGCAGCAGCGCGGCTACAGCAGTGAGGCGAGAGTGAAAGTCGCCGACGGCTGCACGATGA AACAGAGACAACATCTCAAGGTTTCAAGACTTACTACAGAGAGCTGCCATCGGATCAAGGTACACTTGGAACTAG CTGAAAATGCCACACCTCAGTCAAGACTTCTGCAGTACAGACAAGTTCAGCTAGAAATCCGCCAGCGTCCCGTCTCCC CCTTCTCCACAGACCAACAGTAGCCAGTTTGCTAACTTTAATGACAGCAGCAGAGACATTTGAATGAGCCAACAGCCCCAGC ATTCCCGCAGCGCTCCCGCTCAGCTATTGGCTCCCTTTCTCGTTGCCATCTGAACACCTTGCCTCCCTCCTCTCTGA AATACCTGGCTCCGGAAGGAGCATGGAATTTTGCTAACTGCAGCAGAATCACTTAATAGGCGCGGCTTTCCCTATGGC CTACCTCCATTGCCCTCCAGGCCACACAGAAACCTTTTATACATCCAGAACCATCAACACGCTGCTGTCAGAGACC ATTTACCCACTGTCTATCTGAACAGTGTCTGTTCTTCGCTCCACGCTTAGAAGATATGAGCCACAGAGCACTGGTC GGCCCTTGTAACAAAGAAATCTCATCTAGCTCAGCCACGCTTGTGTGAAGAGCAAGCGCTCCCAAGACAGCCTG CTCAGGGCAAGAAATCGCAGGGCCACAGCAACCCACTGCCCTTCAACTTCCCGGCCCGAGTCTGGGCCAACACCCAC CTCATGTGCCCTTCCAGAACATCTCCGTGAATGGATCCAGAGCAGAGTGCAGTCCCTTCAACTACTCGATGCTGCAG AGACTGTCAAAACCCCTCAGGATCAGCTGAAGCCGAGAGCGGGAGGTGTCCAGTTCCTTCAACTACTCGATGCTGCAG CACCTTGGCAGATTCCCAACCTCATGCCCAACAGCAGATCGAGATCCGCCAACTGCAGCAGCCAGCAGAGCCCGG AGGAGCAAGCGGCCATGTCTACGCCAGTGCCTGGGGGCCCGGCCAAGCCAGGCCGCCACCCGAGCAGGCCAAGA AGGGCAGCGACCGCTGTCCCTGCTCCAGAGCTCAGTCTGGCAGCAGCCCGGGCAGCAATGGCTTCTACTCTTACTTC AAGTGACCCGCTCGCTGCTCTCAGAGAAATATGCGGTTCCTGTCCAGTCTGCAGATGAGGTGCGGCTCTGTGTGC GTGACGCCCTCCATTACGTTACGTGCGCTCTCAGCCCTTGTGCTGACACCTCGCCCTACGTTTAAAGTATATTCCAT TATTTTGCATTTTGTGATGTGAGTCAGATTCAGACTTTTATGTAGAAATAAAATATTTTAAATTTGAAAAA AAAAA	MPPPQSRLLQYRQVQPRSPPAV PSPPSSTDHSSQFANFNDSRRD IEVANSFAPQRLPPLQIFGSPF LPSHLAPPPILKYLAPEGAWN FANLQNHILIGPGFFYGLPPLP PRPPQNPFIHIQNHQHAAGQEP FHLPSRTVSASSLSLEEYEP RGPRPLYQRRISSSSAQPCVE EASAPQDSLAQKESQGHSNPP AFNFPAPESWANTTSSAPQNI PCNGSRSTSQPRELLAPPTVK PPEDQLKPESGEVSSFNYSML QHLGQPPPLMPNKQIAESANCS SQSPAGSKPAMSYASALRAPP KPRPPPEQAKKGDPLSLQL SLGSSPGSNGFYFYFK
SEQIDNO . 27	SEQIDNO . : 120
CGCGCGCTTGAGGGCGCGGTGAAAGGTCAAGCGCGCGCGGGTCTGGCTGGCGGACGCTGCGGGCGGAGCGGAGTG TCCGAGTGACGCTGTGAGAGAGCGGCGCGGCGGACGCGCGGACGATTCCTCCCGCTCTCCCGAGCCTCAGGGCC TGGCTTGGCTTCTCAGCCAAAGACCGGGGTGTGGGTGAGTGTGTGAGTCTCAGCTCAGGGCGGGCGGAGAGCTCCGGCGG ACGAGGACGACGGCTGTGCGGGCTGTAAACGACGGCTCAGCAGCGGGAAGTAAAGGCCGATCGAGTGGGAG ATGTGACGCCACAAATATAAACAGTTGAAGAGACTGAACACAGGTTCATCTTCCAGTCAGCTATAATGATAAATCTAC AAGGATGTGTAGAGTTGGCGAGCTAGCAAAACCTTGATATTTCAATGATATAGTGTAGGTGAGTGTGTCGAGGGT GGATCATTCACAGAAATCAAAAGAGACTTATACATCATGACACTAGGATGCCCTTGACCTTACCGAAGACTAGGAATAGGAA CTAAATGTTAAATCATGCTTAAACATCTGTGAGAAGGATGGCACTTTTGACAATATCTATCTGCAATGTCAGATCAGC AATAGTCAGCATGACTTTTACCGBAAGTTTGGCTTTGAGATTATCGAGACAAAGAAAGAACTACTATAAGAGGATAGA GCCTGACAGCGCGATGTCTCAGAAAAACCTCAAAGTCCCATCTGCTCAGAAATGCAGAGACAGCAAGACAACACT GACAAATCAATGAATCTTCTGCTTGTGCGCCCAATAAAGAAAGACCAATGTGCTTCCCTTCCCTCCCTCTTCT	MKGRIELGDVTPHNTKQLKRLN QVIFPVSNDKFIYKDVLEVGE AKLAYFNIDIAVGAACCRVDHSG NQRLYIMTLGCLAPVRLIGIG TKMLNHLNICEKDGTFDNIYL HVQISNESAIIFYKFGFEIIE TKKNYKRIEPADAHVLQKNLK VPSGQNAETQKTDN

7-11-48

NucleotideSequence (5' - 3')		ORFs
GTACATCTAAATAAACTTATGTGATGTTCTGGTAGTGATCTGTCTGTAACCTGTCATGAAATCATTTATTGTCGTAATT TTACAGTCTGCAACTATGTGATGTTCTGGTAGTGATGATCCATATCATCCATATTTCACTAGGCTTAATTTAAACTCATG AATAATCAAGATATGCTAATTCAGACCTCTTGGAAITGGGAAAGACACAGCAATATATCTGAAATTTAATCTAGGTGA AAAAAGATCCCGAGGATGCTTATGCCATATTTAAATATAGTTACTATAAATAGAACCTTAGGCTTTTATTCTTAGTG AGTAGAATCTGTAATGTCATATCTGATCTATTTCTTTTGTAGTGAAGATTTTAGTTGAGTGGATTTTATGTT AAGTACTTCGAAATTTTGGACAGTGTAAATATATCTAGTCAAAATGGTCTGAATAGTATTTTGTCTTATTACCCAAGAA ACAAAGGATGGCTTTGTCTATTATACCATATCACTACAAAATTTAGCAGTTTAAATAACAGATTTGTTGTATCTCTATA GTTTCCCAATCAAGCAGTGTGACATAAACAGTTAGTCTGACAAAGGATCTTATATCATAGGTATCAGCCAAGCTGCAA ATTGATGAAGCTTGACCGAGCTACTTCATTTTCACTCATGGCTGTTCTGGAACCATTTTGGACAGAACACTAACAT AAGACTTGTCTAAACAAAGCTAGTATTTAGTCTTAAAGTTTATGCTCTTTTGTATATTTGTAATGAAAGCTTAAATCTA ACAATTGGAAGTGGTATTTGTGATAGGATATTTTGTAAATTTACGAACATTCAGTGAACCTCATTTTACTGTCTCTCAACA ATTCAAGACATATGAGTTAAGTATGGATTAAACAATGTTGATACT	SEQIDNO. : 121	MSDNEDNFDGDDFDDVEDEGL DDLENAEEEGQENVEILPSGER PQANQKRITTPYMTKYERARVL GTRALQIAMCAPVMVELEGETD PLLIAMKELKARKPIIIIRRYL PDGSYEDWGVDELIISD
GGCAAAGGCGCGGTTCTCTGCTCTGCGCCCCGGGCGGAGAAAGGCATCATGTTCAGACAACGAGGACAAATTTTCGACGGCGA CGACTTTTGATGACGTTGAGAGGACGAAAGACTTGACGACTTGGAATGCTGAGGAGGAGGCGCAGGAAATGTCGAGA TTCTCCCATCTGGTGAGCGACCAAGCCAAACAGAGCGGATCACTCTCTTACATGACCAAGTATGAGCGTGCCCGA GTGCTGGGCACCCCGGCTCTTCAGATCGCGATGTGTGCCCCGGTGATGGTGGAGTGGAGGGGGGACAGACCCCTTTGCT CATCGCCATGAAGGAACCAAGGCGCGGAAGATCCCATCATCATCTGCGCGGTACTGCCAGACGCGCAGCTATGAGGACT GGGCGTGAGACGAGCTTATCATCAGCGACTGAGCCGGGCGGCTCGGCCCTGCACGACTCTGTGCGGCACCCCTCTCTGTG CCCGTTTATATGTGTAAATAATAAACCTCACCTTTCCAAAAAATAAATAAATAAATAAATAAATAAATAAATAAATAA	SEQIDNO. : 122	MAGDSEQTLQNHQDPNGGEPFL IGVSGGTASGKSVCAKIVQLL GQNEVDYHQQVILSODSFYR VLTSEQKAKALKGQFNFDHPDA FDNELIFKTLKETEGKTVQIP VYDFVSHSRKEETVITIYPADV LFEGLIAFYSQEVRDLFQMKLF VDTADATRLSRRVLRDLISERGR
SEQIDNO. : 28	SEQIDNO. : 29	

FIG. 50

NucleotideSequence (5' - 3')	ORFs
GAGGGACATCAGCGAAAGAGGAGGACCTTTGAGCAGATTTATCA CAGTACATTACGTTTGTGAAGCCTGCCTTTGAGG AATTCTGTTGCCAACAAAGAAATACGCCGATGTGATCAATCTCTAGAGTGCCGACCAATCTCGTGCCCATCAACCTCATC GTGCAACACATCCAGGACATCCTCAACGGGGGCTCTCAAGCGGCAGACGAACGGGTATCTCAACGGCTACACCCCTTC CCGAAGAGAGCGCGCTCAGATCCAGACCGACACATATGACTCCGCTGCCCTTGACTCCAAACCTCCAGCCCCCAGC TCCAAAGACACAGGAGGGTCCAGAGGCTCTGGTGACCTGTACATCGCTCTCCAGAAATTAATCTATTAAAGAAACA CCACGGAGATGAATGCCCTTGATTTCCCTTCTGCTCTTTTGTAATTTGGAAACAGCAAAATCTTGATGGAACCTTGACCCCTG AGCTTAAGTGAACAACGTGCAAACTAGTACTGGTGAIGCCTAAATTAATGAACCCCAACGCTGTAAACGATTATATAATACACA CATACATACGCTATATATAAAAAAAAAAAAA	DLEQILSQYITFVKPAFEFCL PTKKYADVII PRGADNLVAINL IVQHIDILNGGLSKRQTNGYL NGYTPSRKRQASESSRPB
SEQIDNO . 30 CTGCGCTCCGCGCGGAGTAGAATGAACGTGTAA CAAAAAAGCCGAGCCTTTGTATCTGCTTAAAGGGGCCGCGGCCA CTTCCCTCGCTCCCCCTCACCCCGCCCGCGCTCGCTCTCCAGGCTCCCGGCAACTAGCTTGAAAGGGCTTCCC TCGCGCTGAGAGCGCGCGCGGAGCAGCGCGCGCTGTGTGAGAGAGCGCGGAGCGGAGCGAGCGGGCCCGG CGCGCGGAGTGAATCTGTCTCCGGAGCGCGGTCCGCGCCCGAAACCGGACCCGAGGCAACCGAAATGCAACAAAG CTCGCGGCGCGCTGAGGCTCTTCA CGGAGCCCCGAAAGTTTGTATTATGATGCTTTGAGCGCGAGAGTCCGG CGAGGAGCTCGAGTAGCTCGCTCCCGCTCCGAGAGATCTTCTCCGTGAGCCCGCGCTCCGCGGGCTCTGCTCTGT GGGGCACCTGTCTCTGCTTTAGCAGTCTTCTTTCTTTCTTTTAAATTTGAAATTTGTCTTTCGAGGAGGG GTGTTAACTCATATGTGGAAGTATCCAGAAAGAACCACTGGATGGCGGTTCCGTACCGTGAAGCGGG GACCCAGGGCGAGCTGGGGTGACCGTCTTGGGGGCGGAGCATGGGAGTTTCCGTACCGTGGCGGCTGCGCGG GCCAGCGCGCGGCTTCCCGCGGTGGCGAGGGCGGAAAGTGGCAGGTGAGCTGCTGTGGAGTGCAGGGGGT CCGGGTCTCGGCTTCCCGCTATGACTGTCTGGAGTATCGACACTGCAAGAGCGCGTCACTTCAAAGCGTCA GACAGGAGGAGGCTCAACAGGACCTACGACATTTCTTCAAACCAACGGTTCAGAAAGGCTCTCCAGATCATGAGCTC CAGCAGACCAAGAGGACCACTCTACCGCATGCTGTGCTTGCACAAACCGGTCTCCAGAGAGGAGAGTGCCTGG CGTGGAATTACAGCTTTCTGACTGTGAAGAGTCTTGTGACCTCGAGCAGCGGACCTTGTGGAAGTCGGACCTATG AAGAAA CTATTATGGGACACCCAACTCCAGCAGCAGTCAGTGGGAAAGTGATCA CGACGGATGCTTGCACAGC CTGCAGTCTGGTCCAAACAGTCCGACCCCTAAGCGAACAAAGTCTCTAAATGATATGCAAAATGCTGGCATAGTCCACG GGAGATGAGGAGGAGGAGTCCCTGAAATGAACAGTAGCTTTACAGCCGACTCTGGAGACGAGCAGCAGCACTC TCCAAGAGCAACGCTCCACCTGTGAA TAGTAGCATCTCTCGTGTCTCCATCAGGACCTTCTCAGAAATTCCTCAG TACCTACCTCTTCTGCAGAGGATAATTTAGTCTCTTACCTGAAACTGGGAGATGGCCTATACTGAAATGAGAGAT CTATTTCATATAGACCAACACAGAAAACAACATCATGTGTAGACCTCGTGCCTGAAACAAACAGCAGAAAGCCTCTGGAAG AATGTGAAGATGATGAAGAGGTACACACGAGGAGCTGGA CAGTGAATAGAGTTGCTGTGCTGGGAAAGCTATGAA GACCTGTCTACGGTGTCTATGTAGACCATCAACAGGAAAGCGCAATATGAAACCCGATCTAGAGCCAAAG GAGAAACAGTCTTGAACAGTACAGCAACACAGCAGCAGTCCGACCGCACAGTGTGACAGAGTGTGACAGGATCATGCTAT THTKPK SRRGEGTVAIVGGDEP	MSKVIQKNHWTGRVHECTVTR GPQELGVTVLGABHGEFPYV GAVAAABAAGLPGGEGPKLAE GELLLEVOGVRVSGLPYDVLG VIDSCKEAVTFKAVROGGRINK DLRHLNQRFOKGPSDHELQQT LRDNLRYHAVPTCTTSPREGEV PGVDYSLTVKEFLDLEQSGTL LEVGTYEGNYGTPKPPSQPVS GKVIITDALHSLQSGKQSTPK RTKSYNDMNAGIVHPENEEEE DVPEMNSFTADSGDQDEHTLQ EATLPVNSIILAAPIITDPSQK FPQYLPISAEDNLGPIPENWEM AYTENGEVYFIDHNTKITSWLD PRCLNKQKPLECEDEDEGVHT EELDELELPAGWEKIEDPVYG VYVVDHINRKTQYENPVLAKR KKQLEQQQQQQQPOQPQPEEW EDHVSVPVPVAPSHPSNPEPA RETPLQKQPFTRNPSLXGKF THTKPK SRRGEGTVAIVGGDEP

NucleotideSequence (5'-3')		ORFS
CTGTTGTGCTCCTCTTGTCTCCTTCCCATCCCGCAGGCAATCCGGAGCCAGCCAGGAAAACCTCCACTTCAGGCGCAAAACCT TTTTTTTACAAGAAACCCCTCTGAGCTGAAAGCCAAAGTCAATTCACACGAAGCTACGGAAGAAAGACGCCAGGCTTGGCTTT CAGCGTGGTTGGAGGAGACGAGCTGATGAGTTCTCTGCACAGCCCTCGTCTCGATGCTGCTGCGGCACATCGGATG GCAAGATGGAGACAGGGGATGTAATTGTAGTGTGAATGACACTGTGTTTGGGACACACATGCTCAAGTTGTGAAA ATCTTCAGTCCATTCCTTCAGTGTGCGAGTGTGGACCTTGAATCTGTCAGAGGTTATCCATTGGCCTTTTGACCCGGATGA CCCTAATAACAAGTTTAGTGACCTCGGTGGCCATTTTGGACAAAGAACCAATATTGTAAATGGACAAGAGACCTACGATT CACCAGCGAGCCACAGTAGTAAACAGGCAAGTACAGCAGCATGAAGGACGCCAGGCCAAAGCAGCCCTGCTGATGTGGCT TCCAACAGCTCTCATGTTTACCCCAACGACACAGTCTCTTGGCTTCTCTCATAGCCACCCAGCCAGAGCTAATAACTGT TCACATAGTCAAGGGCCAAATGGGATTTGGCTTTACGATCCGACACAGTCCCGGTGGGGTGGCCAAAGAGTGAAACACA TTGTTTGACAGTCCACGCTGCAGAGGCCCTCAAAGAAAGGGATCTTATCGTGGAGGTGAATAAGAAACGTCGTGACGGCCCTG ACGCACAAATCAAGTCGTGATATGCTGATTTGAATGTCCCAAGGGAAGTGAGTCACTGTTGGTGCAGCGAGGAGGCT ACCATTCCTCAAGAGAGCCCAAAGTCGCCACTGGAGAGGAAAGACAGCCAGCAATAGCTCCAGCACAGCGTCTCCAGCC ACGGAGCCTGCACACTGCTCCCCGAGCCACGGCATAACAGTGTCTCCCTGAGTACCTACCTGCAGACGCCCTGCTCTCA GATCAGACCGACAGCTCTGGGCAGAAAAGCCAGATCTCTTTTAAATCTGGGCCAGTCCAGGAGCATGTATGAAAACCG ACTTCCAGATTACAGGAAACAGGACATCTTCTCTGGAGAAAAGAAACCGGATTTGGAATTTAGGATTTCTGGGTGGAATG AACCAGGGAAACCATTTATATCGGTACACTGCTACCGTGGGTGCTGTGACACAGACGCCCGCTGAGGTCTGGAGAT GAAATTAATCTGTGTGGATGGGACACCACTAATTGGGAATCACACAGCTCTGCTGCTTATGCAACAGCTGCCAAC GCAAGGCCATGTCAATCTCACAGTGAGCGGAAAGTGTCTTTGCCGTCCCCAAAGCAGAGAAATGAGTGCCTCACCA CCTCATCACACACAGTAGCAACACAGCCCGCTCCCTGACGGAGGAGAAACGCCACACCCGCAAGGCAGCCAGCAACTCTCTG AACACTGTGAGCTTGGCAGCGGCAGCACCACTGGGCATTTGGCAGTGTGTGGCGCGGGGCGAGCGGTGTGGTAGCGCTGT GCTGCAGCCCTATGATGTGAGATTTCGGCGTGGGGAGAACGAGGGCTTTGGGTTTGTCTATCGTGTCTCTCCGTGAGCAGGC CCGAAGCGGGCACAACCTTCGAGTCTCAAAATGCCACGCTGCTGACTAATGCTGAGAAGATTGCCACCATCACCACT CATGCCCTCTCAGCAGGGGACCCAGGAAACAAAGGACCAACCAAGCAGGATTCCTCAGTTTGAGTTCAAAGG ACCGAGGCTGCACAGGACAAGATTTCTACATGTGGAATTGGAAAGAGSGGCCAAGGATTTGGCTTTAGTCTTCCAG GGGCGCGAGAAATATAACATGGATCTTTATGTTCTGCGCTTGGCAGAGGATGTTCTTCGAGAAAAGATGTGGGAAGATGAGG ATTGGCGATGAAATTCATAGATCAATGGTGAGACCACCAAAAACATGAAACACTCTCGGGCCATAGAACTGATCAAGAA	DEFLOIKSLVLDGPAALDGRME TGDVIVSVNDTCVLGHTHAQVV KIFQSTPIGASVDLELCRGYPL PFDPDPTSLVTSVAILDKEP IIVNQETYSVPASHSSKTGKV SSMKDARPPSPADVASNSSHY PNMTVSLASSIATQPELITVHI VKPMGFGFTIADSPGGGQQRV KQIVDSPRCRGLKEGDLIVEVN KKNVQALTHNQVVDMLIECPKG SEVTLLVQRGGLPVPKSPKSP LERKDSQNSSQHSVSSHRSLHT ASPSHGIIQVLPYLPAADAPAD QTDSSGQKKPDPFKIWAQSRSM YENRLPDYQEQDIFLWRKETGF GFRILGGNEPGEPIYIGHIVPL GAADTDRLRSGLDELIICVDGTP VIGKSHQLVVLQMQAAKQGHV NLTVRRKVVFAVPAKAEVPS ASSHHSSNQSPASLTTEKRTPOG SQNSLNTVSSSGSTSGIGSGG GGSGVWSAVLQPYDVEIRRG NEGFGFVIVSSVSRPEAGTTFE SSNATLLTNAEKIATITTTTHAP SQQGTQETRTTTKPKQDSQFEF KGPQAAQEQDFYTVLELRGAKG FGFSLRGGREYNMDLYVLRLAE DGPAERCGKMRIGDEILEINGE TTKNMKHSRALELIK	
SEQIDNO. 31	SEQIDNO. : 124	
GGAAATCCTGGAAGGATTTATATCTCCTCTGTGTTCTTGGTGGGAAAGGACTCGTGC CGAAATTCGGCACCGAGTGGAGCT GGCTGAACTTTGGACCTTGTCTTCCAGTAGGAAATCAGTCTCTCAGAAAGGCGATCATGGCCTCCAAGCCTGAGAAAAGG	MASKPEKRVASSVFITLAPRR	

FIG. 52

NucleotideSequence (5' - 3')		ORFS
GTGGCCTCCTCTGTCTTCACTACCCCTGGCACCGCCACCGCGAGATGTAGCCGTGAGTGAGAAAGTGGGCAGGCAGCTTGTG TGAAGCCAGACGGCTCGGCCCTGGAGATGCTTCCACAAAGACACCTGGGGCCGACGTGGGAGGAGCCCAAGACCT GGACGCCCTCTGGCAAGACCAATGCTCTCACTCTGTGGATCAACCTCAGCTCTCCAATGAGGATGCTCTCTCCCACT CCTTCCCTGAATGAGGAGCACTAGACCTCCGCTCCTCCACCGCCCTTCTGCTTCCCTACTCTGCTCTCCACGAAGAGGA GCCTCTGTCTTACAGGGAAGTCGTCATTTCCGACTTGGAGCAACTGCACCTGCCCCACACCCCGCTCCACCCCGC CACAGCTCCATCAAAGGGATCGTCTGTCCACCTCCGCTGGTCAAGCAGACCTCGGAAGAGGAGCTTCTCTCTCT CCAGAGAGCCTGTACACTCCAGAGAGAGAGTGTCTACSGATGTCTGTGGTTTCTGTGTCACAAAGCCTGTCTCTCTCG AGAGCTGGCTGTGTAGGCCATGAAGAGGCAGTACCAGCCAGTCTTCACTGTCTGTAACCTGCGCGCGCAGTTGGCTG GACAGAGATTCTACAGAAAGGATGGCGCCCCCTGTGCGAACCTGTCTACAGGATACCTCTGGAGAAAGTGTGGCAAGTGC GGAGAGGTGTCCAAGACAGCTGATCCGGGCCCTGGCAAGGCCCTTCCACCCACCTGCTTCACTCTGCTGACCTGTGC CCGCTGATCAGCGAGAGAGCTTTGGCGTGGACAGCCAGAAACAGGTGTACTGTGTGGTGTGATTTCTACAGGAAATTTG CCCCGTGTGCAGATCTGCAGAAATCCCATATCCCCGAGACGGGAAGACGCCCTTCAAAATCGAGTGCATGGGAAG AATTTCCAGAGAACTGTTACCGCTGTGAGGACTGACGCTGCTCTGTCTGTGAAACCTACCGAACAAAGGCTGTACCC ACTGAATGACCACTTCTTGCAAGCCCTGTCACTGAAAGCGGAGTGTCTGTGTGCTGTGAAAGAGTCCCGATAGCTG GCCCTTCCCTGACTTGGTTTCCCTCCTGACTTTCTTGTAGTACTTTCTTTTGAACCTCACTTGGCACAGCACACTGC TCAGCCCATAGTGTCTAAATGCACAGACAGGCTTGAGACACTGGGCTTTGGCCTCTCTAGTACACAGCACCCCCACCC AGACTTTCTACTCTCTCTCATTTGACACAGGAGGCCCTCACCCAGACTGCAACCTTGGTCCATCTCTAGTGTGCCCC TGACATGTTTATGGGACAGGTCTCAGGATGATACCTGTGTCTCTGACCATGATGCTTAGCTGCCCTAGCAGAAAGGCGCTG AGACTCAGCTTAGATGTAGAGTAAAGTTGTTTGAAGTGGCCCTTCTACGCCACTCCAAAAGATATTTTGTAGAAATAT AAGTGTGTAGATGATAGACACACACTTAAATCCAGCACTTTGGGAGGACAGGACAGGTGGATTTCTATGTTCAAT CTAGTCTGATCTACTAAAGATTCAAAAACAATTTCTTTGGATTTGGGGAGAGAAATCTTTGAAATTTTCTCTTTTCT TTTTTTGGTGGGTAAATCAGTAAACATCTTCCCTTGGTTTTCAGGGCTGCGAAGATGGCTCGGTGATGAAGAGCGAGCT CTTGCTCTCTTTGGGAGGACAGAGTTCTATTTCCAGCATCTCCCTCATGGAGGCTCATAACTACCTGTCTCTGCAACTCCA GTTTCCGGAGAGCTGGCGCCTCTGTCTGGCCTCTCTTGGAACTTAAATGCATGTGTGTACACGCTTACACTCAGGCACAC ACACATACATTTAAAAAACAATTTAGCCTGTCTAATGGCAAAACACATTTAATCTCTAGCTACTTGGGAGGCGAGAGACA		DVAVSEEVGQAACEARRARPWE MLPTKTPGAAVGRSPKWTTPSG KTNASLSGVTPLQSLNGGCSLPP PSLNEEDLDLPPPPPPPSAYLP LPEEPPVPLPGKSLISDLEQLH LPPPPPPPPQAAPSKGSSVHPP PGHARPSEEEELPPPEEPVTLIP BREVSTDVCGFCHKPVSPRELA VEAMKROYHAQCTCRTCRRQL AGQRFYQKGRPLCEPCYQDTL EKCKGCEVVQEHVIRALGKAF HPPCFTCVTCARCISDESFLD SQNQYCVADFYRKFAFVCSIC ENPIIPRDGKDAFKIECMGRNF HENCYRCEDCSVLLSVEPTDQG CYPLNDHLFCCKPCHLKRSAAGC C
SEQIDNO. 32		SEQIDNO. : 125
GACACTTCTGTCAACCGGGGCTTTGGGAAGCTGAATCCAGTAAACACGCTTCCCGGAGAGATGGACTCCATGCGGAC CATGGCCTTTTCCCTTTGTAAATCTGCTGCAGCCGTGGAACCTGCACTTTGACATCTTACACTGATGCAGAAAGACTCA GCTTACCTCAGCCTTAAGTTCAGCTTCCGGGTCCAGCTGAGCCGAGATGCTTCCATTTCTCTGGCTGGATGGA GAGGCCACATCAGGATGCTTCTTGTCCAAATAAAGATGCTGCACTTACCCACCTAGGAGGAGATCAGGCATG CCCAGTGCAGGATGCAGGTCAACTGAAGCTGTCCATTTGATGATGCCAGGATCGGGTTCTGTCTGCCGACATCATAGAAGC AAAGGCCTGATGAGCAGGAGCCTGGCATCTGCGATCCCTATGTGAAGTTCCTTTGATCCCAAGAAAGACAGCCAGCTCCC		MERPHQDASLSKKDACTQTYPP RRRIRHAQVQDAGQLKLSIDAQ DRVLLPHIIEGKGLMSREPGIC DPYVKVSLIPEDSQLPCQTTOI IPDCRDPAFHEHFFFPVPEEGD

FIG. 53

[illegible]

NucleotideSequence (5'-3')		ORFs
CTGAGAACTCCGTTTTTGGCTTTCTGTAGGGCTTTAAAGGACGACGACCGGTGGCCAGGACCAAGTGTAGCTCAGCAA CCTTTACAGAGACAAACATGAAGGAATCTTGCCAGGTCCAGTATGAGAGCTGGGTCCACTCCCATGCTCTGGGCTAGG TAGCTCACCCCTTTTCTAATGTAGAGACCCAGCAGGACAGAACTCTCAAGGCTGTGATTTGGAAGGACGAGGCCATATGC TAGAGAGTATTTGTTCGGGTAGGTACTGAGCACGACGACGAAGCTGCAGTATGAGTAAAGCCAGAGAGCCCCAG ACCTGAGCTTTAAGTACCTTAAGGACGATTTCTGTGCTCTTTTGGATTTTAAATACAGAGCCACCTGAGGCCCTTAA ATGGTGGCCAGGAGTGCATGTCCCTTATTTTCTTCCAACTTTGGAAAATGAGCCATGTGAGTTATCAGTCTAAC AGGGAATGGGTGACTCTGAGGAATCAGGCTAACACCCAGCCCAAGAAAGATGGTTGGTTCAAGGTTGTGTA GCACACACTGCCAGCAGTATCAGCCACGGGGTAAATCCGAACAGCCGGGTCTGTGCAGACAGCAACCAACTTTG ATTTCACTTGAATCTCTCACCTAATGATGTATCGTAGGTCTATGAGCCAGGAGACCACCTGCGTGGGAAATCAGCTA TCTTGTTCGCTTGCTGCTGCGGCACAGACCTCTGTCCAACAGATGGGCACAGAGACAGAGGATCTGAACATAACA CCCACCCGGGACGAGCCGTTCTCCCTGATCAGCAACTTCTGAGTGAACAGATTCTCCATCAAGTCCAGGCCCTAC TGGCTGATGGGGAAGAGGAGTACTCTCTGGCAAGTCTTGGGTAGCTTGTCTCATGACTGTGGTGAGCCAGGCCAT GGCCATCTTGTCTCAATAATCAATGTGACAAATTAATTTGGTGTCTGGGCGGAGAGGATGAATATGACCCGGTGGCT CCGCTCTTCACTCCAGCTGTTCAAGAGGAGGAGGAGCTCTGAGCGTGGCTCTGAGAGTCATAATCAGCGGAACC AGCCGGCCCCCTCCCTGCCACATAAATCAGCTAAGAACACACAGACTTCTTCTCTGATGGGCTAATTTGTCTTGGG TGGTGTCTCCGGCCCCAGGAGCGGGAGGTGGGAGCACAGCCACTTATTTGTGAAAGGCCATCTGTGAGATTGAATA CAAAAGTGCCTCTTTGAGTCTCTACCCGTTCTGGATCCCATTTCTGTCTCCACTCTGAGTCTCTTGAAGCTCATCT CTCATAGAGCCCTCATTTGCTGAGTCTTGGCCCTTTGGAGCTGGAAATTAACAGACCTTCTGAGAAATGGTGATTCT TATTTGTACATGTCTTATTAATTAATAATAATTAATTAATAATAATAATAATAATAATAATAATAATAATAATAATA		SEQIDNO. : 126 MSVRFSAATSMKEVLAPAESEFD EWEPEGTATLGGPVTAIIPTWQ ALTTLDLSHNSICEIDESVKLI PKIEYLDLSHNGLRVVDNLQHL YNLVHLDLSYNKLSLSEGVHTK LGNVKTNLNAGNFLESLSGLHK LYSLVNVVDLRDNRLEQLDEVKS IGSLPCLERLTLLNNPLSIIIPD YRTKVLSQLFGERASEICLDDVA TTEKELDTVEVLKAIQKAKDVK SKLSNTEKKAGEDFRLPPAPCI
SEQIDNO. 33	GGCAGAGAGGAGAGCAACTTCTAGGAGCCGCTGAGGTCTTTGCCATCAGGCCCTTGCAGCTCTATGCTATCACAGAAC AGCTGCAACAGGGAAAGCCTACTTGTGCCAGTGTGATGCCAGCTTGGACACATCTTAGACTTCACTTCACTGTGCG CTTAAGTATCTTAAGTTTCAGGCACAGAAAGGACCTTTTGGGACAGCAATATTAAGGAGAGCTCTTGCCCTTTGATCT TTCAATATTTCAAGTCTCTTACCAGGTGAGATAAGTCAATGTGATGCCAAGCATATCCGAGGGCTGGTCACTCCCAAGC CCACTTTAGCCACGATGATGTAGATTCTCAGCAACCTCAATGAAGGAAGTGTGTCTCTGAAAGCTCAGAAATTTGAT GAGTGGAGCTGAAGGCACTGCTACCCCTCGGAGCCCTGTGATCTGCTATCATCCCAACATGGAAGCACTGACTACTCT AGACCTGAGCCACAACAGCATCTGTGAGATCGACGATCTGTGAAACTGATCCCAAGATAGAGTACCTGGACCTGAGTC ACAAATGAGCTCGGAGTTGTGGATAACCTGACGACCTATACAACTCTGTCACCTTGAACATCAACAGCTCTCC TCCCTGGAAGCGGTGCACATAAATGGGCAATGTCAAAACCCCTGAACCTGGAGGCAACTTCTTAGAGGTCTGAGCGG TCTGCACAAACTCTACTCTCTTGGTTAATGTGGACCTAGGACCAACCGGATTTGAGCAGTTGATGAGTCAAGAGCATTTG GCAGCCTGCCATGTCTGGAGCGTTTGAACCTTGTGACCAACCCCTTTGAGCATCATCCCTGACTACCGGACCAAGGTGCTT TCCCAGTTTGGAGAACGAGCCCTCTGAGATTGTCTAGATGATGTGCAACACACAGAGAAAGAGCTGGACACTGTGTGAAGT	SEQIDNO. : 126 MSVRFSAATSMKEVLAPAESEFD EWEPEGTATLGGPVTAIIPTWQ ALTTLDLSHNSICEIDESVKLI PKIEYLDLSHNGLRVVDNLQHL YNLVHLDLSYNKLSLSEGVHTK LGNVKTNLNAGNFLESLSGLHK LYSLVNVVDLRDNRLEQLDEVKS IGSLPCLERLTLLNNPLSIIIPD YRTKVLSQLFGERASEICLDDVA TTEKELDTVEVLKAIQKAKDVK SKLSNTEKKAGEDFRLPPAPCI

FIG. 55

NucleotideSequence (5' - 3')	ORFs
ACTGCTTCTCAGCATCTGATGCTTGTGCTGTCTCTCCCTGGAGCGCACACCCCTCGCTGAGCCTGTTGACAAGGACTTCT TACTCAGAAATTGGGGACAAGAAATACAGGAAAAATGGAGAACTATGAGCTGATCCATTCCAGCCGGCTCAAGTTACACCTA CCCCAGTAAGGAAGAGTTGGGACCTGACTATATTGTTCGACAGAGATGGCTGATCTTCGAAAGAATCCAGCCCTCA GCATCTTAGTACATCCAGGCTTCCAGGTGTACACACACACTTTGGCGGGGACAGGGCCCACTGCGCTCCCAAGAGC CTGCTCTTGACACGCGCCGAGACTTCTCTCTGGAATGAGGACTACATCCACTATCCATTGCTGAATTTGCCAAAAGAGCC ACCGCAGAGGACAGATACCGGCTAGACGATGGCGCGCGGTCCGGGATTTGGACCGGTGCTCATGGGCTACTATGCCCT ACCCACAGGCCCTCACTCTTGTGTTTTGATGACACACAGGTCACGACCTCATGGGAGTGTCACTCCAGGACCACTTTGGG GAGATGCCAGGTGTTCTGGCAGGGTTGGCCAGGGCCGAGAGGTACAGTGGCAGGTGTTTGTCCCACTGCGGAGAGCCG AGAAAAGCTCATCTCACTGCTCGCACGACAGTGGGAAGCTCTTTGTGGCAGGAGCTGCTGTGGAGCTCACTGCGTAGT GCCAGCCATAGCAGCCCTGGCTCTCGCATGCCAGCTAGCTGTGTCCTGAGGACGAGGAGCGGCTTCTGCGT TCTTTTAAAGTCTTCTCCCTCTCCCTTGGTTCCTACATGTTGTTGCTGTGATGATGATGCTGTTGCTGTGCTCATTTAGTGGGCGTGC GGACTTGAATACCCCCCACTCTTCTGAAGTGTAACTCCAGTCTTCTGTTGCTGTTGCTGTCTCATTTAGTGGGCGTGC GCTGCTAATTACAAAGCTGTGAGCAGGTATACACAGCAAGCTCCCACTGTGGGCTTTTCCAAATGGAGGCTCCTCCTC AAGTCCAGAGCAGAGGAGGCCCTATGGGAGTTCCAGGTTCATGGTCCAAAGAGGAGCCAGTACAGGGGACCTAGAGCTG CCAGACCAAGTATAAATCTCTGTTGCTTACGTTCTCTAATCTAATAAATGGAGTTTGACACAAAAAATAAAAAA CTCGTGCCGAATTCGGCACGAGGAA	AIIDLHNSIAEVENELRHLL WSSVVFQTPGLEVTACVLLSS KAVFILDHGLRIFYSEPLQDF WHQKNTYNNSPFHVSQFVLK LSDLQSVNVGLFDQYFRLTGSS PTQVVTCLTRDSYLTHTCFLOHL MLVLSLERTPSPEPVDKDFYS EFGDKNTCKMENYELIHSRVK FTYPEEVEGDLTYIIVAQKWD PAKNPALSIILLYIQAFQVTPH LGRGRGPIURPKTLTLLTSAE1FL LDDEDYIHYPLPEFAKEPEQRDR YRLDDGRVRDLDRVLMLGYYPY PQALTLVDFDDTQGHDLMGSVTL DHFGEPMGPGPRVGQGREVQWQ VFVPSAESREKLIISLARQWEA LCGRELPVELTG
SEQIDNO. 34	SEQIDNO. : 127
GCGTCAGCTCTGAGCCGACTTTACTGTCCACAGAGCCTAGACTGCCCGCCCGAGGAGCGTGGAGGACGAGGACGAGCCCGCG GGAGAGACAGTGTGGGGCCCTGGCAGGACCTCGCGCAGCTCGTACCTGTCACTCAGCATCCCAATCGGTGTGCGC CCGCGCCCGCCCTGCCCGAGGGCGGGCTGCTTGTGGTACCCAGAGTCTGCCACGCTGAGTGTGCCCTGCC AGTGAAGGACCTGGGACTGGGCATGCCAGCCCGACAGCTCAAGGTGGGAAGAGGACCGCATCCAGCAGCCGGTGAAGCA CCCGCAGCTTTGGCCGCTCCAGAGAACTTCGGCACCCCTCCAGGAGTGAAGTGAAGAGTTTGACAGGATCTGTGCTCCCG GAGCTGTGTGGAACACGAGCGGTGTGATTTTTCATACCGGCTCCAACTCAACCTCCAGGTTTCTGCTTTTCGACATCTCT AGGCAAGAATGCTCTCGTGAATGGCAAGCGGAGTTGTGTAGCAAGTGCCTTTCATGCTCATCGCATCTATCGAT TCGATACGTGTCATGGCAGGATCGAAGCCCTTTCTTTGAGCGCTTACAGAAAGTGTCTCTGGAAGAGATCGCTCAAG TTCTGTCATTCAGATATGTATCGGAAGAAATAATGATGATCTCTGGCAGGAGAAACAAGCGGGGAGTGGGACAGTAGACAT TTCCGGCTTGGCAGATAAGAGTACGCTCGCTGCCAAGAGACTTTTGCCATAITTCGGGATTTGAGTGTGGGTAGAA ATGAGGATCAGATAACGACTCACACAGTGTATGTTCCGAAGGGCCCGGAAACCGAACCGACCCAGGAGATTCGCGGTGTG CGAGCTCTGCGGTTGCGGATTCGACTAAGAACCTTTGAAGTGCTCGAAAGTGGCCCGCAAGATATTTCTTATGCG CCCCCTAGCAGGTGCTACACGACTGAAGAACCGGCATTTGTACAGGTTGTGGGCCACAGACTTACAGGACA CAAAAGTACCCCGGATGGAGAAAGCATAGGAGGAAGGACACCAAGTCTCCGCTGGAGTCTCTGAGTGTCTGAGTGTCTGAGTCCAG AKELVKDQYCSDEOAOHLCNH	MKEICRICARELCGNQRRWIFH TASKNLQVLLSHVLGKDVSRD GKAEFACSKCAFMLDRIYRFDT VIARIEALSRLRLQKLLKENDR LKFCIAVMYRKNNDLSGHEKDA GSGTVDISGLPDMRYAALLQED FAYSGFEWENEDQINDSHSC HASEGPNRPRRCRCGAALRVA DSDYEAI CKVPRKVARSI SYAP SSRWSTSTCTEEPALSEVGPPD LASTKVPDDGMEEGTGPSSV ESLDSAVQASPPQKDEPTERS AKELVKDQYCSDEOAOHLCNH

Nucleotide sequence (5'-3')		ORFs
GTCAGTAGCAGCAAGGAGCAGCTGGAGTCTTCTTACTCCCTGCACGGACCTAGTTCCTTAGCTAACTGAGGTCTTGA AGCATACTGCACATCTTAAATCATTCATTTCCCATTTACTACTGTCTTCTCCCTGGCTGTCTCATTCCTTT ACCCCTTCCATGGGCCAATAAAGTTTACTCCCCCATCTTACCACCCCGCCACAACTGCCACGTCATGTCAATCAATGCA TGTGTGTGTATTATTTTGGCATCCAATCAATCCTTCTTGTGAAGCAATTTTAATCAATCAATCAATCAATCAATCAATG AGTTTAGTTTAAAGAAAGGTAGAGTCCCGTCAGAGTGGCTGGGAGGGGTATAAACCCTACTAAGGATAAT CAGAACTAGACAGAGGGTGGCTGGCTCAGGACAGAGACCTTAGTGTCCCAATAAATTTGCCCTCGAAGGCCCT CTTCAGAGTTGACTGTCTAGGGAAAGATGAAGTCAGATCAGTGGACAGCATGGTGTAGTCCATAAAGGCCATACAACTC ATGTTCTTCACTGGCCCTAGGGTTTCTTCAAGCCTCAGGCATGGCTTTAGTCAGAACATGACTTTAAAAACCGGTTTCCC AAATCAGAACTCTAGATAAAAAATCATCTTCTATGTGATATTTCCACCCCTCTTTTATTTATTTTGGTTTGT TTTTTGGTATTTTATTTGTTGTTTGAGACAGGATATCACTGTGGCTGGCTGAAATGCATGGGTAAACCCAGACTGGCA TTGAACTCAGACAGATGAGCTGTCTTACCTTTGGTGGCTGGGATAGAGGCAATGGCTGCCCTGCCCTGTCTCAGCAT CCCCCTTAAAGACAATAGTTTCCAGGATCCCGAGATCAGGGGAAGTATAATTCCTGGATGCTCATTAGGAGTGAAGCGG GTGGCGTCCCTTCAATGACCTCTGCTTTGGTGGGAGTAAATCTTGTATAGTGGAGTAAAGACGATGTGAGATGCTGTCAI GTCAGGTCACTCAGAAAGGAGCCCTTAGATCTCATGTAGTGTCTTACTCACCCTCTCTGCTTTCTGGACAAACCCGACAG GTGGGAGGTGTAGATTGTTTCTAGCATCTTAAATGTCAAGATAGGAAAGTAAACAGTTACTTTGCAAGGGCT GTGGATTCTGCCCCAGAACCTTCTTAGTGTGAAGGTATGAGTAAAGTAAATCCATGCTTTCCAGCACCTTGAGAAAGA CTGAGCCCCCTCCGAGCTACACTGAGCTTCCCTTCTCTTCTTATTTATTTTATTTTATTTTATTTTATTTTATTTTATTTT ACACTACATCATGTGTTGACATGGCATGTGTTCTAAATCTATTCAAGATTCTGTAACTCAGCTGTGTGACACACTTT AACTGATGTGTATCCATCAGCTTGAAGTGACAGGAGAAATAATTTACCAGAGAGCACTTGAAATCTTCTGTGTAAG TAGTTACAAAGATTGATAGCCATGGCTTCTTAAATGATGTGCTATTACAGTTTACAACTTTTAGGGGGGAAAGG ACTCATTTAATTAAGATAGAGATGTGAAGCAGAGCCATCCAATGTTCTTAGTAAACCCATTTCTAAGATACTCTAA GGCCTGCCCTGAACAAACCTTATGTAACTAAAGGAGACATATAGAGTTGAGCTATAGCATGTCAACAAATTAAG ACCAGCTGTGTAGTCAATACAAAGGCAATTAGGAAATGTGTTTACTCAACTTTACCAATAGACAAACAAAGTTCTGCAAAGC TGCTATTAAAGTTTCAACTTAGTAACTCTAGGGTTCTGAGGGCTCA CAGTGATTAATAATGAAGGTTAAATAATTAGT GCAACTGCCAACCTCTAA CAAAGTAGGTTGATAGACAAAGTAAATAAGATTTGTTATCAATCCATAAATGTGACTAT AAAACTCTGGTACTGACTTTCTGGTCTGATGCTAGAAAGGTGGAGACCCTTGTGCTGGAGGGAATGTGCTTGGCCC ACAAAGCTTGTGCAATAAATTTGACACACCTAGCTACCGAACACAGTTCTGATGAATGTACAGCGTGAGCCACAGGTGGATGG TACTATGATTAACAGTCAATCATATAAATTTGGAATTTAGCATGCTGTAATCTTCACTTCTCTGTAGGATATGGACT ATGTTAGATGTGCTGCTTGTGGAATTTTATTAATTAATAAATAAATAAATAAATAAATAAATAAATAAATAAATAAATAA AAAAAAAAAAAAAAAAAAAA		RSRLNEALQAERQLYSSLVKFH AQPENSRDGTTLQVELEGAQVL RTRLEEVLGRSLERLSRLES LA AIGGGELESVQARHKHAF
SEQIDNO. 35	SEQIDNO. 128	

7173-59

Nucleotide Sequence (5'-3')	ORFs
CGACAGGGCGGGCGGGGGGTGAGTGGAGGGGAAGCGCAGAGCGCGGCAACTCTGGAGGAGCGGATGTTAAGTCAG AGTACAAACAGAAAATGTCCTGAACGAACTTCATGGACAAACCTGTCCACTATTTCAGAAAAATAGCCCTGGCCCTAGGAA TTCAGCAAGTGCACACAGTTGCCATCATCTGTATCTGTGATATAGGAAAGCAGAGAAGAGAGATTGACATTTCTTTGGA GAAAGTACATTTAGATAGAGATCGAGTCCCGCAGAGGCTGTGAAGCTCATCTATGGTTCGACAGGAGCCAAATATTAA ACAGTTGCGGAAAACAGACAGCGCGCGGATGATGTGACACAGAGGATGTAGCGATGCTGCTTATCATAGT GGTTTCTCTTTCAGGTGTGCAAGGCCAAACAGACCAATCCATCATGATCTTGACAGAAAACACCCCGATGTTTATGCAAACTC TCAGTCCCTCAGAGATCTGTGGGCAGAAATCATAGGGAGGCGGTGAGACGATTCGTCTATCTGTAAGGCTCTTCGGAGC CAAAATCACTTTGCGCAAAAGAAATCAGAGGAAACGTTACTACTCTACGACTTATAAAAATCTCAGGAAACACAGAAAGAA TGGCAGCAGCTAAGCATCTGATACTTGAGAAAAGTTTCAGAAAGATGAAGAACTTCGGAAGAGAAATGCCCATTTCTGCAGAA ACCAGAGTCCACGAAAGCACCAAATCAGTGTGAGAGAGAGGAAGTACAGAGCTCGTGTGAGCTGGAGAGCAGACTTT ATGGAAGAAATACAAATTCCTAGCATGGCAGCAGCTACACCCCTGGAAGTTCTCTCCGCAAAAGGAGTGGTGATATGTTG TTGTAGGACCAAAAGAGGTTCTTGGAGAAAACCTAATGATGACAGCTTTTCAGAAATTCAGATTCGGTCCCGCAGCAGCTCCAG ACGTCATGTTTGAAAATCCCAAGTCTCTGAGTTCAGTTTCCATGCTGATGAGTACCTTAGAAGTCTACGTTCTTCTCTCTGA ACACCTTAATCACTTCTGGATCCAAATGTTGTTCCCGCAGCTCGAGTTGGATGAATCTTGTCACTGAGATGACCCAGC ACTATGAGAAATAGTCTGCTGTAAGACATTGACTGTGCATGTAGGAGACATTTGAGCAGCACCTTTATCTACAAATGGTTCC TGGTATCGAGCCCGGGTTCTTGAAACCTTTGAAAAATGGAACCTTGGACCTCTACTTTTGTGTGACTTTGGAGATATGGAGA TTGTGCACATAAAGGATCTCAGGGCTCTCAGGAGTGACTTTTAAGCTCCCAATTTCAAGCAATAGAAATGCAATGCACTCGGCAC GGATGCCCCCAGAGTGAAGAGTGGGAAGGAAGCTTAGATAGTTTGAACAGACTCAGACACTCAGTCTGCTGCTGAGTGAAG CCCCGTGGCGCAAGATTTCTGACTATGTCAGACATGGAATCTCAACTTGGCCAAAGATCTATTTGTATGATACCACTGA TGAGAAAGAACTTGATATTTGGCTAGAAATAGTTTCTGTAAGGGTATCGCACTTGAACCTCTGTAAGACATGGAAGAAAA GAACTGTCCCAAATATGTTGAAGGACATGGCCACAGAAACAGATGATTTCTTTCGAAGCATACTCACTGAAACAAAAAAG AGCCCTGAGAGATGCCATACACCTGTCTGCCCTCAGTTTGTCAAGAGCTGCCCTATGTCTGTGTGATGATAAACCTTGA AGACGACTTATTTGAAAATCTGGGCTTCAGCTGTGATCAGCCATCTGCTTTGTGTGATGTGTGTGCTCCGAGAGAGAGT CTATGATAGAGAGATCCATGAAGTCTTTACTTTCACATGGTGTGGCTGTGTGAATCAAAATCCATTTTGTGTTCATTG GATCTACCGAAAAGTAAACAGACGGAGGCAAAATGGAGACAGATTTCTCCACTCCCTCCTGCTTCTCCCTTACTTTCT AAATGTTTGAATGTGATTAATTTCCCAATACAGATTCAGTTTCCCTCTGCGCAGTAATTTTGCATTTACTGCT GGGCTATGTTTTTGAGCTTGAGAAAACGCCAAGGTTTTGGGCATTTGGAAGTGAATGATTCGCAAGATTTCTGACTCGACTTA TCAGGTGCTGTAGTTATAGGAAGTATTTGGTGGACTTCAGAAGACTTCAGAGATATCAGGAGATAGGCAAAAATCAGCATAA CTATATTTAAAAGCCTCATAAAAGGGGAAGAGTGATCTACCTCTCACCCACAGTTGGCCGAGGTTATTTGGAGATGGGTCTCT CCAGCTATTTCTTTGTGAATTCAGTTTAAAATAACAATGAAAGGGAAGATATCTTAGGAAATGTGTAAACCGTGTACAA ATATGTGCTGTATACACCAACTAGAGAGAAAGAAATGAATATATATAGTTCTGTCTTAAATAATTTTGGGGAATGTTTGTCT ATAAAGCTTTCTCAAAAATTTATCTAAAACACATACACTCAGCTCACAACGTGGGATAGGCCCTGTGGGTAAAAGTCTCTTCTGA GTAAGGCTTTGGTAGTAATTTGCCAGCACTCATACTCGGAAGCATTTTGAGACAAATGTCTCTTCCCATACAAGTATTCACA TCTCTCCCGCTAGATCACTCAGCAAGCTTCACTCTCCCTCAGAACCATATACCACTTTTATGCTATATACAAACACTTACTT	MSTERTSWTNLSTIQIALGLG IPASATVAYILYRRYRESREER LTFVGEDDIEIEMRPVQEAVKL IIGRGQANIQLKQKQIGARIDV DTEDEVGERVLLISGFPVQVCK AKAAIHOILLTENTPVFEQLSVP ORSVRGRIIGRGGETTIRSLICKAS GAKITCDKESEGTLLLSRLIKI SGTQKEVAAAAKHLILEKVSDE ELRKRIAHSAEATVRPKQPIVS RREEVTEFGGAGEAALWKNTNS RREEVTEFGGAGEAALWKNTNS SMGPAITPLEVPLRKGGGDMVVV GPKEGSEWKPNDSDSFQNSGAQS SPETSMFEIPSPDFSFADEYL EYVVSSEHPNHFWIQIIGRS LQLDKLVSEMTQHYENSLPEDL TVHVGDIVAAPLSNTGWSYRAR VLGHTLENGLDLYFVDFDNGND CALKDLRALRSLDFLSLPFQAI CSLARIAPTGEWEERBALDEFD RLTHCADWKPLVAKIUSYVQTG ISTWPXIYLYDTSDEKLDIGL ELVRKGVAVELPEDMBENRTVP NMLKDMATETDDSLASILLTETK KSPEEMPHTLSCLSLSEAAASMS GDDNLEDDLF

Nucleotide sequence (5' - 3')		ORFs
AAATATTTCTAATAAATAATATTTTGTCTCTCAAAAAAAAAAAAAA		
SEQIDNO. 40	CGTGTCTACAGGTCCAAAGTGACGAGGCCAGACGACTGAACCAAGACAGTCTTTCATTTCTTACGATATTTATCC AGTGTGAAGGTAGCTCTGGGCGAGCATTCCTTCGGAACCATGGTGGCTGGTGTGAAGGTGCTGATGGCGTCGG TCCTCTCGCCCTACCCAGCGGCTTCTCAGCTGCTCAGCATCGCTCTCATGCGCGACTGACAGAAAGAAAGTATGAGC CGTGGCGGGATATAGTTCTCAGACCTTTTGGCTTTTGGCTTACCTGTACGGCGTGTCTATCTGACAGGGAC TTTAGAGACAGGATGACACTTCGGAACCTAAAGGATATGACATTTGACACCTTAAGGAATCGCCCGTCTTTTACGTGT TCACCGTTCTGGCTACCGACTGTTCCAGCGTCCGGATTCAACCCATTCTTCAACCTCAGCGCTCATCTTCTGACTTAC CGTTGAAGTTTGAAGCTCAATCACCGCACCATTCAGCTTTTAAACGAGTTAAGTAACAGCACAGCACGAGAATTAAG TACCGGATTTGGGATGTGAACAACCCCAACACATCAGTATTTTCTGATATTTTACAGCTTAATTAATAAAAAA AAAA	SEQIDNO. : 132 QHRSHARLTKKYEPLPADIVL QTLLAFALTCYGVVHTAGDFRD RDATSELKDMTFTLRNPSFY VFHRSGYRLFORPDSHSSNLS ASSDDLPIKF
SEQIDNO. 41	CCACGCTCCGCTTAGCTTAGCTTCTCGGGGGAAGATAAGGGGAGTCAAACTCTCAAAATCCGGCGGAGGAGGCC AGACGAGGTCAACCGAATGTAAAAGTCCGCGGGTTCGGCTCAGCCGGGAATCGGCTGGCGGGGTGGGCGCGGAAGC CGAAATCAACAGTTGAGGCGCAGAGCGCGCTGCGGCTCAGAGCTGAGCTGAGCTGAGCCGCCCGCGCCAGCAGCAGCCG GAGCGGACAGCGTGACACCCCGCAGCCGACACGAGCTCTTTGGCGGACGCCCGGACCATGAGCCGCCCGAGCTCCG AGAGCAGCTCGGTTGAGTGAGAGCAGCCCGCGCTGAACCGCAATCCGGACTCCGAACCGCGCGGAGAGAGTTAAG AATCATGGCTGCGGGAAGTTTGAAGCTTCCAGAAACATGCTGTGAATCAACAGTTCCCTTGGCTTCGTCCATGG ACCTCTGAGCAGCAAGTCCCTTCTGCTGAGCGTCGACAGATGCCTATCAAGAGTGTCTATACATGGCACTCTTCCA CGGAAGAAAAGGGCCCTCTTCCATACGCTCTGTGACAAATGTGGCCACTCCAAATCCCAAGAGCTGAGAGTCACTCT GACCCAGGACATCATCCAGGAAACCCACTGAAGACCGAAAGGGGAAACTTCATCTTCAGGGATCCATATCTTCTGG ACCCAACTCTGGAATACGTGAAGTTCTCCAGAGAGGACACATCATGGAAGAGCCCTGAGAGGCTGAAAAGGAATTG GAGGAGGAGCTGCTGTGAGCAGCGAAGACCTACGAGCCACCGCTGTGTAACCGCGGATCCCCGACAGAGTGTCTGA AAACCTTGTGAGCGGATGGGACTTCTGTTTCGCACTCTCTGAGCCCGGAACTTGTCTGACCTGTGAGTCACTG GGAAGAACTCGCTAGCATTTAGATCAACCGGACTGTCTCGGCTCAGGAGGCTTACGCGGTGAGTACCA TTTCGAGATGAGAGCTTTGACTCCATCCCGGGTGGTCCGCTACTCGTGGCAACCGCGGCCCCATCTCCCAACAGAG TGGTGGCCATCATCTTCAGCCCATCAATAGGACAGTGGCCCTCTGCTGTCTGAGGAGCGTATGGCACCTCCCGGGCC GAGCCGGGAGGGCAGCTGGCTGAGGAAAGCCAGACGTGGTGAAGAGGCTGAGCTTCAACAGGAGCAGCATCCAG GCTCGGGAACACAGCTGCCCCGAGGAAACCTCTCAGGAATAAAGAGAGTGGCAGCCAGCCCGCTGCTGGATCA CGTGCAGACAGGAAGGCTTAACCTCAAAGCTCACCGAGTCACTGCGGAGTCACTGCGCAATAGGCTGCAAGCTGCCCCC	SEQIDNO. : 133 MAAGKFASLPRNMPVNHQFPLA SSMDLLSSKSPLAERRTDAYQD VSIHGTLPKPKKPPSIRSCDN AGHSKSPRSSPLTQDIIQENP LQDRKGENFI FRDPYLLDPTLE YVKFSKERHIMDRTPERLKKEL EEBLLSSDLRSHAWYHGRIP RQVSENLVQRDGLVLRDSLSS PGNFVLTCQWKNLAQHFKNRT VLRLEAYSRVQYQFEMESFDS IPGLVRCYVGNRRPI SQQSGAI IFQPINRTVPLWCLERYGTSP GRREGSLAEGRPDVVKRLSLT TGSSIQAREHSLPRGNLLRNKE KSGSQPACLDHVQDRKALTLLKA HQSESHLPICGCKLPPQSPMDT SPCPSSPVFRITGSEPTLSPALV

FIG. 64

SUBSTITUTE SHEET (RULE 26)

[illegible]

[illegible]

[illegible]

Nucleotide sequence (5' - 3')		ORFs
CTTTAGAGAGGCTATTCCCTCATAGAGAGGCGCGCGAAACTATTCTAGATCATGAACTTCTGAGAAATTAAGAAGAAAA TATAAATTACACTATAGGACACTAAACCTATGACTCAGTACATGTCAGATTATATAACAATATATCTTTTGTGCTGGGT AATCAAGAATAAGATATTCTCAGACACCTGGCACAAATCCCGAATTAACTTTAGGATTATTTATTTAAGATAAAGATT GGGTTTTTGTGTTTTGCTGCTGTTACGTAGCATTTCCAACTAGTATCATAGGGTGAATTTCTTTGTGTGTATACC TTGTCTTTCTTAAGCATAGGTTGTAATGTAATAAGTAATCAGTTCATGGGAACACTCAGCAACTCAGCAACTCAGAA CACTTGGTATTCTTTCGAGAAACCTGAGTTCTATTCCAGCACTCCCGGGTGGCTCAAGCATCCAGAACTCTTGT CAGGGTATCTGATGCTCGCTTCTGGCTCCAGAACACAGGCACCCAGGCATTCATATTGCACATACAGGCAAAACATTC ATACATGCAATCAATAGTAATAATATCTTCCCTCCCAATTAAGAAAGTTAAATCTTTCTGATGATTTTGGTAT TTTCTAAGAGAGCTGATAAATCTTTGGCCACAATTTAAAAAACAAGTATAATGCACTGTTGTACTCATTCTTTTACTACTA GTGTGAAATTACATAAGGCTCTTTTGTGTTTAAATTTAAATAAACCAATATTAAAGCATAAATGCTGATACCTGGAA GACACATGTGTGTTTTCTAAAAAATAGAAATGTTTTTGTGGAATGTTTCTTAATGTGTAATATATAAAGCTGAACA GGACGGGAAGGGATTTTTTTTTTTTTTTTTTTTTTAAGATTTATTTATTTATTTATTTAGTAACTGTTGCTGCTTTC AGACACACAGAGAGGAGTCAGATCTGTTACGGATGGTTGTCAGCCACCATGTGTTGCTGGGATTTGAACTCTGGA CCTTCGGAGAGCAGTCGGTCTCTTACCCACTGAGCCATCTCCAGCCCATGAAGGATTTCTTTTACACTCTGCTT CTGGGAGGTGTTTGAAGAGAGCACCTTCCCAATGATGGAATTTTGTAGTCCCTTGGCTGTGATCTCCACAAGTCTCA TCACGCAGATGCAGCTTGCCTGGCATTTCTAGGTAGCCAGGCTGGCTTGAATTCATAATGGATAAAGGAATGTTTGGAGAAAT TCCTGAGTACTGGTTTTGCAGGTTTTCGGTTACCACATCAGCTTGATTTTCAATGGATAAAGGAATGTTTGGAGAAAT AATTTCTTCTGCAGTCTTTTATTCTGCTAAATTTAAAAATCTGTACTTCTTAAAGAGAGCTAATAAAGGTTTTTGA TGTAATCTTACATCCAGTTTCATGCCATCTCTGTCAGTTTGGATTTGTATATATTTCTGTTGTTTTTTTAAATTTGT GTTGTTTTTCATGTCAGCAGTATTGTATCCAACTTAATTTATTTCTCAAGTATTAATAATGTCAGCATAAACCCACTCT GTTTGTCTTTTAAATGTAATTTAACTGTGTTTTGATTTATTTGACCATGTTGGAATTCATATATGAAACTGATAAAT AAGAGTTTTAAATATTATGTTATTTTAAACATTTTTTATTGTTATTTTCTCGATATTTTTCAGAAAGACAGACTCG TGGCTAATTATCTTTGAGATAATGGAATGATCAGTTATTAAGTCAAAATTTTATAGGACACACCAACACTGTGCTTACA GAAAGTCATGATAATAGAAATTTCAACTTCTTTTCCCATAGTCTGTTTTCAGGGTCACACTTGTATACCGTAAATG TATTTGAAATCCTTTTTTAAATGTTTATGACAGAGCAATTAATAAATGGAGTTAACCTACTATGTAATTCCTGG GCTGTTCTAAGAAATAAATCCCAATGAAGTTTTTATGTTTGCCTAACTTTTATAAGTGTAAAAATTTAAGTGTAAAGT ATTTTATGACATCTTGGAAGAAGATGAGCACACTTAAAAACCTTTTGGGTAAATATGAAAAACACAGCAAAATCTTAAGT GGTTTTACAAATATCTATGTTAATGTAAGAAACCAAACTTTGAAGGAATTAATGCAAGATAATGTTTTCTCTTTCT ACATTAGGTGGGAACAATTTAAGCACTGGTTGGAGATATAGCCTCAGTACACACCAATTAATAATTAACCTCT	SEQIDNO. 45	SEQIDNO. : 137
AAGAGGACTCGCGCGCGGCGCTTCCGCTTCTTCTCGGGCTGCTCCCTCGGGGCTTCCCGGCTTCCAGCGGCCACC ATGGGAAACGGGATAATCGCGTGGCTACATGAATCCAAATAGCAATGGTCCATCAAGGGTCCAAATCCAGTCTTCAGG ACCAACAATCCAGGATTATCTGAATCGAACCAAGGCTTACCTGGGAGGAAGTCAAGGAACAGCTGGAAAGAAAAAGG	SEQIDNO. 46	MGKRDNRVAYMNPFIAMARSGP IQSSGPTIQDYLNRPRPTWEEV

FIG. 70

Nucleotide sequence (5' - 3')	ORFs
GCTCCAAGGCTTTGGCTGAGTTTGAAGAAAAAATGAATGAGAAATGGAGAAAGAACTAGAAAAACATAGAGAAAAATTA TTAAGTGGAAATGAGAGCTCATCCAAAAAGACAGAAAAAGAAAAAGAAATCTGGTAGGGTGAGCAAAG TTTTCATTTTCTAAAATGTTACAGCTAAGGGCTGTAAAGCAAAGTAGAAATGATTGGGTTTTCTTGATGCGAACGCT AACTTAGACTTGGGTTTACCACGCGAGCCACAGGTCCTCTCTCTCTGACATGAAAGACGTGACAATGTCTCATAG CCTGTAAACGTCCTGCTGCTACTACGAGGACAGTGTGTCTCATTTGCTGCACTTGTGTTTTTTTGGAGCTTTTGGGGGAG GGAGGAGACTTTTATATATTTTAGCTTCTAAATCCTATGAATATGGCATCTGTTTCTTAGACACTAGATTGAGTTCACTAAG TGCTTGAGAGACTTAGTAAAAAGAAACCAATTCCTGCATCTCAAGCTTTAAATGTTGTGCTTGGTCAAATATTCATC TTCTTCTTCATCGAGCTCTGATTTCTCCAGAGTTCTTCAGATTCGGAAGATGAGGATAAAAAACAAACAAAAAGAGGA AGAAAAAGAGAGCCGTTGCCATAAGTCTCTCTGAGAGCTCGGGTCGGATTCGGCTTCAGACAGCAAGGATGGTTCAAAA AAGAAAAAGAACTCCAAGGATGTAACTGAAAGAGAAAAAGACACTAAAGGCTTCAGCAAAAAGAGAAAGATGTACGAAGA TAAACCGTTGTCTATGAGTCGCTGTGAGTCAGACTGAGTGTGAGAGGTGCAAGCAAAAAAGGAAGAAACGGTGTGAAGAGC GTGAGAGAACAAACAGACAAAGACCAAAAAAGAGAAAGAACAGCAAGCAAGCAAGAAAGAAAGAGCCGCCAGC TCCAGCTCAGACTCGCGGTCCATGAAGACCGAGGACCCCTTACCAGGTGAGCTTCAAGGAGCTCAACCTGTGAAGA TTGCGACACACTAGTAAACGTGCATGAATTCCTTGTCTTAGACTTTCCTGGACTAGTCAGTAGCCACTTGGATTCTGTG CTGTGTGAAGGCCATGATTGTTGCTGCTGTCTCAACACCTTTTCCCTTCCAGTCTTGGTGACTCTGGGAGATAGTA CTTTGCAGTCTATAGTGATTAAGATATCTGGAAATAAAGCTAAATATTTTTTACTAGAAAGTACTTAAGAAATAAATCAACA GAAACTGAATCTGGATTCTATCTTTTAAGATGTAAACGAAAAAATGAGATGACTCTAGTAAAAAATTTTCAAAGTAGGGAT ACGATTAATATTTCAGAACTCTGCTAGATAAGTATATTTTAATTTCCCATGTATATCTTTGATTTACTTTGGGGA TAGACTTTTAAAGGGGTGGTTGCTATCTCTTTAGCTACCAAGACAGTGTGCCCTTGATCTCACACATCCTACTTTTA TGACACAGTAGCCATGCTTCTCTGGGAGGACAGAGCTGGGACCGCTCACTCTGCCAGCTGAGGTATGACATCCTTAG ACTTTGTTGTAATGCTGCTTCGAATGAACAGAGATACCGGGCCCTTTGACAGCATGAGAAAGCCCCAAAGCTCTGGAATT TACCTCCACATCAATAATAAGTGAATGTTTTCAGGGTTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	KEQLEKKKKGSKALAEFEKMN ENWKKELEKHREKLLSGNESS KKRQKKKEKKKSGRVSKSFLF SKCYs
SEQIDNO. 46	SEQIDNO.: 138 MEVSCQAESESSEKPNADMWTSK DIYFDSYAHFGIHEEMLKDEVR TLTYRNSMFHNRHLFKDKVWLD VGSGTGLICMFAAKAGARKVIG IECSSISDYAVKIVRANKLDHV VTIIGKGVVEEVELPVEKVDII SEWMGYCLIFYESMLNTVLHARD

715-77

[illegible]

717

Nucleotide Sequence (5' - 3')	ORFs
GATGGTGAGGACGGGAGAGGCCCTGATCAGTGGCCCACTCGTCCGGCCCTATGTGGGCATTCATCTGGCGCATTGGCTCCG ACTGGAAGAAATGCTGTGCCATGCTGAAGGATGGAACCTGCAGGGTCACACTTCATGGCTTCCCCTCAGTGTGTGGCTAT AGCGGACGACACGAGCCCTCTCACCATGACCATGTGCTCCCTGACCTGAAGGAATCCAGCGGGCTGTGACGCTTGG GGTGAGACCATGTAATGCCAGATCGGTCTATCGCCACAGACATCTGAGAGCTACGTTGTAGAGATCCAGACGACTCTTCA AGACAAAGGTGAGGGTGTAGCCTGAAACCCGAGGTGGCCAGATCGAACCTGTATCATCTCCGCGCAGGCTGACCACTTCA ATTGGAACCTGTCTCTCTGCTCACTGCTCTGTAAGCGGGAGCGGACCTCCATGGGAGGCACTGCTCTTCTTCTTGG CATGACAGACCCCTCCAGCTTCGGGATGAATTTTGATCCCATCTGAAGCCCCCACTCCCAACCCCTCAACACGAGCTTGGC TGCTAAGGATGCTCTGGATTACATCCCTTTTCTTTCTGCCAGAGGTGGAGAACAGTACCAAGGACGTCCTCGTGAAG AGAAGGCATTCCATCCCAAGGCATTGGCTCCCATGGTCCCAAGCCAGGCTGCTCTGGCTGCATGATCATGACACATACAA AGACGCCACCTCAGCCTGGGCACACCCCTGATATATACACATACATACATAATATATATATATATATATATAAAAAA AAAAAAAA	ASYKEQWTQRFPAKEHPVLALP GAPAQFPVLEEHRLELQKXWVWS DEMVRTGBALISAHLRVPYVGI HLIRISGDWKNACAMLDKGTAGS HFMAISPCQGVYSRSTAPLTMT MCLPDLKBIQRAVTLWVRALNA RSVYIATDSYSYVSEIQQLFKD KVRVSLKPEVAQIDLYILGQA DHFIGNCVSSFTAFVFKRDLH GRQSSFQGMDRPSQLRDEF
SEQIDNO. 49 TTCTCTCGGAGGCGCGCGCCCATGTTGTTGTGGGCTGAGGCGCGCGCGGCTGAGAGCCCAAGCAGCCGTGACAGGCTG CGCAACAGGTTCTGCTCGCGCGGCTGACGACTGACCCGCGCGCGCGCGCGCAAGCAGGCTTCTCCCGAGACTTG GCGCGCCCAAGCGCGGCTGAGGAGCGCGCGGCTGCGCGGAGCTGCGCGAGCGCGCAGATGGCTGAGAGCTGC AAGAAAGTCAAGGATCATGATGGCTCAGTTTCCCAAGCATGAAATGGAGGGCCAAATATGTGGCTATTACATCTGAA GAAAGTCTAAGCATGATAAACAGTTTGATAACCTCAACCTTCAGGAGGTTACATAACAGTGATCAAGCCCGTACTTT TTTCCCTACAGTCAGGCTGCGCGCGCGGCTTTAGCTGAAATATGGGCTTATCAGATCTGAACAGGATGGGAGAGATGG ACCAGCAAGGTTCTCTATAGCTATGAACATCAAGTTAAAGTTGCGAGGCCCAACAGCTGCCTGTAGTCTCCCTCCT ATCATGAAACAACCCCTATGTTCTCTCCACTAATCTCTGCTCGTTTGGGATGGGAAGCATGCCAAATCTGTCCATTCA TCAGCCATTGCTCCAGTTGCACCTATAGCAACACCCCTGTCTCTCTGCTACTTCAGGACCCAGTATTCCTCCCTTAATGA TGCTCTGCTCCCTAGTGCTTGTGTAGTACATCTCTATACCAATGGAACCTGCCATTTCATTCAGCCTTTATTCCTCAT CCTTATCTTCTTCAACATTGCTCATGCACTATCTTACAGCTGATGAGGAGATTTGGTGTGCTGATGATCCAGAA GCGCCAGTCTCTGATTGATTAGGATCTAGTAGTCACTTCTCACTGCTTCCCTCTCAGGGAACCTCACTTAAGACAG GGACCTCAGGTGGGAGTTCTCAGCCTTCAAGATTAAAGTATCGGCAAAAATTTAATAGCTAGACAAAGGATGAGC GGATACCTCTCAGGTTTTCAAGCTAGAAATGCCCCCTTCTTCAGTCAAAATCTCTCAAACTCAGCTAGCTACTATTGGAC TCTGGTGCATCATGATGGTGACGGACAGTTGAAAGCTGAAGAAATTTATTTCTGGCGATGCACCTCACTGACATGGCCAAA CTGGACAGCCCACTACCACTGACGTTGCTCCCGAGCTTGTCCCTCCATCTTTTCAGAGGGGAAAGCAAAGTTGATCTGTT AATGGAACCTGTGCTTTCATATCAGAAAACAAGAAGAGAGCCCTCAGAAAGAACTGCCAGTTACTTTTGGAGCAAAACG GAAAGCAACTATGAACGAGAAACATGGAGCTGGAGAACGCAACGCCAAGTGTGATGGAGCAGCAGAGGGAGCTG AACCAGAAAGCCAGAAAGAGAGAAAGATGGGAGCGGAAACAGAGAACTGCAAGCAAGAAATGGAAGAACAGCAGCTG GAGTTGGAGAAACGTTTGGAGAAACAGACAGAGCTGGACAGACAGCGGAGGAGGAGAGAGGAGAAAGAGAGATAGAAAGACG KOIHLKRLKORELELROREEE KQKQKEBEWERKQRELEQOEWEK	SEQIDNO.:141 MMAQFPPTAMNGGPNMWAITSEE RTKHKQFDNLKPSGGYITGDQ ARTFFLOGLPAPVLAELIWAIS DLNKDGKMDQQEFSIAMKLIK KLQOGQLPVVLPPIIMQKPPMF5 PLISARFGMGSPMNLSTHQPLP PVAPIATPLSSATSGT5IPPLM MPAPLVP5VSTSSLPNGTASLI QPLSIPIYSSSTLPHASSYSLMM GGFGGASIQKAQSLIDJGSSSS TSSTASLSGNSPKTGT5SEWAVP QPSRLKYRKFN5LDKGWSYL SGFQARNALLOSNL5OTQLATI WTLADIDGQQLKAE5FILAMH LTDMAKAGQPLPLTLPPELVPP SFRGGKQVDSVNGT5LPSYQKTQ EEEPOKPLPVT5FEDKFKANYER NMELKRRQVLM5EQOQREAEER KQKQKEBEWERKQRELEQOEWEK

Nucleotide sequence (5' - 3')	ORFs
AGAGGAGCAAAAACAGGAGCTTGAGAGACAAACGCCGTTTGAATGGAAAGACTCCGTCGGCAGGAGCTGCTCAGTCAGA AGACAGGAAACAAGAACATTTGCTAGGCTGAGCTCAGAAAGAAAAGTCTCCACCTGGAAGTGAAGCAGTGAATGGA AAACATCAGCAGATCTCAGCAGACTACAAGATGTCCAAATCAGAAAGCAACACAAAAGACTGAGCTAGAACTTTTGGAA TAAACAGTGTGACCTGGAATATATGGAATCAAACTTCAACAGAGCTTAAGGAATATAAATAAGCTTATCTATC TGGTCCCTGAGAAAGCAGCTATAACCGAAAGAAATTAATAACCTGAGCTCAGTAAACACACCTGATTCAGGATCAGTTTA CTTCATAAAAAGTCAACAGAAAGGAAGAAATATGCCAAAGACTTAAAGAACTATAGATGCTCTTGAAAAAGAAACTGC ATCTAAGCTCTCAGAAATGGATTCATTTAACTAATCAGTGAAGAACTCAGAGAAAGCTATATACACAGCAGTGTAGCCC TTGAACAACTTCATAAAATCAAACTGACAAATTTGAAGAAATCGAAAGAAAGATTTAGAGCAAAATTCAAAAAGAAA CTAGAAATGAGGCTGCAAGAAAGCAAGCAAGGAAAGAACTTGTGGAGAGAAAGTATTAGAAAGGAAGAGAGGA AAAGCAAAAACGACTCCAGGAAGAAAGTCAAGGACAAACCTCAAGAAAGAGGAAAGCTGAGGCAAAACAAAGTG AGACAGCCAGTCTTGTGTAATTAACAGAGCAGTGTACCTTTTGAAGCAAGAAACCATGATGAGATGAGTTTAGTTCT GGGATATAATTCAGTTGATGAAATAAAGTGTAGAGAGCCCTGTTGGCTTTATGGTAGTTTTCAGGGAAGATTTGGCTG GTTCCTGCTGCAACTTCTCCAGCAGCAGCATCAGTACTGATTTATCAATGATATCTCTCAAACTT TGCTCTCTGCTACCTCAACTTCTCCAGCAGCAGCATCAGTACTGATTTATCAATGATATCTCTCAAACTT ACTGTTAATACAACTGAGCAGCAGAACTGTTTACCCGACTGTGTCCCTGGATCTGTGTCCCTCACTTCTCA GGGCGAGGCTGTAGAAAACCTGAAGCCAGGCCCTTTGTTCTCGACGGCAAGAAAGGAGAACCACTGAACTTCTCAA AGCAGACGTCATCACTGCTCGAGCAGCAGGAACTGTTGGTGTGGGAGTGCACGAGGAAAGAGATGTTTCCC AAGTCTTATGTCAGCTTCTGGAATGAAGTACAGCGAGGAGAGCCAGAGCTTTGTATGAGCTGTGACTAAGAA ACCTACCTCACAGCCTATCCAGCTATCCAGCTATCCAGCTGAGAGAACTATCTGCTTATTCATCTCA GTGTAGAGCCGGGATTTGACTTTTCACTGAAGGTGAAGAAATTTAGTGACCAAGAAAGTGAAGTGTGGACAGGA AGTATTGGAGAGAGAACTGGAATCTTCCCGTCCAACTACGTAGCAAGAAAGTCAAGAGAAATTTTGGGAAATGCTAGCAA ATCTGGAGCATCAACAAAAACCCGAGATCGTCAAGTAACTTCAGCATATGCTGCTTCAGGAGTGCAGCAGTCAAGC TTGCGCCAGGACAGTAAATTAATCTTAAAGAAACACAAAGCGGTGTGGCAAGGAGAGTACAGCCAGAGGGAAG AAACGACAGAGGATGGTTCTGCGAGCCATGTAAAGCTGTAGGTCCAGCAGTGAAGAAACCATGCTTCTTTCA CGCTGTATGTCAGATGTTGATGACTACATGGCGAATAAGAAAGTGAAGTCAATTTCTCCAAAGGACAGCTGA TTAAATGTTATGAACAAAGATGACCTGACTGTTGGCAAGGAGAAACCAATGCTGCTGCTTTCTCCAAAGGACAGCT GTTAAGATGACAAACAGACTCAGATCCAACTCAAGTGTGTGACCTCCAGCCCTGGACACAAATGACGCTTACGGA GAGGAAGCAGAGGCTACATTCAGAGCTCATTACAGAGAGGCGGTACATGGACGACTGCAGCTGGTTCATCGAGG TCTTCCAGAAACGGATGGCTGAGTCCCTCACTGAAGCAGACATGGCTGTGATCTTTGTGAATGGAAGAGCTC ATCATGTCAACACAGAGCTGTGAGGCTTGGGCTGAGGAGAGTGGGCTGAGAGATGCGAGTTCAGATGAT TGGAGACATCTGGCGGAGAGCTGTCCCATGAGGCCCTAATCCCGCTTTCAGAGCTGTGAGCTTAATGCGGCAACCC TGTTCAGCAGAAACAGACAGGACAGGACTTCAAGGAATTTCTAAAGAACTTGGCATTCAGACCCACGATGCAAGG ATGCCCTCTCCAGCTTCTGCTGAAGCCCATGACAGAGGATCACTGCTACCCGCTGCTCATCCGAGATCTCTGGAGAA CACTCCACAGAGTCAATGTTGACCACTCTCTCCCTGAGCTGGCCCTAGAAAGCTGCTGAGGAGCTGTGCTCTCAGGTTGAACG	RRKEIERREAAKQELERQRRL WERLRRQELLSSQKTRQEDIVR LSSRKSLHLEFAVNGKHQOI SGRLQDVQIRKQTKQLEVL KQCDLEIMEIKQLOQELKEYQN KLIYLVPEKQILNERIKNMQLS NTPDGGISLLHKKSSSEKEELQ RLKQDLDALEKETASKLSEMD FNNQKELRESYNTQOLALEQL HKTKRDKLKEIRKRLEQIOKK KLEDEAARKAKQCKENLWRESI RKEEKKQRLQEEKSQDKTQE BERKAEAKQSETASALVNYRAL YPFEARNHDEMFSFGDIIQVD EKTIVGEPGLYSGFQKGFWFP CNVVEKVLSSERKALSPKKALIF PTVSLSATSTSSQPPASVTDYH NVSFSLNTVNTTWQOKSAFTRT VSPGSVSPHGGQQAVENTLKAQ ALCSWTAKKENHNFSGHDVIT VLEQQENWFWFGEVHGGRGWFPK SYVKLI PGNEVQRGEPEALYAA VTXKPTSTAYPVTSTAYPVGED YIALYSYSSVEPGLTFTTEGEE ILVTQKDGWWTGSGIGERTGIF PSNYVRPKDQENFGNASKSGAS NKKPEIAQVTSAYAAASGTEQLS LAPGQLIILIKNTSGWQOGL QARGKKRQKGNFPASHVKLLGP SSERTMPTFHVCQVLIAMVDYM ANNEDELNFSGQLINVMNKDD PDWQGETNGLTGLFSPSYVKM TTTDSQSQWCADLQALDTMQP TERKRQGYIHLELIQTEERYMDD

NucleotideSequence (5' - 3')		ORFs
AGGAGTCCGGGAGAGGAAATTCAGACCGCTGGAGTGATCAGGCACACGTGCACTGCGAAGCTTGGCAGAGCAA CTTATTTCAAATCCCTCACCAATGCTGGGCCCCGGGAAGCTTTCACACAGCGGAAGCTGTACAAGACCAAGAGCAA TAAGAGCTGCAGCGCTTCTCTTCAACGACTTCCTGCTGCTCACTACCTGTCAGGCAAGTTTCCGCGCGCTCTTGCC ACGAGAAGCTCTTCAACTCCAAGTCCAGTGTCTAGTTCCGGATGTACAAACGCCCAATTTTCTCGAATGAAGTGTGGTG AAACTTCCACAGACCCCTTCCAGCGATGAGCCGCTTCCACATTTCCACATTCGTGCTGTACACACTCCGAAACAGA CAACATCAACGAGAGGACGGCTGGTCCAGAAGATCAAGGTGCTCAGAGCAGTACATCGACACTGAGAAGAGAAAC GGGAAAAGGCTTACCAAGCCCGTTCTCAAAAGACTTCAGGTATTGGCGTCTGATGGTGCATGTCTTGAAGCTACAGAA TTAAAGCCTGCAAAACCAACCGGAAAGTAATCCATCTGTGAAGTCAGCATGGCTCCCAAAGCTATACCACAGGAC CCTCAGGACACACTAAACCCCAAGTGAACCTTCAACTGCGAGTCTTCTCAAGAGTCTTTACCAGGACGTTCTGTGTC TCATATGTTTGACAGAGACCACTTCTCCAGATGACTTCTTGGGTCTGTAAGTTCAGTGGCAAAAATCCGAACA GAACAGGAAAGCAAAAGGCCACACCCCGGACTACTACTGACGAACTCCCACTGGAGAGTCTGGGTCCGCTTGA CCTGCAACTTTTGAACAAAACCTCTCTTGGGCTGGGAAAGCAGAACCCAGGGAGCTGCCACAAAGCTGGGT CTAAGACAGATTTGCTCTCCAGGACAGAGGAGCATCATGGCTTCACTCCATCAACAGCCACACTCGCTGGGCTG TATTTATTGCACTAAATTTGCTAGCAATCTATGCAACATGATCTTTTAAACAAACGCCACAGCAGTGCCTTGTAC TAGGTGTAACCTGTTGAGTGTAGATGCCAGGTTTCCATTTTCAAGGCTATAAAGTATTATGTGAAATGAGGCA TCAGACCAACCGGAGCTTACCACTTGGCAATCTGTCCACTGTGGAGTTGGTGTATGTTGGAACCATTCACACTATGTGAC CTCTGCTGGTTCACACACTCAGGAGGTGAAGGCTGAGATGAAATGCTGCAGCCTTGGGCTTGTGCAGCCTGATCTGA AATAGCATCCACTTGTGCACTGAATAAATAGAACTTGTATCTGTTATTCTGACTAGATATTATCATTTCTCTGCTAAGAC AATAAGTTTGAATAATTATAGTTTGAATAATAAGGAGGAAAGCTTGATGATCTTTAAATATACTGTGAACCTCTAATAATG TGGGATATTTTTCAACTTTTAAATTTTCTTAAGTATAAATTTATGTAAATCTTTTGTGTTGCAATTTTCATAGAACAT GCATCTTTAAGCTTTTATCATTTGCCAACAAATGTACAGAAAGAGAAATAAAGTATAAGTTTATGAATGTAAAAA A	LQLVIEVFQKRMAESGFLTEAD MALIFVNWKELIMSNTKLLRAL RVRKKTGGEKMPVQMTGDI ELSHMQAYIRFSCQLNGATLL OQKTDEDTFKEFLKKLASDPR CKGMPLSFLLKPMQRI TRYPL LIRSILENTPQSHVDHSSLKLA LERAEECSQVNEGVREKENS D RLEWIOAHVQCEGLAEQLIFNS LTNCLGPRKLLHSGKLYKTKSN KELHAFLFNDLFLLLTYLVRQFA AASGHEKLFNSKSSAQFRMYKT PIFLNEVLVKLPDTPSSDEPVF HISHIDRVYTLRTDNI NERTAW VQIKGASEQYIDTEKKREKA YQARSQKTSIGIRLMVHV I EAT ELKACKPNGKSNPYCEV SMGSQ SYTTRTLQDTLNPKNFNC QFF IKDLYQDVLCLTMFDRDQ FSPD DFLGRTEVPVAKIRTEQES KGP TTRRLLLHEVPTGEVWVR FDLQ LFEQKTL	
SEQIDNO. 50	SEQIDNO. : 142	MTQSC TMA STKPLSR FWEWGKN IVCVGRNYADHV KEMRSTVLSE PVLFLK PSTAYAP EGSPVLM PA YCRNLHHEVELGVLLGKRGEAI PEAAAMDYVAGYALCLDM TARD VOE CKKKGLPWT LAKSFTSSC PVSAFVPKEKIPDPH ALRLWLK VNGELRQEGKTS SMIFSIPYII SYVSKIITL BEGDLIL LTGTPKG

73 - 75

[illegible]

五五.七五

NucleotideSequence (5'-3')		ORFs
TCACTGCCCGGGCTCCTTAGTCAGGTGAGGGCCCTGGATAGGTTCCAGGTGCCCTACCACTGAGGTCAATGCTTGGCTG GTCCACCGAGACCCGGAGGGGTCTGTCTCTGGCAGCCAGCCCAACTCAGGCCCTCGCCCTCGAGAGTTCAGTGGCTCCA AGATGTGACAGGCCCAGACACCGGGTGAGAAAGCGAAACGGAGCAGGATTCGGTGAAGATTGGAGGACCTGGGG CTGTAGCCCTCTCTGTAGTGAGACTTAACCAAGAGGATATAGATCTGATCTGATCTCTTGGCGACAGGATATGAT CTGGGGCTGGCGTGAGGTTTGTACTACAGTCACTCGCAGAAAGCAGGATGTGGATAAGGAACTGCAAGATGGACG AGAACGAGAGCACCTGTCAGGCGAGGGTGGGAAGCTCTGGCCCGAGACCTGTGTAGTAGTGGAGAGACTGGGGAGA GCTTCCCTGCACAGTCCCGACTGACGTTCCAGCATCCAGAAAGAGTGCCTAGTGAGAGTGATGCCCGCCCTTCAG AACAGCCTTCTATCTCTCTCTGACGGGACAGAAATCACTTTGATTTGGAACAGAGTGGCAAGATCTCATGTCCAT CATGGAATGAGGCTATGGAAGTAAATACATCAGCAAGTGAGATTCTGTACAATGCCCCCTCTGGAGACCCCTCTTAGCA CCAACTACAGCCTTGCAACCAACTCCCATCAATCAGAAATGTAGCCTGCATCAGCGTCCCTGGGGGCTGCAGTCAG GACTTCTCCCTCTCAGCCCGAGGTGGAGAGCCTGCCTGTGGCTAGCAGCTCCACATGCTTCCACTCGTCCCGAGCAA CTCCACAGTCAACTCACTTGGCTTACCAACCTAGCAGGGCTTTCTTTCCATCCCAGTCAATGGCACAGCCCA ATGACACATCAGGCCCTGAGTACCTGACCCCTTGGGGCTGTGTAGACGAAGTATGCTGGATGAGATCAGCCTGATG GACCTGGCCATTGAGGAGGGCTTCAACCCGGTGAGGTTCCAGCTCGAAGAGGAGTTGACTGACTCAGGCTCTC CTTGGACTCCAGCATAGCCCTTCTCTGTAGCAGCTCTGAAGGAGCTCTTCTTCTCCTCCTCTCTCTCTCTCTCT CTGCTTCTCTCTCTCTCTCTGAGGAGGTGCTGTGGTTACAGCTGACTGACTGTGAGACCCCTAGACCTA GAAAGGCTGAGGGTGAGTGGCTACAGCGGAATCTCAAGTTCTGCCGATGAGCTATCAGGATCCTTCTCAGCT TACTCCACCCAGCACCTCAAGAAAGGTAGCAAGGAAAGCAGGCTGACTTCTTGCAACAGCAGATGAGCCGAGATGAG CACAGAGCCCGAGCCATGAAGATCCCATTCACCAATGCAAGATCAATCAACCTGCTGTAGAGAAATTCATGAGCTGCT GTCCAAATACAGCTGAGCGAGGCCAGCTCAGCTCACTCCGGGATATCCGGCGCGGGGCAAAACAAGATGGCTGCAC AGAACTGCCGCAAGCGCAAGTTGGACACCATCTTAACCTAGAACCTGTATGTGGAGACTTGCAGCAGAGATAAGCCCCGA TTGCTTCGAGAAAAGGTAGAGTTCCTTCGGTCTCTGCGACAGATGAACAGAGAGGTCCAAAGCTTATACAGGAGGTGTT TGGCGGCTGGGGATGAGATGGGAGGCCCTACTACCCAGTCACTATGCCCTTCAATATGCTGGGATGGCAGTGTCC TCCTCATTCCTCGCACGATGGCTGACAGAGGCTCGGACAGGAGAAAGCCAAAGGACCGGAGGAAGTGAAGCCTGG GGAGGCAGGGGTGGACGCTCACTAAGACCGAACTGGAGAGGGCTGGGCTGGACCTAACATTTGGGACTTAAATGCC TCTTATCCCAATATATCTCTCAGATGGATGACTGCGGTGAGTCCAGCCGAGAGCGGCGGCGCTGTCTGGCTC AGCTGCCCCCTTGGGTGGCAGGGAGGACAGACTGCTTGGGTGATTTGGGTCCCGAGCTATTCCTTCTCTCTGAGG GGAGGTTAGTCTCGGCATGCTGGAAGTGAAGGAGCTGTGTGAGTGAAGAGAAAGTGTGGAGATCTCATTTGCTGGA AGGAGAAAAGGAAGGAATCCCGGAAATCAAAAGCAGTCAGAAACACAGAGCAGTGTAAAGGCTTTGGCCAGCTTTC TAGGACAGGATGACAGTGAACACCGTGTGTAGGAGATTACTGGTATGGAACACAGACATGGCGGGGCCCCAGAGG CCTTTGTAACCTGTTTCTTCACTCTTGTGATCCCTGAAGGGAAGATGCTTGTGATGCACTCTTAATATCTTGTACTGA ATGGGAAGCTGTAGGGGCCGAGAGGGGACAGGGTATAGGAAGTGAACAGGAGGCTGTGTGCGAGCAGCCCGACATCAA GCATGTACACACTGCCCTGCCACAGCCACTCCCTCCCTGGCCATCCCGAGCGAGGCTCCCTGTCTCAGAGAGC		VTGPNQVRESETEQGFGE DLGAVAPPVSGDLTKEDIDLID ILWRQDIDLGAGREVFDYSHRQ KEQDVKELQDGREREDTWSGE GAELARDLLVDGETGESFPAQ FPADVSSIPEAVPSESESPALQ NSLLSPLLTGTESPFDLEQQWQ DLMSTMEMQAMEVNTSASEILY NAPPGDPLSTNYSLAPNTPIQ NVSILHQASLGGCSQDFSLFSPE VESLPVASSSTLLPLVPNSNST LNSTFGSTNLAGLFFPSQNLNGT ANDTSGPELDPPLGGILLDEAML DEISLMDLAIIEGFNPVQASQL EEEFDSGLSLDSSHSPSSLS SSEGGSSSSSSSSSSSSSSAS SSFSEGAVGYSSDSETDLEE AEGAVGYQPEYSKFCRMSYQDP SQLSCLPYLEHVGHNTYINMAP SALDSADLPPSTLLKGSKEQ ADFLDKQMSRDEHRARAMKIPF TNDKIINLPVEEFNELLISKYQL SEAQLSLIRDIRRRRGKNKMAAQ NCRKRKLDITILNLERDVEDLQR DKARLLREKVEFLRSLRQMKQK VQSLYQEVFGRLRDEHGRPYSP SQYALQYAGDGSVLLIIPRTMAD QQARRQERKPKDRRK

FIG. 77

7月27日

[illegible]

NucleotideSequence (5' - 3')		ORFs
CACATTCATAAGTAACTTAAAGGGCTGTTTACTAGCAATAGCATATAATTAGCATTTGTTCTGTTTACTCATGTGCTTATGTGACATTCATCAAAACAGCTCTTGATGTGGGTACAGTTCTTACAAATGCATGTGTTGAGGTTTCTTACCAGCAGA AAGCTTCAGGCGGACCTTGAGATTGGCACCAGCACCTTCTTAAACATTTCTGGGGTCTGTTTCTTGTCTATATAAAG GATCTTATAGGATAGAAAGTTGTGATATGTTTCTGTTACAGCAGATTTCGAACAGGAAACCACTTAGTGATCTGAA GTGCAAAAAGTGATGAAAGATTAAACAGAGTTCATAAGGATCTGAGCTTCTGCTACATTTTACACCTTACAAAGTGAGCT TTATACATCGATGAGATAGTAGTGTAAAGTCTCAAGGCTCAGAGTTAGAGGGTCTGGGTGTGCTCTAGCTAAGGAA GCCCTCCAAAGCTAGGGCATTAAGCCACACCTCAGTTCAGTTTAAACAGTTCACGTACCTTTGTGATGAGTGGCTATGT TGGTTGAGCACACAGACTATCTAAACACTGACATTTATGTATCTGAAAAAGCCAGTTTCAGGTGTTTGGTAAAGGAAAGCCCAAT ATGCAAAAATGGCTTTGTTTTTAGCAGCTGAGGAGCAGCTGCTCCGGCATGCCACTAGCCCTGCTCTCAGGAACTCCA TTCAGTCGCTGTCAGGGCTTTATCAGTCTGTGATGATGCTTAACTTCGAAGTTTCGATGTGTGATAAGCATCTCTGGTC TGAGTGTTTTAGGAAGAAGCTCAGTGCTTTCAGTGGCTGAGCCAGAGGTGATCTTATGAAAAAGAGATGATTCGAAGTG TTAGTAAAGAGGTGCGATTGAAAAAGTAACTTGAACTATGTAAGCAGCCAGCGTATCCCTTCAGTCTTAACTAGACAACTG TGTGCTTTTGTGCTGGCCCTATGTCATTTACTGTGCTCATGCTGAAAGGAAAGTAAACAGCTTTAGAAAACTGTTGAAAAAT AAAAAGGAAAACAGGCTGGGTGAAATCCCTTTGCTGGGAATTTTAAACAGCTCTTCAGTGGTCTTTCTAGCCAGTTAT TCTGTGAAAGATTTGAACTTTGAGGAGCTTAAAGCTTTGAAATGGGGCTGGTGACGGGCTGGGAGTGGAGAGCTGTGCTT TCAGATACCTTTAACTCGGAGCTGTGACCTTTGATTTGTAGCAAAACATCGAATTTCAAAGCTTCTTTTGTCTTCAGTCACA AGCTGCGTACCTTACTGCGAGACTGCCAATGCTTCAAAGATGATGTTTGAAGAAAGTTCTTTCATAGTTTATGAAAT TTGGGAAGTTGTTTACTTAAACAAATGCAACAAGAAAATAATTCATAAAATACTGAATATATATGTGCAAAATTTTCTTT AGCTACAAATAAATGTTCAACATTTTCTATAAAGAATTTTTTCTGAGTAAAAAAAAGGAAAAAAGGAAAAA	SEQIDNO. : 147	MGLEPSWYLLLCIAVSGAAGTD PPTAPTAEERQROPTDILDCF LVTEDRRHGAFASSGDRERALL VLKQVPVLDDSGLEGITDFQGS TETKQDSPVIFEASLDLVQIPQ AEALLHADCSGKAVTCHISKYF LQARQEATFEKAHWFISNMQVS RGGPSVSMVMKTLRDAEVGAVR HPTLNLPLSAQGTVKIQVEFOV TSETQTJNLHLLGSSVSLHCSFS MAPDLDLTGVEWRLQHKSGQL VYSWKQGOAKRKGATLEPER
CAGGTTTTGAAATCACCTGGGGATTTCTTGGGTGCGGTGGACCTTAGGGAGAACAGAAAAAGCAGAGCTGGCTGCAGCCA TTACTGGCCTCGGGCGGGCCAGCAGCTTGAGTGAAGTGAAGTGAAGAGAAACGATGAAGAGAAACGAGACACACAGG TGTAAGTAGGTGTCTACAGAACCCCTCTTCAGCCAGAGATCACTAGCAGGGGAATCTGTGGAAGAGCGACCCAGCAA GGAAGAGCCTTGAGATGACCTTCAATGGCTTGGAGCCACAGTGTCTGCTGCTCTGTTTGGCTCTCTGGGGCAGCA GGGACTGACCTCCACAGCGGCCACACAGCAAGAAAGACAGCGGCGCCACGGACATCATCTTAGACTGCTTCTTGGT GACAGAAGACAGGACCGCGGGCTTTTGGCAGCAGTGGGACAGGAGAGGGCCCTTGTGCTGTAAGCAGGTAACAG TGCTGGATGATGGTCCCTGGAAGGCATCAGATTTTCAGGGGAGCCTGAGACCAAAACAGGATTCACCTGTATCTTT GAGGCTCATTGGACTTGTGTACAGATTCACAGGACAGGCGTGTGCTCACTGCTGACGCGGGAAGCAGTGAACCTG CGAGATCTCCAAGTATTTCTCAGGCGCAGACAAGAGGCGACTTTTGAGAAAGCACAATGGTTCTCAGCAACATGACGG TTTCTAGAGTGGCCCCAGTGTCTCCATGGTGTGAAGACTCTAAGAGTGTGAAGTGGAGCTGTCCGCGACCTTACA CTGAAACCTACTTGTAGTCCCGGACAGTGAAGACTCAAGTGGATTCAGGTCAGATCAGACACCAACCCCTGAA CCACCTGCTGGGTCTCTGTCTCCCTGCACTGAGTTTCTCATGGCACCAGCCTGAGACCTCATCTGCGGTGAGTGGC	SEQIDNO. 55	MGLEPSWYLLLCIAVSGAAGTD PPTAPTAEERQROPTDILDCF LVTEDRRHGAFASSGDRERALL VLKQVPVLDDSGLEGITDFQGS TETKQDSPVIFEASLDLVQIPQ AEALLHADCSGKAVTCHISKYF LQARQEATFEKAHWFISNMQVS RGGPSVSMVMKTLRDAEVGAVR HPTLNLPLSAQGTVKIQVEFOV TSETQTJNLHLLGSSVSLHCSFS MAPDLDLTGVEWRLQHKSGQL VYSWKQGOAKRKGATLEPER

NucleotideSequence (5'-3')		ORFs
GGCTGCAGATAAAGGAGCGGCGAGCTGGTGTACAGCTGGAAGACAGGGCAGGGCAGGCCAAGCGCAAGGGCGCTACA CTGAGCCCTGAGGAGCTACTCAGGGCTGGAACCGCTCTCTCACTTACCCACCTCACTCTAAAGGATGAGGGGACCTA CATCTGCCAGATCTCCACCTCTGTATCAAGCTCAACAGATCATGCCACTTAACATCTGGCTCCCGCCCAAGTACAAC TGCACTTGGCAACAAGGATCTCTGCTTCCCTGCTGCGAGCTTCCGCTACTATCTCTGGAGTGGGAGTGACG TGGATTCGAGGAGCTGGGTGGAATTCAGCCCAAGTCTCTGGTGGCTCTTCTCCAGCTCAGGCAGACGATGGG AACCTACAGCATTTCTTCCAGGTGATGGCTGACCCAGGCCCCACAGGTGCCACTTATACCTGCAAGTCGCCACGTC CCCTGGAGGAGCCCTTACAACAGCATGAGGGTTTTGCCAAATCCAGAGCAGAGAGAACCTTGGGAGTCACTTTTGGC AGCATCATCTTCCCTTCTGCGCTGTGTGTGTCTGGGACTTTCACAGACAGCAAGCTTCTTCGTCAGGTCACACGCCC TATGAGGCATTTCTGGGTAGCCGCTGCCCTCCGATACAAAGTAAAGTACTCCACATCTCTGGCTACTTAAAGGACCC CGTGTAGGTGGGGCTGAGCTGGGCTGAGGTGCGAGCACTTGGGAGTGCATGAGGAGGAGGAGGAGGAGGAGGAGG TCTGTCTTCTGTCTATTGAGAGAGAGGCGCTGGGCTGATGAAAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGG GGAAGCTAACACCATCTATGTAGGTATTAAGAAATTGGGGTGGGGCTGGTGGATGGCTCAGTGGGTAAAGACACCC GACTGCTTCCGAGATCTGGAGTTCAAAATCCAGCAACCATCATGTGGCTCAACCATCTGTAAACGAGATCTGACTC CCTCTCTGGAGTCTTGAAGACAGCTACAGTGTACTTACATATATAAATAAATAAATAAATAAATAAATAAATAAATAA AAAAA		LLRAGNASLTLPLNLTLKDEGY ICQISTSLYQAOQIMPLNILAP PKVQLHLANKDPLPSLVCSIAQ YYPLDVGVTWIRELGGIPAQV SGASFSSLRQSTMGTYISISTV MADPGTGAITYTCQVAHVSLLE PLTTSMRVLNPEQRGTGLVIF ASIIFLSALLFLGLHRRQASS SRSTRPMRHSG
SEQIDNO. 56	GTGCTTTGTGCTGTGGAGAACCTAAGCGGAACTTAGACACAGGGAGAAATGAGGCTCTGGACCTGGGCACCAGTATTT TCCCTGAGGCTTTGGGGACTTATGTGTTCACGAAAGCCCTAGCTGGCTGGACTTCCATCCAGCATTTGGGAGCTGTGTG TTTGTGGCTTCCCTTCGGTGAGCCTCTCTGTGAGCCTTTTACTGGATCCTGCCACCCGTTGCCCTGCTCTCTCTGT CTGATGATCAGCTGTGTTTTCTATGCTTTTCCAGCGGACAGATGCTTCACTTCTGGCGGTTCTGTCTGTGGCC TCCGTGAAGGTAGGAACGCTTTGATTGCGGCTGGCACTGGGTAGTATCTTTGGACATGTGGAAAAATATTTTATTAAC TTCAGAGGCTCTCTAGACAGATGACTTGCACCTAGGGGCAAGAGCTTTTCACTACATTTCCCACTTTTAAACCGTA TACTGAAGCCATCCAGTGGATTTAAGGCTTTGCCCTGAGTCACTCCGCTGAATCTATTGATGACCTTGTCTTTGGAACCACTC TGGTGTCTCTCTTTTAGTCCAGCCATGCCCTGGAGGCTCATATGAATGACACTAGAGGAGAGTCTTGGAGTCCCTG CACCATATGTGGTCACGACAGAGCTGTGACTTCCGTGGGCCAGAAATGCTTCCCTTGGCGGCTTCTGCTCATCT AGTCAGCACTGGCCTCTTCTGAAGCGAATTCCTGGGCCCTTGTGGCTGGAATGAGAAATGCTACATCAACAAAT TTGTTCCGTTTGTATGAAAGGAGAGGACCAACAGCGGCCCTGTCTCCCTCCGCTGAATAGAGGAAAGGAGAAATAT GTCACTCGTCCCATCTTTGACGCTGACTCCTAAGGAGAGAAACCCCTGGGCTGTCTTCTCTCTCTGCTGACCTATCT CTACATGTGGGTGCTGTTTCCGCTGTGACTATCTGCTGTATCGGCTCATCTCTCCATGAACAAACAGTTCCAAAGCT TGCCAGGGCTGGAAGTTCACTTGAACCTAGCTGGAGAGCTTAAATCTCGTGTAGTCTCTCTTACCCCAAGGTGGAG AGGAGAGAAATGAATACCTGCAATGCGAAGCTCCTTGAGAAACGATCAAGCAAGCCATGAGAGAGGCTGACGGGAAACC GAGCCTGTACTTTAAAGAGATTCATTTCTGGTTTTCCAGTCTGTGAATGATTAGGAAGAGCAGACAAATCCCTGCAATG	SEQIDNO. : 148 MRLWTLGTSIFLRLWGTYYVFP SPSWLDFFIQHLGVCCFVAFLSV SLFSAAFYWIPLPVALLSSVMM ITCVFLCCSKRRCFILLAVLS CGLREGRNALIAAGTGVVIFGH VENIFYNFRGLSDMTNLRK SFSVHFPLLKRYTEAIQWIYGL ATPLNLFDDLVSNWQTLVSLF SPSHALEAHMNDTRGEVLGLH HNVVTELLTSVGQKLLALAGL LLILVSTGLFLKRFPLGPCWKY ENVYITKQFVRFDEKERHQRP CVLPNKKERKKYIVPSLQLT PKEKKTILGLFFLVTLYLYMWV LFAAVDYLLYRLISSMNKQFQS LPGLLEVHLKLRGELKILVSVSF

FIG. 81

Nucleotide Sequence (5'-3')	ORFs
AAGATGATCTATGAGCAACACAGTCCCTCTTTCTGGGCCAACTGCTGCTTCTGTCTACTCAACAAGAGGGGCTATCTGA GAAGGTCTACAGATGTTTGAGTTTGCAAGGCTGCCCTTCTCTTTGGTGATCCTTCAAGATACATGTCGATCATAATGCCA AATAGCCCCCTAGGTAAATAGTTTCAGAGTCTGTCTTCCAAACAAAACACAGTATCTAAACTGTGTCTAGTTAAAGCTAT GGTGATGGCTGGCATGGAAATGTCTCCAAAGGCTTAGATATTTGAAAACTTGGTCCCCAGTTAGTGCATCTTGGGGGAG GCTTATAAGGTGTCTATGTTGCTGGACAAAGTGTGACTCCAGAGGAGTGTGTTTGCAGTTTTTAAAGTCATGTGCTACTCCT GTTCACTCTACTCAGCCTGTGGCTGGAGATGTGGGCTCTCAGCTGCCCTGCCTCCATGTCTGTCTGTAAATAGAGTTCCC AACTGTGATATTGATGGAGTCTTACCTCTCTGAACCTTAAGCCCCAAATAAATCCTTCCTTCTAT	YPKVERERIEYLHAKLLEKRSK QPLREADGKPSLYFKKIHFVFP VLKMIRKKQTI PANEDDL

File - 02

SUBSTITUTE SHEET (RULE 26)

Nucleotide Sequence (5'-3')		ORFs
TAGGTGGCAGTGGGGAAAGACATTTGGAGGACGTGTTTACGAGCGTGAGGTACAAATGAATGTGCTGGCATTCAACAGA CAGTCCACTACGGTGTGTTTATGCAATATGTAAGCTCAAGGAACAGGAAATAGAAATATTTGTGTGATGAGAGAAATG TATTTACAGAGGCATCGAACTAAATCAACAGTTACATTTCAATTTTATAACCCAGCTAGAGTGAATGGCGTGATCT CGGCTCACTGCAACCTCCACCTCCAGATTCAAGCACTCTCTGCTCCCTCAGCTCCCGAGTAGCTGGGATTAACAAGCACCC ACCACATACATCAGCTAAATTTTGTATTTTAGTAGACCGGGGTTTACCATCTTGCCAGGCTGATCTTGAACCTCTT GAGTCATGATCCACCGCCTCAGCCTCCCAAAGTGTGGGATTAAGGCCCTTGTTCAGCCACTGCACCTGGCCCTT ATTTGTGTTTGTGTTTCTAATATACTTTTGATGTAATCAGCTTGAGAAAGCAACACAAATTTCAAATCCTATCTTCTAGATG CAAGCAG	SEQ ID NO. 85	TFGKLYPEGRLRLLAQAEFDQM KNVADHYGVYKPLFEAVGGSGG KTLEDVFYEREVQNMVLAFNRO FHYGVFYAYVKLKEQEIRNIVW IAECISQRHRTKINSYIPIL
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FILE - 04

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FIG. 85

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SEQUENCE LISTING

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<212> DNA
<213> Mus musculus

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<211> 2382
<212> DNA
<213> Mus musculus

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<211> 1072
<212> DNA
<213> Mus musculus

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<210> 18
<211> 5400
<212> DNA
<213> Mus musculus

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<212> DNA
<213> Mus musculus

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<213> Mus musculus

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<213> Mus musculus
<400> 22

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<210> 23
 <211> 1660
 <212> DNA
 <213> Mus musculus

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<210> 24
<211> 1455
<212> DNA
<213> Mus musculus

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<210> 25
<211> 3168
<212> DNA
<213> Mus musculus

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<213> Mus musculus

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<213> Mus musculus

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Mus musculus

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 <212> DNA
 <213> Mus musculus

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
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<210> 92
 <211> 4395
 <212> DNA
 <213> Artificial

<220>
 <223> pCMX-HA expression vector

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 ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240
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<210> 93
 <211> 439
 <212> PRT
 <213> Mus musculus

<400> 93

Met Glu Pro Trp Cys Gly Ala Glu Val Arg Gly Gln Gly Pro Gln Gly
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Pro Arg Val Pro Gly Ala Ser Arg Ser Arg Ser Arg Ala Leu Leu Leu
 20 25 30

Leu Leu Leu Leu Leu Leu Leu Leu Pro Arg Arg Pro Ala Gly Glu
 35 40 45

Arg Ile Arg Pro Arg Arg Pro Pro Arg His Ala His Pro Arg Pro Pro
 50 55 60

Leu Thr Arg Trp Arg Pro Ser Thr Gly Tyr Leu Ala Ala Gly Ala Ser
65 70 75 80

Pro Gly Thr Leu Ser Thr Thr Val Pro Thr Gly Pro Gly Val Ser Cys
85 90 95

Gly Ser Arg Gly Ile Cys Pro Ser Gly Arg Leu Arg Leu Pro Arg Gln
100 105 110

Ala Gln Thr Asn Gln Thr Thr Thr Ala Pro Pro Asn Ser Gln Thr Met
115 120 125

Ala Pro Leu Lys Thr Val Gly Thr Leu Gly Met Met Asp Thr Thr Gly
130 135 140

Ser Val Leu Lys Thr Val His Ser Ser Asn Leu Pro Phe Cys Gly Ser
145 150 155 160

Ser His Glu Pro Asp Pro Thr Leu Arg Asp Pro Glu Ala Met Thr Arg
165 170 175

Arg Trp Pro Trp Met Val Ser Val Gln Ala Asn Gly Ser His Ile Cys
180 185 190

Ala Gly Ile Leu Ile Ala Ser Gln Trp Val Leu Thr Val Ala His Cys
195 200 205

Leu Ser Gln Asn His Val Asn Tyr Ile Val Arg Ala Gly Ser Pro Trp
210 215 220

Ile Asn Gln Thr Ala Gly Thr Ser Ser Asp Val Pro Val His Arg Val
225 230 235 240

Ile Ile Asn His Gly Tyr Gln Pro Arg Arg Tyr Trp Ser Trp Val Gly
245 250 255

Arg Ala His Asp Ile Gly Leu Leu Lys Leu Lys Trp Gly Leu Lys Tyr
260 265 270

Ser Lys Tyr Val Trp Pro Ile Cys Leu Pro Gly Leu Asp Tyr Val Val
275 280 285

Glu Asp Ser Ser Leu Cys Thr Val Thr Gly Trp Gly Tyr Pro Arg Ala
290 295 300

Asn Gly Ile Trp Pro Gln Phe Gln Ser Leu Gln Glu Lys Glu Val Ser
305 310 315 320

Ile Leu Asn Ser Lys Lys Cys Asp His Phe Tyr His Lys Phe Ser Arg
325 330 335

Ile Ser Ser Leu Val Arg Ile Ile Asn Pro Gln Met Ile Cys Ala Ser
340 345 350

Asp Asn Asn Arg Glu Glu Phe Cys Tyr Glu Ile Thr Gly Glu Pro Leu
355 360 365

Val Cys Ser Ser Asp Gly Thr Trp Tyr Leu Val Gly Met Met Ser Trp
370 375 380

Gly Pro Gly Cys Lys Lys Ser Glu Ala Pro Pro Ile Phe Leu Gln Val
385 390 395 400

Ser Tyr Tyr Arg Pro Trp Ile Trp Asp Arg Leu Ser Gly Glu Pro Leu
405 410 415

Ala Leu Pro Ala Pro Ser Arg Thr Leu Leu Leu Ala Phe Leu Leu Leu
420 425 430

Leu Ile Leu Leu Gly Thr Leu
435

<210> 94

<211> 350

<212> PRT

<213> Mus musculus

<400> 94

Met Leu Glu Thr Ala Glu Leu Tyr Phe Asn Val Asp His Gly Tyr Leu
1 5 10 15

Glu Gly Leu Val Arg Gly Cys Lys Ala Ser Leu Leu Thr Gln Gln Asp
20 25 30

Tyr Val Asn Leu Val Gln Cys Glu Thr Leu Glu Asp Leu Lys Ile His
35 40 45

Leu Gln Thr Thr Asp Tyr Gly Asn Phe Leu Ala Asn Glu Thr Asn Pro
50 55 60

Leu Thr Val Ser Lys Ile Asp Thr Glu Met Arg Lys Lys Leu Cys Arg
 65 70 75 80
 Glu Phe Asp Tyr Phe Arg Asn His Ser Leu Glu Pro Leu Ser Thr Phe
 85 90 95
 Leu Thr Tyr Met Thr Cys Ser Tyr Met Ile Asp Asn Ile Ile Leu Leu
 100 105 110
 Met Asn Gly Ala Leu Gln Lys Lys Ser Val Lys Glu Val Leu Ala Lys
 115 120 125
 Cys His Pro Leu Gly Arg Phe Thr Glu Met Glu Ala Val Asn Ile Ala
 130 135 140
 Glu Thr Pro Ser Asp Leu Phe Lys Ala Val Leu Val Glu Thr Pro Leu
 145 150 155 160
 Ala Pro Phe Phe Gln Asp Cys Met Ser Glu Asn Thr Leu Asp Glu Leu
 165 170 175
 Asn Ile Glu Leu Leu Arg Asn Lys Leu Tyr Lys Ser Tyr Leu Glu Ala
 180 185 190
 Phe Tyr Lys Phe Cys Lys Asp His Gly Asp Val Thr Ala Asp Val Met
 195 200 205
 Cys Pro Ile Leu Glu Phe Glu Ala Asp Arg Arg Ala Leu Ile Ile Thr
 210 215 220
 Leu Asn Ser Phe Gly Thr Glu Leu Ser Lys Glu Asp Arg Glu Thr Leu
 225 230 235 240
 Phe Pro Thr Cys Gly Arg Leu Tyr Pro Glu Gly Leu Arg Leu Leu Ala
 245 250 255
 Gln Ala Glu Asp Phe Glu Gln Met Lys Arg Val Ala Asp Asn Tyr Gly
 260 265 270
 Val Tyr Lys Pro Leu Phe Asp Ala Val Gly Gly Ser Gly Gly Lys Thr
 275 280 285
 Leu Glu Asp Val Phe Tyr Glu Arg Glu Val Gln Met Asn Val Leu Ala
 290 295 300

Phe Asn Arg Gln Leu His Tyr Gly Val Phe Tyr Ala Tyr Val Lys Leu
305 310 315 320

Lys Glu Gln Glu Met Arg Asn Ile Val Trp Ile Ala Glu Cys Ile Ser
325 330 335

Gln Arg His Arg Thr Lys Ile Asn Ser Tyr Ile Pro Ile Leu
340 345 350

<210> 95
<211> 400
<212> PRT
<213> Mus musculus

<400> 95

Met Gly Pro Arg Ser Pro Ala Ala Ala Leu Leu Val Leu Leu Cys Val
1 5 10 15

Gly Cys Ala Pro Thr Pro Gly Arg Gly Gln Tyr Glu Arg Tyr Ser Phe
20 25 30

Arg Asn Phe Pro Arg Asp Glu Leu Met Pro Leu Glu Ser Ala Tyr Arg
35 40 45

His Ala Leu Asp Gln Tyr Ser Gly Glu His Trp Ala Glu Ser Val Gly
50 55 60

Tyr Leu Glu Val Ser Leu Arg Leu His Arg Leu Leu Arg Asp Ser Glu
65 70 75 80

Ala Phe Cys His Arg Asn Cys Ser Ala Ala Thr Pro Ala Pro Ala Pro
85 90 95

Ala Gly Pro Ala Ser His Ala Glu Leu Arg Leu Phe Gly Ser Val Leu
100 105 110

Arg Arg Ala Gln Cys Leu Lys Arg Cys Lys Gln Gly Leu Pro Ala Phe
115 120 125

Arg Gln Ser Gln Pro Ser Arg Ser Val Leu Ala Asp Phe Gln Gln Arg
130 135 140

Glu Pro Tyr Lys Phe Leu Gln Phe Ala Tyr Phe Lys Ala Asn Asp Leu
145 150 155 160

Pro Lys Ala Ile Ala Ala Ala His Thr Tyr Leu Leu Lys His Pro Asp
 165 170 175
 Asp Glu Met Met Lys Arg Asn Met Glu Tyr Tyr Lys Ser Leu Pro Gly
 180 185 190
 Ala Glu Asp His Ile Lys Asp Leu Glu Thr Lys Ser Tyr Glu Ser Leu
 195 200 205
 Phe Val Arg Ala Val Arg Ala Tyr Asn Gly Glu Asn Trp Arg Thr Ser
 210 215 220
 Ile Ser Asp Met Glu Leu Ala Leu Pro Asp Phe Leu Lys Ala Phe Tyr
 225 230 235 240
 Glu Cys Leu Ala Ala Cys Glu Gly Ser Arg Glu Ile Lys Asp Phe Lys
 245 250 255
 Asp Phe Tyr Leu Ser Ile Ala Asp His Tyr Val Glu Val Leu Glu Cys
 260 265 270
 Lys Ile Arg Cys Glu Glu Thr Leu Thr Pro Val Ile Gly Gly Tyr Pro
 275 280 285
 Val Glu Lys Phe Val Ala Thr Met Tyr His Tyr Leu Gln Phe Ala Tyr
 290 295 300
 Tyr Lys Leu Asn Asp Leu Lys Asn Ala Ala Pro Cys Ala Val Ser Tyr
 305 310 315 320
 Leu Leu Phe Asp Gln Ser Asp Arg Val Met Gln Gln Asn Leu Val Tyr
 325 330 335
 Tyr Gln Tyr His Arg Asp Lys Trp Gly Leu Ser Asp Glu His Phe Gln
 340 345 350
 Pro Arg Pro Glu Ala Val Gln Phe Phe Asn Val Thr Thr Leu Gln Lys
 355 360 365
 Glu Leu Tyr Asp Phe Ala Gln Glu His Leu Met Asp Asp Asp Glu Gly
 370 375 380
 Glu Val Val Glu Tyr Val Asp Asp Leu Leu Glu Thr Glu Glu Ser Ala
 385 390 395 400

<210> 96
 <211> 266
 <212> PRT
 <213> Mus musculus

<400> 96

Met Lys Leu Asn Glu Arg Ser Leu Ala Phe Tyr Ala Thr Cys Asp Ala
 1 5 10 15

Pro Val Asp Asn Ala Gly Phe Leu Tyr Lys Arg Gly Gly Arg Gly Thr
 20 25 30

Gly Ser His Arg Arg Trp Phe Val Leu Arg Gly Asn Ile Leu Phe Tyr
 35 40 45

Phe Glu Ala Glu Gly Ser Arg Glu Pro Leu Gly Val Ile Leu Leu Glu
 50 55 60

Gly Cys Thr Val Glu Leu Val Asp Ala Arg Glu Glu Phe Ala Phe Ala
 65 70 75 80

Val Arg Phe Ala Gly Gly Arg Ser Arg Pro Tyr Val Leu Ala Ala Asp
 85 90 95

Ser Gln Ala Ala Leu Glu Gly Trp Val Lys Ala Leu Ser Arg Ala Ser
 100 105 110

Phe His Tyr Leu Arg Leu Val Val Arg Glu Leu Glu Gln Gln Leu Ala
 115 120 125

Ala Met Arg Glu Gly Ser Pro Ala Asn Ala Leu Pro Ala Asn Pro Ser
 130 135 140

Pro Val Leu Thr Gln Arg Pro Lys Glu Asn Gly Trp Val Val Trp Ser
 145 150 155 160

Thr Leu Pro Glu Gln Pro Ser Val Ala Pro Gln Arg Pro Pro Pro Leu
 165 170 175

Pro Pro Arg Arg Arg Ala Ser Ala Ala Asn Gly Pro Leu Ala Ser Phe
 180 185 190

Ala Gln Leu His Ala Arg Tyr Gly Leu Glu Val Gln Ala Leu Arg Asp
 195 200 205

Gln Trp Arg Gly Gly Gln Ala Gly Leu Ala Ser Leu Glu Val Pro Trp

210 215 220
 His Pro Gly Ser Ala Glu Thr Gln Thr Gln Asp Gln Pro Ala Leu Arg
 225 230 235 240
 Gly His Ser Gly Cys Lys Val Leu His Val Phe Arg Ser Val Glu Trp
 245 250 255
 Pro Val Cys Asn Pro Gly Ser Gln Gly Thr
 260 265

 <210> 97
 <211> 447
 <212> PRT
 <213> Mus musculus

 <400> 97
 Met Arg Glu Ile Val His Ile Gln Ala Gly Gln Cys Gly Asn Gln Ile
 1 5 10 15
 Gly Thr Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Gln
 20 25 30
 Ala Gly Gly Tyr Val Gly Asp Ser Ala Leu Gln Leu Glu Arg Ile Ser
 35 40 45
 Val Tyr Tyr Asn Glu Ser Ser Ser Lys Lys Tyr Val Pro Arg Ala Ala
 50 55 60
 Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Pro
 65 70 75 80
 Phe Gly Gln Leu Phe Arg Pro Asp Asn Phe Ile Phe Gly Gln Thr Gly
 85 90 95
 Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
 100 105 110
 Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Cys Glu His Cys Asp
 115 120 125
 Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
 130 135 140
 Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Ile Arg Glu Glu Tyr Pro
 145 150 155 160

Asp Arg Ile Met Asn Thr Phe Ser Val Met Pro Ser Pro Lys Val Ser
 165 170 175
 Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Val His Gln Leu
 180 185 190
 Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
 195 200 205
 Asp Ile Cys Phe Arg Thr Leu Lys Leu Thr Thr Pro Thr Tyr Gly Asp
 210 215 220
 Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Ser Leu
 225 230 235 240
 Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
 245 250 255
 Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
 260 265 270
 Leu Thr Ala Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
 275 280 285
 Leu Thr Gln Gln Met Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
 290 295 300
 Pro Arg His Gly Arg Tyr Leu Thr Val Ala Thr Val Phe Arg Gly Pro
 305 310 315 320
 Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Ala Ile Gln Asn Lys
 325 330 335
 Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Val Ala
 340 345 350
 Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ala Ser Thr Phe Ile
 355 360 365
 Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
 370 375 380
 Phe Ser Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Phe Thr Gly
 385 390 395 400

Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
 405 410 415

Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Val Asn Asp
 420 425 430

Gly Glu Glu Ala Phe Glu Asp Glu Asp Glu Glu Glu Ile Asn Glu
 435 440 445

<210> 98
 <211> 202
 <212> PRT
 <213> Mus musculus

<400> 98

Met Ser Cys Val Pro Trp Lys Gly Asp Lys Ala Lys Ala Glu Ser Ser
 1 5 10 15

Asp Leu Pro Gln Ala Ala Pro Pro Gln Ile Tyr His Glu Lys Gln Arg
 20 25 30

Arg Glu Leu Cys Ala Leu His Ala Leu Asn Asn Val Phe Gln Asp Ser
 35 40 45

Asn Ala Phe Thr Arg Glu Thr Leu Gln Glu Ile Phe Gln Arg Leu Ser
 50 55 60

Pro Asn Thr Met Val Thr Pro His Lys Lys Ser Met Leu Gly Asn Gly
 65 70 75 80

Asn Tyr Asp Val Asn Val Ile Met Ala Ala Leu Gln Thr Lys Gly Tyr
 85 90 95

Glu Ala Val Trp Trp Asp Lys Arg Arg Asp Val Gly Val Ile Ala Leu
 100 105 110

Thr Asn Val Met Gly Phe Ile Met Asn Leu Pro Ser Ser Leu Cys Trp
 115 120 125

Gly Pro Leu Lys Leu Pro Leu Lys Arg Gln His Trp Ile Cys Val Arg
 130 135 140

Glu Val Gly Gly Ala Tyr Tyr Asn Leu Asp Ser Lys Leu Lys Met Pro
 145 150 155 160

Glu Trp Ile Gly Gly Glu Ser Glu Leu Arg Lys Phe Leu Lys Tyr His
165 170 175

Leu Arg Gly Lys Asn Cys Glu Leu Leu Leu Val Val Pro Glu Glu Val
180 185 190

Glu Ala His Gln Ser Trp Arg Ala Asp Val
195 200

<210> 99
<211> 191
<212> PRT
<213> Mus musculus

<400> 99

Met Ser Ala Glu Leu Glu Leu Leu Trp Pro Val Ser Gly Leu Leu Leu
1 5 10 15

Leu Leu Leu Gly Ala Thr Ala Trp Leu Cys Val His Cys Ser Arg Pro
20 25 30

Gly Val Lys Arg Asn Glu Lys Ile Tyr Glu Gln Arg Asn Arg Gln Glu
35 40 45

Asn Ala Gln Ser Ser Ala Ala Ala Gln Thr Tyr Ser Leu Ala Arg Gln
50 55 60

Val Trp Pro Gly Pro Gln Met Asp Thr Ala Pro Asn Lys Ser Phe Glu
65 70 75 80

Arg Lys Asn Lys Met Leu Phe Ser His Leu Glu Gly Ser Asn Gln Glu
85 90 95

Pro Asp Ala Ala Tyr Val Asp Pro Ile Pro Thr Asn Tyr Tyr Asn Trp
100 105 110

Gly Cys Phe Gln Lys Pro Ser Glu Asp Asp Asp Ser Asn Ser Tyr Glu
115 120 125

Asn Val Leu Val Cys Lys Pro Ser Thr Pro Glu Ser Gly Val Glu Asp
130 135 140

Phe Glu Asp Tyr Gln Asn Ser Val Ser Ile His Gln Trp Arg Glu Ser
145 150 155 160

Lys Arg Thr Met Gly Ala Pro Met Ser Leu Ser Gly Ser Pro Asp Glu
 165 170 175

Glu Pro Asp Tyr Val Asn Gly Asp Val Ala Ala Ala Glu Asn Ile
 180 185 190

<210> 100
 <211> 163
 <212> PRT
 <213> Mus musculus

<400> 100

Met Met Pro Gly Gln Ile Pro Asp Pro Ser Val Thr Ala Gly Ser Leu
 1 5 10 15

Pro Gly Leu Gly Pro Leu Thr Gly Leu Pro Ser Ser Ala Leu Thr Thr
 20 25 30

Glu Glu Leu Lys Tyr Ala Asp Ile Arg Asn Ile Gly Ala Met Ile Ala
 35 40 45

Pro Leu His Phe Leu Glu Val Lys Leu Gly Lys Arg Pro Gln Pro Val
 50 55 60

Lys Ser Glu Leu Asp Glu Glu Glu Arg Arg Lys Arg Arg Arg Glu
 65 70 75 80

Lys Asn Lys Val Ala Ala Ala Arg Cys Arg Asn Lys Lys Lys Glu Arg
 85 90 95

Thr Glu Phe Leu Gln Arg Glu Ser Glu Arg Leu Glu Leu Met Asn Ala
 100 105 110

Glu Leu Lys Thr Gln Ile Glu Glu Leu Lys Leu Glu Arg Gln Gln Leu
 115 120 125

Ile Leu Met Leu Asn Arg His Arg Pro Thr Cys Ile Val Arg Thr Asp
 130 135 140

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

Asp Lys Lys

<210> 101

<211> 627
 <212> PRT
 <213> Mus musculus

<400> 101

Met Ala Gly Glu Arg Pro Pro Leu Arg Gly Pro Gly Pro Gly Glu Ala
 1 5 10 15

Pro Gly Glu Gly Pro Gly Gly Ala Gly Gly Gly Pro Gly Arg Gly Arg
 20 25 30

Pro Ser Ser Tyr Arg Ala Leu Arg Ser Ala Val Ser Ser Leu Ala Arg
 35 40 45

Val Asp Asp Phe Asp Cys Ala Glu Lys Ile Gly Ala Gly Phe Phe Ser
 50 55 60

Glu Val Tyr Lys Val Arg His Arg Gln Ser Gly Gln Val Met Val Leu
 65 70 75 80

Lys Met Asn Lys Leu Pro Ser Asn Arg Ser Asn Thr Leu Arg Glu Val
 85 90 95

Gln Leu Met Asn Arg Leu Arg His Pro Asn Ile Leu Arg Phe Met Gly
 100 105 110

Val Cys Val His Gln Gly Gln Leu His Ala Leu Thr Glu Tyr Met Asn
 115 120 125

Gly Gly Thr Leu Glu Gln Leu Leu Ser Ser Pro Glu Pro Leu Ser Trp
 130 135 140

Pro Val Arg Leu His Leu Ala Leu Asp Ile Ala Gln Gly Leu Arg Tyr
 145 150 155 160

Leu His Ala Lys Gly Val Phe His Arg Asp Leu Thr Ser Lys Asn Cys
 165 170 175

Leu Val Arg Arg Glu Asp Arg Gly Phe Thr Ala Val Val Gly Asp Phe
 180 185 190

Gly Leu Ala Glu Lys Ile Pro Val Tyr Arg Glu Gly Thr Arg Lys Glu
 195 200 205

Pro Leu Ala Val Val Gly Ser Pro Tyr Trp Met Ala Pro Glu Val Leu
 210 215 220

Arg Gly Glu Leu Tyr Asp Glu Lys Ala Asp Val Phe Ala Phe Gly Ile
 225 230 235 240
 Val Leu Cys Glu Leu Ile Ala Arg Val Pro Ala Asp Pro Asp Tyr Leu
 245 250 255
 Pro Arg Thr Glu Asp Phe Gly Leu Asp Val Pro Ala Phe Arg Thr Leu
 260 265 270
 Val Gly Asn Asp Cys Pro Leu Pro Phe Leu Leu Leu Ala Ile His Cys
 275 280 285
 Cys Ser Met Glu Pro Ser Thr Arg Ala Pro Phe Thr Glu Ile Thr Gln
 290 295 300
 His Leu Glu Gln Ile Leu Glu Gln Gln Pro Glu Ala Thr Pro Leu Ala
 305 310 315 320
 Lys Pro Pro Leu Thr Lys Ala Pro Leu Thr Tyr Asn Gln Gly Ser Val
 325 330 335
 Pro Arg Gly Gly Pro Ser Ala Thr Leu Pro Arg Pro Asp Pro Arg Leu
 340 345 350
 Ser Arg Ser Arg Ser Asp Leu Phe Leu Pro Pro Ser Pro Glu Ser Pro
 355 360 365
 Pro Ser Trp Gly Asp Asn Leu Thr Arg Val Asn Pro Phe Ser Leu Arg
 370 375 380
 Glu Asp Leu Arg Gly Gly Lys Ile Lys Leu Leu Asp Thr Pro Cys Lys
 385 390 395 400
 Pro Ala Thr Pro Leu Pro Leu Val Pro Pro Ser Pro Leu Thr Ser Thr
 405 410 415
 Gln Leu Pro Leu Val Thr Thr Pro Asp Ile Leu Val Gln Pro Glu Thr
 420 425 430
 Pro Val Arg Arg Cys Arg Ser Leu Pro Ser Ser Pro Glu Leu Pro Arg
 435 440 445
 Arg Met Glu Thr Ala Leu Pro Gly Pro Gly Pro Ser Pro Met Gly Pro
 450 455 460

Thr Glu Glu Arg Met Asp Cys Glu Gly Ser Ser Pro Glu Pro Glu Pro
465 470 475 480

Pro Gly Leu Ala Pro Gln Leu Pro Leu Ala Val Ala Thr Asp Asn Phe
485 490 495

Ile Ser Thr Cys Ser Ser Ala Ser Gln Pro Trp Ser Pro Arg Ser Gly
500 505 510

Pro Pro Leu Asn Asn Asn Pro Pro Ala Val Val Val Asn Ser Pro Gln
515 520 525

Gly Trp Ala Arg Glu Pro Trp Asn Arg Ala Gln His Ser Leu Pro Arg
530 535 540

Ala Ala Ala Leu Glu Gln Thr Glu Pro Ser Pro Pro Pro Ser Ala Pro
545 550 555 560

Arg Glu Pro Glu Glu Gly Leu Pro Cys Pro Gly Cys Cys Leu Gly Pro
565 570 575

Phe Ser Phe Gly Phe Leu Ser Met Cys Pro Arg Pro Thr Pro Ala Val
580 585 590

Ala Arg Tyr Arg Asn Leu Asn Cys Glu Ala Gly Ser Leu Leu Cys His
595 600 605

Arg Gly His His Ala Lys Pro Pro Thr Pro Ser Leu Gln Leu Pro Gly
610 615 620

Ala Arg Ser
625

<210> 102
<211> 566
<212> PRT
<213> Mus musculus

<400> 102

Met Thr Ile Leu Pro Lys Lys Lys Pro Pro Pro Pro Asp Ala Asp Pro
1 5 10 15

Ala Asn Glu Pro Pro Pro Pro Gly Pro Leu Pro Pro Ala Pro Arg Arg
20 25 30

Gly Ala Gly Val Gly Val Gly Gly Gly Gly Thr Gly Val Gly Gly Gly
 35 40 45

Glu Arg Asp Arg Asp Ser Gly Val Val Gly Ala Arg Pro Arg Ala Ser
 50 55 60

Pro Pro Pro Gln Gly Pro Leu Pro Gly Pro Pro Gly Ala Leu His Arg
 65 70 75 80

Trp Ala Leu Ala Val Pro Pro Gly Ala Val Ala Gly Pro Arg Pro Gln
 85 90 95

Gln Ala Ser Pro Pro Pro Cys Gly Gly Pro Gly Gly Pro Gly Gly Gly
 100 105 110

Pro Gly Asp Ala Leu Gly Ala Thr Thr Ala Gly Val Gly Ala Ala Gly
 115 120 125

Val Val Val Gly Val Gly Gly Thr Val Gly Val Gly Gly Cys Cys Ser
 130 135 140

Gly Pro Gly His Ser Lys Arg Arg Arg Gln Ala Pro Gly Val Gly Ala
 145 150 155 160

Val Gly Gly Ala Ser Pro Glu Arg Glu Glu Val Gly Ala Gly Tyr Asn
 165 170 175

Ser Glu Asp Glu Tyr Glu Ala Ala Ala Ala Arg Ile Glu Ala Met Asp
 180 185 190

Pro Ala Thr Val Glu Gln Gln Glu His Trp Phe Glu Lys Ala Leu Arg
 195 200 205

Asp Lys Lys Gly Phe Ile Ile Lys Gln Met Lys Glu Asp Gly Ala Cys
 210 215 220

Leu Phe Arg Ala Val Ala Asp Gln Val Tyr Gly Asp Gln Asp Met His
 225 230 235 240

Glu Val Val Arg Lys His Cys Met Asp Tyr Leu Met Lys Asn Ala Asp
 245 250 255

Tyr Phe Ser Asn Tyr Val Thr Glu Asp Phe Thr Thr Tyr Ile Asn Arg
 260 265 270

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

Glu Cys Arg Ala Leu Ile Gln Gln Met Ser Pro Ser Ala Phe Gly Leu
 515 520 525

Asn Asp Trp Asp Asp Asp Glu Ile Leu Ala Ser Val Leu Ala Val Ser
 530 535 540

Gln Gln Glu Tyr Leu Asp Ser Met Lys Lys Asn Lys Val His Arg Glu
 545 550 555 560

Pro Pro Pro Asp Lys Ser
 565

<210> 103
 <211> 102
 <212> PRT
 <213> Mus musculus

<400> 103

Phe Ile Cys Glu Ala Ser Val Gly Val Asp Arg Ser Cys Pro Leu Thr
 1 5 10 15

Val Gln Ile Asp Ile Thr Ile Arg Gly Gln Leu Gly Ile Ala Pro Pro
 20 25 30

Ser Arg Ala Cys Thr Val Lys Met Gln Leu Met Val Leu Ala Val Glu
 35 40 45

Cys Gly Ser Thr Asp Arg Gln Ile Ser Thr Pro Pro Gln Leu Arg Gln
 50 55 60

Pro Ser Pro Ala Ala Thr Gln Leu Leu Val Ser Ala Lys Arg Ser Ala
 65 70 75 80

Glu Thr Arg Ser Leu His Leu Glu Gln His Leu Gly Thr Ser Leu Gln
 85 90 95

Val Arg Thr Leu Ile Asp
 100

<210> 104
 <211> 331
 <212> PRT
 <213> Mus musculus

<400> 104

Met Lys Ser Thr Ser Arg Asp Ala Val Leu Phe Phe Ser Glu Ser Leu

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

Lys Ala Leu Gln Phe Leu Glu Gln Val Lys Val Ser Lys Glu Met Asp
130 135 140

Arg Glu Thr Leu Ile Asp Val Ala Arg Thr Ser Leu Arg Thr Lys Val
145 150 155 160

His Ala Glu Leu Ala Asp Val Leu Thr Glu Ala Val Val Asp Ser Ile
165 170 175

Leu Ala Ile Arg Lys Lys Asp Glu Pro Ile Asp Leu Phe Met Val Glu
180 185 190

Ile Met Glu Met Lys His Lys Ser Glu Thr Asp Thr Ser Leu Ile Arg
195 200 205

Gly Leu Val Leu Asp His Gly Ala Arg His Pro Asp Met Lys Lys Arg
210 215 220

Val Glu Asn Ala Tyr Ile Leu Thr Cys Asn Val Ser Leu Glu Tyr Glu
225 230 235 240

Lys Thr Glu Val Asn Ser Gly Phe Phe Tyr Lys Ser Ala Glu Glu Arg
245 250 255

Glu Lys Leu Val Lys Ala Glu Arg Lys Phe Ile Glu Asp Arg Val Lys
260 265 270

Lys Ile Ile Glu Leu Lys Lys Lys Val Cys Gly Asp Ser Asp Lys Gly
275 280 285

Phe Val Val Ile Asn Gln Lys Gly Ile Asp Pro Phe Ser Leu Asp Ala
290 295 300

Leu Ala Lys Glu Gly Ile Val Ala Leu Arg Arg Ala Lys Arg Arg Asn
305 310 315 320

Met Glu Arg Leu Thr Leu Ala Cys Gly Gly Ile Ala Leu Asn Ser Phe
325 330 335

Asp Asp Leu Asn Pro Asp Cys Leu Gly His Ala Gly Leu Val Tyr Glu
340 345 350

Tyr Thr Leu Gly Glu Glu Lys Phe Thr Phe Ile Glu Lys Cys Asn Asn
355 360 365

Pro Arg Ser Val Thr Leu Leu Val Lys Gly Pro Asn Lys His Thr Leu
370 375 380

Thr Gln Ile Lys Asp Ala Ile Arg Asp Gly Leu Arg Ala Val Lys Asn
385 390 395 400

Ala Ile Asp Asp Gly Cys Val Val Pro Gly Ala Gly Ala Val Glu Val
405 410 415

Ala Leu Ala Glu Ala Leu Ile Lys Tyr Lys Pro Ser Val Lys Gly Arg
420 425 430

Ala Gln Leu Gly Val Gln Ala Phe Ala Asp Ala Leu Leu Ile Ile Pro
435 440 445

Lys Val Leu Ala Gln Asn Ser Gly Phe Asp Leu Gln Glu Thr Leu Val
450 455 460

Lys Val Gln Ala Glu His Ser Glu Ser Gly Gln Leu Val Gly Val Asp
465 470 475 480

Leu Ser Thr Gly Glu Pro Met Val Ala Ala Glu Met Gly Val Trp Asp
485 490 495

Asn Tyr Cys Val Lys Lys Gln Leu Leu His Ser Cys Thr Val Ile Ala
500 505 510

Thr Asn Ile Leu Leu Val Asp Glu Ile Met Arg Ala Gly Met Ser Ser
515 520 525

Leu Lys Gly
530

<210> 106
<211> 144
<212> PRT
<213> Mus musculus

<400> 106

Met Ala Asp Ser Ala Gln Val Pro Thr Leu Val Tyr Leu Val Thr Gly
1 5 10 15

Gly Cys Gly Phe Leu Gly Glu His Ile Val Arg Met Leu Leu Glu Arg
20 25 30

Glu Pro Arg Leu Arg Glu Leu Arg Val Phe Asp Leu His Leu Ser Ser
 35 40 45

Trp Leu Glu Glu Leu Lys Ala Gly Pro Val Gln Val Thr Ala Ile Gln
 50 55 60

Gly Asp Val Thr Gln Ala His Glu Val Ala Ala Ala Met Ser Gly Ser
 65 70 75 80

His Val Val Ile His Thr Ala Gly Leu Val Asp Val Phe Gly Lys Ala
 85 90 95

Ser Pro Lys Thr Ile His Lys Val Asn Val Gln Gly Thr Gln Asn Val
 100 105 110

Ile Asp Ala Cys Val Gln Thr Gly Thr Gln Tyr Leu Val Tyr Thr Ser
 115 120 125

Ser Met Glu Val Val Gly Pro Asn Ile Lys Gly His Pro Phe Tyr Arg
 130 135 140

<210> 107
 <211> 313
 <212> PRT
 <213> Mus musculus

<400> 107

Met Ala Ala Thr Ala Ala Val Ser Gly Val Leu Gly Arg Leu Gly Trp
 1 5 10 15

Arg Leu Leu Gln Leu Arg Cys Leu Pro Val Ala Arg Cys Arg Pro Ala
 20 25 30

Leu Val Pro Arg Ala Phe His Thr Ala Val Gly Phe Arg Ser Ser Glu
 35 40 45

Glu Gln Lys Gln Gln Pro Pro His Ser Ser Ser Gln Gln His Ser Glu
 50 55 60

Thr Gln Gly Pro Glu Phe Ser Arg Pro Pro Pro Arg Tyr Thr Asp Gln
 65 70 75 80

Ser Gly Glu Glu Glu Glu Asp Tyr Glu Ser Glu Glu Gln Leu Gln His
 85 90 95

Arg Ile Leu Thr Ala Ala Leu Glu Phe Val Pro Ala His Gly Trp Thr
100 105 110

Ala Glu Ala Ile Ala Glu Gly Ala Gln Ser Leu Gly Leu Ser Ser Ala
115 120 125

Ala Ala Ser Met Phe Gly Ser Asp Gly Ser Glu Leu Ile Leu His Phe
130 135 140

Val Thr Gln Cys Asn Ala Arg Leu Asn Gln Val Leu Glu Glu Glu Gln
145 150 155 160

Lys Leu Val Gln Leu Gly Gln Ala Glu Lys Arg Lys Thr Asp Gln Phe
165 170 175

Leu Arg Asp Ala Val Glu Thr Arg Leu Arg Met Leu Ile Pro Tyr Ile
180 185 190

Glu His Trp Pro Arg Ala Leu Ser Ile Leu Leu Leu Pro His Asn Ile
195 200 205

Pro Pro Ser Leu Asn Leu Leu Thr Ser Met Val Asp Asp Met Trp His
210 215 220

Tyr Ala Gly Asp Gln Ser Thr Asp Phe Asn Trp Tyr Thr Arg Arg Ala
225 230 235 240

Val Leu Ala Gly Ile Tyr Asn Thr Thr Glu Leu Val Met Met Gln Asp
245 250 255

Ser Ser Pro Asp Phe Glu Asp Thr Trp Arg Phe Leu Glu Asn Arg Ile
260 265 270

Asn Asp Ala Met Asn Met Gly His Thr Ala Lys Gln Val Lys Ser Thr
275 280 285

Gly Glu Ala Leu Val Gln Gly Leu Met Gly Ala Ala Val Thr Leu Lys
290 295 300

Asn Leu Thr Gly Leu Asn Gln Arg Arg
305 310

<210> 108
<211> 914
<212> PRT
<213> Mus musculus

<400> 108

Met Asp Met Phe Pro Leu Thr Trp Val Phe Leu Ala Leu Tyr Phe Ser
 1 5 10 15

Gly His Glu Val Arg Ser Gln Gln Asp Pro Pro Cys Gly Gly Arg Pro
 20 25 30

Asn Ser Lys Asp Ala Gly Tyr Ile Thr Ser Pro Gly Tyr Pro Gln Asp
 35 40 45

Tyr Pro Ser His Gln Asn Cys Glu Trp Ile Val Tyr Ala Pro Glu Pro
 50 55 60

Asn Gln Lys Ile Val Leu Asn Phe Asn Pro His Phe Glu Ile Glu Lys
 65 70 75 80

His Asp Cys Lys Tyr Asp Phe Ile Glu Ile Arg Asp Gly Asp Ser Glu
 85 90 95

Ser Ala Asp Leu Leu Gly Lys His Cys Gly Asn Ile Ala Pro Pro Thr
 100 105 110

Ile Ile Ser Ser Gly Ser Val Leu Tyr Ile Lys Phe Thr Ser Asp Tyr
 115 120 125

Ala Arg Gln Gly Ala Gly Phe Ser Leu Arg Tyr Glu Ile Phe Lys Thr
 130 135 140

Gly Ser Glu Asp Cys Ser Lys Asn Phe Thr Ser Pro Asn Gly Thr Ile
 145 150 155 160

Glu Ser Pro Gly Phe Pro Glu Lys Tyr Pro His Asn Leu Asp Cys Thr
 165 170 175

Phe Thr Ile Leu Ala Lys Pro Arg Met Glu Ile Ile Leu Gln Phe Leu
 180 185 190

Thr Phe Asp Leu Glu His Asp Pro Leu Gln Val Gly Glu Gly Asp Cys
 195 200 205

Lys Tyr Asp Trp Leu Asp Ile Trp Asp Gly Ile Pro His Val Gly Pro
 210 215 220

Leu Ile Gly Lys Tyr Cys Gly Thr Lys Thr Pro Ser Lys Leu Arg Ser

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

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<210> 109
<211> 240
<212> PRT
<213> Mus musculus
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<400> 109

Met Ala Thr Asp Glu Leu Ala Ser Lys Leu Ser Arg Arg Leu Gln Met
 1 5 10 15

Glu Gly Glu Gly Gly Glu Ala Thr Glu Gln Pro Gly Leu Asn Gly Ala
 20 25 30

Ala Ala Ala Ala Ala Ala Glu Ala Pro Asp Glu Thr Ala Gln Ala Leu
 35 40 45

Gly Ser Ala Asp Asp Glu Leu Ser Ala Lys Leu Leu Arg Arg Ala Asp
 50 55 60

Leu Asn Gln Gly Ile Gly Glu Pro Gln Ser Pro Ser Arg Arg Val Phe
 65 70 75 80

Asn Pro Tyr Thr Glu Phe Lys Glu Phe Ser Arg Lys Gln Ile Lys Asp
 85 90 95

Met Glu Lys Met Phe Lys Gln Tyr Asp Ala Gly Arg Asp Gly Phe Ile
 100 105 110

Asp Leu Met Glu Leu Lys Leu Met Met Glu Lys Leu Gly Ala Pro Gln
 115 120 125

Thr His Leu Gly Leu Lys Ser Met Ile Gln Glu Val Asp Glu Asp Phe
 130 135 140

Asp Ser Lys Leu Ser Phe Arg Glu Phe Leu Leu Ile Phe Arg Lys Ala
 145 150 155 160

Ala Ala Gly Glu Leu Gln Glu Asp Ser Gly Leu His Val Leu Ala Arg
 165 170 175

Leu Ser Glu Ile Asp Val Ser Thr Glu Gly Val Lys Gly Ala Lys Asn
 180 185 190

Phe Phe Glu Ala Lys Val Gln Ala Ile Asn Val Ser Ser Arg Phe Glu
 195 200 205

Glu Glu Ile Lys Ala Glu Gln Glu Glu Arg Lys Lys Gln Ala Glu Glu
 210 215 220

Val Lys Gln Arg Lys Ala Ala Phe Lys Glu Leu Gln Ser Thr Phe Lys
 225 230 235 240

<210> 110
 <211> 280
 <212> PRT
 <213> Mus musculus

<400> 110

Met Pro Met Tyr Gln Glu Thr Ser Glu Pro Ser Leu Gln Ala Leu Glu
 1 5 10 15

Ser Arg Gln Asp Asp Ile Leu Lys Arg Leu Tyr Glu Leu Lys Ala Ala
 20 25 30

Val Asp Gly Leu Ser Lys Met Ile His Thr Pro Asp Ala Asp Leu Asp
 35 40 45

Val Thr Asn Ile Leu Gln Ala Asp Glu Pro Thr Thr Leu Ala Thr Asn
 50 55 60

Thr Leu Asp Leu Asn Ser Val Leu Gly Lys Asp Tyr Gly Ala Leu Lys
 65 70 75 80

Asp Ile Val Ile Asn Ala Asn Pro Ala Ser Pro Pro Leu Ser Leu Leu
 85 90 95

Val Leu His Arg Leu Leu Cys Glu Arg Tyr Arg Val Leu Ser Thr Val
 100 105 110

His Thr His Ser Ser Val Lys Asn Val Pro Glu Asn Leu Val Lys Cys
 115 120 125

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

Phe Thr Leu Ile Trp Lys Asn Val Pro Lys Thr Gln Met Lys Phe Ser
 145 150 155 160

Val Gln Thr Met Cys Pro Ile Glu Gly Glu Gly Asn Ile Ala Arg Phe
 165 170 175

Leu Phe Ser Leu Phe Gly Gln Lys His Asn Ala Val Thr Leu Thr Leu
 180 185 190

Ile Asp Ser Trp Val Asp Ile Ala Met Phe Gln Leu Arg Glu Gly Ser
 195 200 205

Ser Lys Glu Lys Ala Ala Val Phe Arg Ser Met Asn Ser Ala Leu Gly
 210 215 220

Arg Ser Pro Trp Leu Val Gly Asn Glu Leu Thr Val Ala Asp Val Val
 225 230 235 240

Leu Trp Ser Val Leu Gln Gln Thr Gly Gly Ser Ser Gly Ala Ala Pro
 245 250 255

Thr Asn Val Gln Arg Trp Leu Lys Ser Cys Glu Asn Leu Ala Pro Phe
 260 265 270

Ser Thr Ala Leu Gln Leu Leu Lys
 275 280

<210> 111
 <211> 1436
 <212> PRT
 <213> Mus musculus

<400> 111

Met Lys Asp Ile Asp Met Gly Lys Glu Tyr Ile Ile Pro Ser Pro Gly
 1 5 10 15

Tyr Arg Ser Asp Arg Asp Arg Ser Ala Val Pro Gly Gln His Arg Asp
 20 25 30

Pro Glu Glu Pro Arg Phe Arg Arg Thr Arg Ser Leu Glu Cys Gln Asp
 35 40 45

Ala Leu Glu Thr Ala Ala Arg Val Glu Gly Leu Ser Leu Asp Ile Ser
 50 55 60

Val His Ser His Leu Gln Ile Leu Asp Glu Glu His Ser Lys Gly Lys
 65 70 75 80

Tyr His His Gly Leu Ser Val Leu Lys Pro Phe Arg Thr Thr Thr Lys
 85 90 95

His Gln His Pro Val Asp Asn Ala Gly Leu Phe Ser Tyr Met Thr Phe
 100 105 110

Ser Trp Leu Ser Pro Leu Ala Arg Val Val His Lys Lys Gly Glu Leu
 115 120 125

Leu Met Glu Asp Val Trp Pro Leu Ser Lys Tyr Glu Ser Ser Asp Val
 130 135 140
 Asn Ser Arg Arg Leu Glu Arg Leu Trp Gln Glu Glu Leu Asn Glu Val
 145 150 155 160
 Gly Pro Asp Ala Ala Ser Leu Arg Arg Val Val Trp Ile Phe Cys Arg
 165 170 175
 Thr Arg Leu Ile Leu Ser Ile Val Cys Leu Met Ile Thr Gln Leu Ala
 180 185 190
 Gly Phe Ser Gly Pro Ala Phe Val Val Lys His Leu Leu Glu Tyr Thr
 195 200 205
 Gln Ala Thr Glu Ser Asn Leu Gln Tyr Ser Leu Leu Leu Val Leu Gly
 210 215 220
 Leu Leu Leu Thr Glu Val Val Arg Ser Trp Ser Leu Ala Leu Thr Trp
 225 230 235 240
 Ala Leu Asn Tyr Arg Thr Gly Val Arg Leu Arg Gly Ala Ile Leu Thr
 245 250 255
 Met Ala Phe Lys Lys Ile Leu Lys Leu Lys Asn Ile Lys Glu Lys Ser
 260 265 270
 Leu Gly Glu Leu Ile Asn Ile Cys Ser Asn Asp Gly Gln Arg Met Phe
 275 280 285
 Glu Ala Ala Ala Val Gly Ser Leu Leu Ala Gly Gly Pro Val Val Ala
 290 295 300
 Ile Leu Gly Met Ile Tyr Asn Val Ile Ile Leu Gly Pro Thr Gly Phe
 305 310 315 320
 Leu Gly Ser Ala Val Phe Ile Leu Phe Tyr Pro Ala Met Met Phe Val
 325 330 335
 Ser Arg Leu Thr Ala Tyr Phe Arg Arg Lys Cys Val Ala Ala Thr Asp
 340 345 350
 Asp Arg Val Gln Lys Met Asn Glu Val Leu Thr Tyr Ile Lys Phe Ile
 355 360 365

Lys Met Tyr Ala Trp Val Lys Ala Phe Ser Gln Cys Val Gln Lys Ile
 370 375 380
 Arg Glu Glu Glu Arg Arg Ile Leu Glu Lys Ala Gly Tyr Phe Gln Ser
 385 390 400
 Ile Thr Val Gly Val Ala Pro Ile Val Val Ile Ala Ser Val Val
 405 410 415
 Thr Phe Ser Val His Met Thr Leu Gly Phe His Leu Thr Ala Ala Gln
 420 425 430
 Ala Phe Thr Val Val Thr Val Phe Asn Ser Met Thr Phe Ala Leu Lys
 435 440 445
 Val Thr Pro Phe Ser Val Lys Ser Leu Ser Glu Ala Ser Val Ala Val
 450 455 460
 Asp Arg Phe Lys Ser Leu Phe Leu Met Glu Glu Val His Met Ile Lys
 465 470 475 480
 Asn Lys Pro Ala Ser Pro His Ile Lys Ile Glu Met Lys Asn Ala Thr
 485 490 495
 Leu Ala Trp Asp Ser Ser His Ser Ser Ile Gln Asn Ser Pro Lys Leu
 500 505 510
 Thr Pro Lys Met Lys Lys Asp Lys Arg Ala Thr Arg Gly Lys Lys Glu
 515 520 525
 Lys Ser Arg Gln Leu Gln His Thr Glu His Gln Ala Val Leu Ala Glu
 530 535 540
 Gln Lys Gly His Leu Leu Leu Asp Ser Asp Glu Arg Pro Ser Pro Glu
 545 550 555 560
 Glu Glu Glu Gly Lys Gln Ile His Thr Gly Ser Leu Arg Leu Gln Arg
 565 570 575
 Thr Leu Tyr Asn Ile Asp Leu Glu Ile Glu Glu Gly Lys Leu Val Gly
 580 585 590
 Ile Cys Gly Ser Val Gly Ser Gly Lys Thr Ser Leu Val Ser Ala Ile
 595 600 605

Leu Gly Gln Met Thr Leu Leu Glu Gly Ser Ile Ala Val Ser Gly Thr
 610 615 620
 Phe Ala Tyr Val Ala Gln Gln Ala Trp Ile Leu Asn Ala Thr Leu Arg
 625 630 635 640
 Asp Asn Ile Leu Phe Gly Lys Glu Phe Asp Glu Glu Arg Tyr Asn Ser
 645 650 655
 Val Leu Asn Ser Cys Cys Leu Arg Pro Asp Leu Ala Ile Leu Pro Asn
 660 665 670
 Ser Asp Leu Thr Glu Ile Gly Glu Arg Gly Ala Asn Leu Ser Gly Gly
 675 680 685
 Gln Arg Gln Arg Ile Ser Leu Ala Arg Ala Leu Tyr Ser Asp Arg Ser
 690 695 700
 Ile Tyr Ile Leu Asp Asp Pro Leu Ser Ala Leu Asp Ala His Val Gly
 705 710 715 720
 Asn His Ile Phe Asn Ser Ala Ile Arg Lys Arg Leu Lys Ser Lys Thr
 725 730 735
 Val Leu Phe Val Thr His Gln Leu Gln Tyr Leu Val Asp Cys Asp Glu
 740 745 750
 Val Ile Phe Met Lys Glu Gly Cys Ile Thr Glu Arg Gly Thr His Glu
 755 760 765
 Glu Leu Met Asn Leu Asn Gly Asp Tyr Ala Thr Ile Phe Asn Asn Leu
 770 775 780
 Leu Leu Gly Glu Thr Pro Pro Val Glu Ile Asn Ser Lys Lys Glu Ala
 785 790 795 800
 Thr Gly Ser Gln Lys Ser Gln Asp Lys Gly Pro Lys Pro Gly Ser Val
 805 810 815
 Lys Lys Glu Lys Ala Val Lys Ser Glu Glu Gly Gln Leu Val Gln Val
 820 825 830
 Glu Glu Lys Gly Gln Gly Ser Val Pro Trp Ser Val Tyr Trp Val Tyr
 835 840 845

Ile Gln Ala Ala Gly Gly Pro Leu Ala Phe Leu Val Ile Met Val Leu
 850 855 860
 Phe Met Leu Asn Val Gly Ser Thr Ala Phe Ser Thr Trp Trp Leu Ser
 865 870 875 880
 Tyr Trp Ile Lys Gln Gly Ser Gly Asn Ser Thr Val Tyr Gln Gly Asn
 885 890 895
 Arg Ser Phe Val Ser Asp Ser Met Lys Asp Asn Pro Phe Met Gln Tyr
 900 905 910
 Tyr Ala Ser Ile Tyr Ala Leu Ser Met Ala Val Met Leu Ile Leu Lys
 915 920 925
 Ala Ile Arg Gly Val Val Phe Val Lys Gly Thr Leu Arg Ala Ser Ser
 930 935 940
 Arg Leu His Asp Glu Leu Phe Arg Arg Ile Leu Arg Ser Pro Met Lys
 945 950 955 960
 Phe Phe Asp Thr Thr Pro Thr Gly Arg Ile Leu Asn Arg Phe Ser Lys
 965 970 975
 Asp Met Asp Glu Val Asp Val Arg Leu Pro Phe Gln Ala Glu Met Phe
 980 985 990
 Ile Gln Asn Val Ile Leu Val Phe Phe Cys Val Gly Met Ile Ala Gly
 995 1000 1005
 Val Phe Pro Trp Phe Leu Val Ala Val Gly Pro Leu Leu Ile Leu
 1010 1015 1020
 Phe Ser Leu Leu His Ile Val Ser Arg Val Leu Ile Arg Glu Leu
 1025 1030 1035
 Lys Arg Leu Asp Asn Ile Thr Gln Ser Pro Phe Leu Ser His Ile
 1040 1045 1050
 Thr Ser Ser Ile Gln Gly Leu Ala Thr Ile His Ala Tyr Asn Lys
 1055 1060 1065
 Arg Gln Glu Phe Leu His Arg Tyr Gln Glu Leu Leu Asp Asp Asn
 1070 1075 1080

Gln Ala Pro Phe Phe Leu Phe Thr Cys Ala Met Arg Trp Leu Ala
 1085 1090 1095
 Val Arg Leu Asp Leu Ile Ser Ile Ala Leu Ile Thr Thr Thr Gly
 1100 1105 1110
 Leu Met Ile Val Leu Met His Gly Gln Ile Pro Ser Ala Tyr Ala
 1115 1120 1125
 Gly Leu Ala Ile Ser Tyr Ala Val Gln Leu Thr Gly Leu Phe Gln
 1130 1135 1140
 Phe Thr Val Arg Leu Ala Ser Glu Thr Glu Ala Arg Phe Thr Ser
 1145 1150 1155
 Val Glu Arg Ile Asn His Tyr Ile Lys Thr Leu Ser Leu Glu Ala
 1160 1165 1170
 Pro Ala Arg Ile Lys Asn Lys Ala Pro Pro His Asp Trp Pro Gln
 1175 1180 1185
 Glu Gly Glu Val Thr Phe Glu Asn Ala Glu Met Arg Tyr Arg Glu
 1190 1195 1200
 Asn Leu Pro Leu Val Leu Lys Lys Val Ser Phe Thr Ile Lys Pro
 1205 1210 1215
 Lys Glu Lys Ile Gly Ile Val Gly Arg Thr Gly Ser Gly Lys Ser
 1220 1225 1230
 Ser Leu Gly Met Ala Leu Phe Arg Leu Val Glu Leu Ser Gly Gly
 1235 1240 1245
 Cys Ile Lys Ile Asp Gly Ile Arg Ile Ser Asp Ile Gly Leu Ala
 1250 1255 1260
 Asp Leu Arg Ser Lys Leu Ala Ile Ile Pro Gln Glu Pro Val Leu
 1265 1270 1275
 Phe Ser Gly Thr Val Arg Ser Asn Leu Asp Pro Phe Asn Gln Tyr
 1280 1285 1290
 Thr Glu Asp Gln Ile Trp Asp Ala Leu Glu Arg Thr His Met Lys
 1295 1300 1305

Glu Cys Ile Ala Gln Leu Pro Leu Lys Leu Glu Ser Glu Val Met
 1310 1315 1320

Glu Asn Gly Asp Asn Phe Ser Val Gly Glu Arg Gln Leu Leu Cys
 1325 1330 1335

Ile Ala Arg Ala Leu Leu Arg His Cys Lys Ile Leu Ile Leu Asp
 1340 1345 1350

Glu Ala Thr Ala Ala Met Asp Thr Glu Thr Asp Leu Leu Ile Gln
 1355 1360 1365

Glu Thr Ile Arg Glu Ala Phe Ala Asp Cys Thr Met Leu Thr Ile
 1370 1375 1380

Ala His Arg Leu His Thr Val Leu Gly Ser Asp Arg Ile Met Val
 1385 1390 1395

Leu Ala Gln Gly Gln Val Val Glu Phe Asp Thr Pro Ser Val Leu
 1400 1405 1410

Leu Ser Asn Asp Ser Ser Arg Phe Tyr Ala Met Phe Ala Ala Ala
 1415 1420 1425

Glu Asn Lys Val Ala Val Lys Gly
 1430 1435

<210> 112
 <211> 458
 <212> PRT
 <213> Mus musculus

<400> 112

Met Ala Ala Leu Lys Ala Gly Arg Gly Ala Asn Trp Ser Leu Arg Ala
 1 5 10 15

Trp Arg Ala Leu Gly Gly Ile Phe Trp Arg Lys Pro Pro Leu Leu Ala
 20 25 30

Pro Asp Leu Arg Ala Leu Leu Thr Ser Gly Thr Pro Asp Ser Gln Ile
 35 40 45

Trp Met Thr Tyr Gly Thr Pro Ser Leu Pro Ala Gln Val Pro Glu Gly
 50 55 60

Phe Leu Ala Ser Arg Ala Asp Leu Thr Ser Arg Thr Pro Asp Leu Trp

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<210>	113
<211>	122
<212>	PRT
<213>	Mus musculus
<400>	113

Met Lys Pro Phe His Thr Ala Leu Ser Phe Leu Ile Leu Thr Thr Ala
1 5 10 15

Leu Gly Ile Trp Ala Gln Ile Thr His Ala Thr Glu Thr Lys Glu Val
20 25 30

Gln Ser Ser Leu Lys Ala Gln Gln Gly Leu Glu Ile Glu Met Phe His
35 40 45

Met Gly Phe Gln Asp Ser Ser Asp Cys Cys Leu Ser Tyr Asn Ser Arg
50 55 60

Ile Gln Cys Ser Arg Phe Ile Gly Tyr Phe Pro Thr Ser Gly Gly Cys
65 70 75 80

Thr Arg Pro Gly Ile Ile Phe Ile Ser Lys Arg Gly Phe Gln Val Cys
85 90 95

Ala Asn Pro Ser Asp Arg Arg Val Gln Arg Cys Ile Glu Arg Leu Glu
100 105 110

Gln Asn Ser Gln Pro Arg Thr Tyr Lys Gln
115 120

<210> 114
<211> 326
<212> PRT
<213> Mus musculus

<400> 114

Met Tyr Gln Asp Tyr Pro Gly Asn Phe Asp Thr Ser Ser Arg Gly Ser
1 5 10 15

Ser Gly Ser Pro Ala His Ala Glu Ser Tyr Ser Ser Gly Gly Gly Gly
20 25 30

Gln Gln Lys Phe Arg Val Asp Met Pro Gly Ser Gly Ser Ala Phe Ile
35 40 45

Pro Thr Ile Asn Ala Ile Thr Thr Ser Gln Asp Leu Gln Trp Met Val
50 55 60

Gln Pro Thr Val Ile Thr Ser Met Ser Asn Pro Tyr Pro Arg Ser His
65 70 75 80

Pro Tyr Ser Pro Leu Pro Gly Leu Ala Ser Val Pro Gly His Met Ala
85 90 95

Leu Pro Arg Pro Gly Val Ile Lys Thr Ile Gly Thr Thr Val Gly Arg
100 105 110

Arg Arg Arg Asp Glu Gln Leu Ser Pro Glu Glu Glu Glu Lys Arg Arg
115 120 125

Ile Arg Arg Glu Arg Asn Lys Leu Ala Ala Ala Lys Cys Arg Asn Arg
130 135 140

Arg Arg Glu Leu Thr Glu Lys Leu Gln Ala Glu Thr Glu Glu Leu Glu
145 150 155 160

Glu Glu Lys Ser Gly Leu Gln Lys Glu Ile Ala Glu Leu Gln Lys Glu
165 170 175

Lys Glu Lys Leu Glu Phe Met Leu Val Ala His Gly Pro Val Cys Lys
180 185 190

Ile Ser Pro Glu Glu Arg Arg Ser Pro Pro Thr Ser Gly Leu Gln Ser
195 200 205

Leu Arg Gly Thr Gly Ser Ala Val Gly Pro Val Val Val Lys Gln Glu
210 215 220

Pro Pro Glu Glu Asp Ser Pro Ser Ser Ser Ala Gly Met Asp Lys Thr
225 230 235 240

Gln Arg Ser Val Ile Lys Pro Ile Ser Ile Ala Gly Gly Gly Phe Tyr
245 250 255

Gly Glu Glu Pro Leu His Thr Pro Ile Val Val Thr Ser Thr Pro Ala
260 265 270

Ile Thr Pro Gly Thr Ser Asn Leu Val Phe Thr Tyr Pro Asn Val Leu
275 280 285

Glu Gln Glu Ser Pro Ser Ser Pro Ser Glu Ser Cys Ser Lys Ala His
290 295 300

Arg Arg Ser Ser Ser Ser Gly Asp Gln Ser Ser Asp Ser Leu Asn Ser
305 310 315 320

Pro Thr Leu Leu Ala Leu
325

<210> 115

<211> 296

<212> PRT

<213> Mus musculus

<400> 115

Met Gly Gly Glu Ala Gly Ala Asn Gly Pro Arg Gly Arg Val Lys Ser
1 5 10 15

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

Gly Ser Gly Ser Thr Asp Thr Trp Asn Gly Lys Met Leu Lys Ile Pro
 260 265 270

Pro Val Thr Pro Ser Ile Leu Asp Cys Cys Ile Ile Arg Val Asp Tyr
 275 280 285

Ser Leu Ala Val Ile Gln Ala Ser
 290 295

<210> 116
 <211> 415
 <212> PRT
 <213> Mus musculus

<400> 116

Met Met Ala Gln Leu Gln Phe Arg Asp Ala Phe Trp Cys Arg Asp Phe
 1 5 10 15

Thr Ala His Thr Gly Tyr Glu Val Leu Leu Gln Arg Leu Leu Asp Gly
 20 25 30

Arg Lys Met Cys Lys Asp Val Glu Glu Leu Leu Arg Gln Arg Ala Gln
 35 40 45

Ala Glu Glu Arg Tyr Gly Lys Glu Leu Val Gln Ile Ala Arg Lys Ala
 50 55 60

Gly Gly Gln Thr Glu Met Asn Ser Leu Arg Thr Ser Phe Asp Ser Leu
 65 70 75 80

Lys Gln Gln Thr Glu Asn Val Gly Ser Ala His Ile Gln Leu Ala Leu
 85 90 95

Ala Leu Arg Glu Glu Leu Arg Ser Leu Glu Glu Phe Arg Glu Arg Gln
 100 105 110

Lys Glu Gln Arg Lys Lys Tyr Glu Ala Ile Met Asp Arg Val Gln Lys
 115 120 125

Ser Lys Leu Ser Leu Tyr Lys Lys Thr Met Glu Ser Lys Lys Ala Tyr
 130 135 140

Asp Gln Lys Cys Arg Asp Ala Asp Asp Ala Glu Gln Ala Phe Glu Arg
 145 150 155 160

Val Ser Ala Asn Gly His Gln Lys Gln Val Glu Lys Ser Gln Asn Lys

165 170 175
 Ala Lys Gln Cys Lys Glu Ser Ala Thr Glu Ala Glu Arg Val Tyr Arg
 180 185 190
 Gln Asn Ile Glu Gln Leu Glu Arg Ala Arg Thr Glu Trp Glu Gln Glu
 195 200 205
 His Arg Thr Thr Cys Glu Ala Phe Gln Leu Gln Glu Phe Asp Arg Leu
 210 215 220
 Thr Ile Leu Arg Asn Ala Leu Trp Val His Cys Asn Gln Leu Ser Met
 225 230 235 240
 Gln Cys Val Lys Asp Asp Glu Leu Tyr Glu Glu Val Arg Leu Thr Leu
 245 250 255
 Glu Gly Cys Asp Val Glu Gly Asp Ile Asn Gly Phe Ile Gln Ser Lys
 260 265 270
 Ser Thr Gly Arg Glu Pro Pro Ala Pro Val Pro Tyr Gln Asn Tyr Tyr
 275 280 285
 Asp Arg Glu Val Thr Pro Leu Ile Gly Ser Pro Ser Ile Gln Pro Ser
 290 295 300
 Cys Gly Val Ile Lys Arg Phe Ser Gly Leu Leu His Gly Ser Pro Lys
 305 310 315 320
 Thr Thr Pro Ser Ala Pro Ala Ala Ser Thr Glu Thr Leu Thr Pro Thr
 325 330 335
 Pro Glu Arg Asn Glu Leu Val Tyr Ala Ser Ile Glu Val Gln Ala Thr
 340 345 350
 Gln Gly Asn Leu Asn Ser Ser Ala Gln Asp Tyr Arg Ala Leu Tyr Asp
 355 360 365
 Tyr Thr Ala Gln Asn Ser Asp Glu Leu Asp Ile Ser Ala Gly Asp Ile
 370 375 380
 Leu Ala Val Ile Leu Glu Gly Glu Asp Gly Trp Trp Thr Val Glu Arg
 385 390 395 400
 Asn Gly Gln Arg Gly Phe Val Pro Gly Ser Tyr Leu Glu Lys Leu

405

410

415

<210> 117
 <211> 328
 <212> PRT
 <213> Mus musculus

<400> 117

Met Val Arg Gly Gly Gly Pro Val Met Ser Ala Ala Ser Asn Arg Ser
 1 5 10 15

Lys Arg Thr Lys Val Leu Arg His Leu Pro Ala Glu Asp Ala Ala Ser
 20 25 30

Ala Arg Gly Ala Ala Val Ala Ser Leu Leu Leu Gln Ser Arg Gln Ser
 35 40 45

Phe Arg Ser Lys Ser Ile Gly Leu Ala Leu Leu Phe Pro Ser Pro Arg
 50 55 60

Ser Pro Ala Phe Asp Leu Leu Trp Arg Pro Gly Gly Arg Lys Gln Gly
 65 70 75 80

Thr Leu Pro Leu Leu Arg Lys Gly Arg Arg Gly Gly Asp Arg Asp Ser
 85 90 95

His Arg Arg Ser Pro Lys Pro Cys Ile Leu Leu Pro Thr Pro Arg Pro
 100 105 110

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

Ser Val Leu Thr Pro Gly Ala Gly Ile Gln Ala Gly Leu Pro Ser Leu
 130 135 140

Arg Val Arg Ser Pro Pro Ala Pro Leu Pro Ala Trp Thr Ser Ala Glu
 145 150 155 160

Lys Glu Asp Lys Arg Val Pro Gly Ala Asn Thr Met Thr Ser Phe Ser
 165 170 175

Arg Tyr Thr Leu Gly Phe Leu Glu Val Asp Arg Gln Arg Ala Gly Ala
 180 185 190

Asp Gly Gly Pro Gly Asn Arg Gly Ala Gly Ser Arg Arg Ala Arg Arg
 195 200 205

Val Arg Ala Gly Arg Ser Ala Pro Arg Thr Ala Pro Cys Ala Arg Ser
210 215 220

Arg Ala Ala Ala Gln Arg Trp Ala Arg Ala Ala Ser Thr Met His Arg
225 230 235 240

Ser Ala Gly Gly Arg Arg Arg Gly Asn Pro Ala Gln Leu Leu Leu Gly
245 250 255

Pro Arg Ala Ser Leu Ala Ile His Arg Arg Arg Ser Arg Ala Leu Leu
260 265 270

Pro Leu Pro Pro Lys Gln Glu Gly Arg Lys Gly Lys Pro Asp Arg Lys
275 280 285

Gly Ala Gly Cys Gln Tyr Lys Val Cys Leu Pro Leu Cys Pro Pro Ile
290 295 300

Arg Asn Ala Pro Arg Asp Asn Val Arg Arg Pro Ala Ile Phe Cys Ala
305 310 315 320

Ser Gly Asn Gly Arg Lys Glu Lys
325

<210> 118
<211> 481
<212> PRT
<213> Mus musculus

<400> 118

Met Ala Gln Ser Pro Val Ser Ala Glu Val Ile His Gln Val Glu Glu
1 5 10 15

Cys Leu Asp Glu Asp Glu Lys Glu Met Met Leu Phe Leu Cys Arg Asp
20 25 30

Val Thr Glu Asn Leu Ala Ala Pro Asn Val Arg Asp Leu Leu Asp Ser
35 40 45

Leu Ser Glu Arg Gly Gln Leu Ser Phe Ala Thr Leu Ala Glu Leu Leu
50 55 60

Tyr Arg Val Arg Arg Phe Asp Leu Leu Lys Arg Ile Leu Lys Thr Asp
65 70 75 80

Lys Ala Thr Val Glu Asp His Leu Arg Arg Asn Pro His Leu Val Ser
 85 90 95
 Asp Tyr Arg Val Leu Leu Met Glu Ile Gly Glu Ser Leu Asp Gln Asn
 100 105 110
 Asp Val Ser Ser Leu Val Phe Leu Thr Arg Asp Tyr Thr Gly Arg Gly
 115 120 125
 Lys Ile Ala Lys Asp Lys Ser Phe Leu Asp Leu Val Ile Glu Leu Glu
 130 135 140
 Lys Leu Asn Leu Ile Ala Ser Asp Gln Leu Asn Leu Leu Glu Lys Cys
 145 150 155 160
 Leu Lys Asn Ile His Arg Ile Asp Leu Asn Thr Lys Ile Gln Lys Tyr
 165 170 175
 Thr Gln Ser Ser Gln Gly Ala Arg Ser Asn Met Asn Thr Leu Gln Ala
 180 185 190
 Ser Leu Pro Lys Leu Ser Ile Lys Tyr Asn Ser Arg Leu Gln Asn Gly
 195 200 205
 Arg Ser Lys Glu Pro Arg Phe Val Glu Tyr Arg Asp Ser Gln Arg Thr
 210 215 220
 Leu Val Lys Thr Ser Ile Gln Glu Ser Gly Ala Phe Leu Pro Pro His
 225 230 235 240
 Ile Arg Glu Glu Thr Tyr Arg Met Gln Ser Lys Pro Leu Gly Ile Cys
 245 250 255
 Leu Ile Ile Asp Cys Ile Gly Asn Asp Thr Lys Tyr Leu Gln Glu Thr
 260 265 270
 Phe Thr Ser Leu Gly Tyr His Ile Gln Leu Phe Leu Phe Pro Lys Ser
 275 280 285
 His Asp Ile Thr Gln Ile Val Arg Arg Tyr Ala Ser Met Ala Gln His
 290 295 300
 Gln Asp Tyr Asp Ser Phe Ala Cys Val Leu Val Ser Leu Gly Gly Ser
 305 310 315 320

Gln Ser Met Met Gly Arg Asp Gln Val His Ser Gly Phe Ser Leu Asp
 325 330
 His Val Lys Asn Met Phe Thr Gly Asp Thr Cys Pro Ser Leu Arg Gly
 340 345 350
 Lys Pro Lys Leu Phe Phe Ile Gln Asn Tyr Glu Ser Leu Gly Ser Gln
 355 360 365
 Leu Glu Asp Ser Ser Leu Glu Val Asp Gly Pro Ser Ile Lys Asn Val
 370 375 380
 Asp Ser Lys Pro Leu Gln Pro Arg His Cys Thr Thr His Pro Glu Ala
 385 390 395 400
 Asp Ile Phe Trp Ser Leu Cys Thr Ala Asp Val Ser His Leu Glu Lys
 405 410 415
 Pro Ser Ser Ser Ser Val Tyr Leu Gln Lys Leu Ser Gln Gln Leu
 420 425 430
 Lys Gln Gly Arg Arg Arg Pro Leu Val Asp Leu His Val Glu Leu Met
 435 440 445
 Asp Lys Val Tyr Ala Trp Asn Ser Gly Val Ser Ser Lys Glu Lys Tyr
 450 455 460
 Ser Leu Ser Leu Gln His Thr Leu Arg Lys Lys Leu Ile Leu Ala Pro
 465 470 475 480

Thr

<210> 119
 <211> 346
 <212> PRT
 <213> Mus musculus

<400> 119

Met Pro Pro Pro Gln Ser Arg Leu Leu Gln Tyr Arg Gln Val Gln Pro
 1 5 10 15

Arg Ser Pro Pro Ala Val Pro Ser Pro Pro Ser Ser Thr Asp His Ser
 20 25 30

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

Leu Met Pro Asn Lys Gln Ile Ala Glu Ser Ala Asn Cys Ser Ser Gln
 275 280 285

Gln Ser Pro Ala Gly Ser Lys Pro Ala Met Ser Tyr Ala Ser Ala Leu
 290 295 300

Arg Ala Pro Pro Lys Pro Arg Pro Pro Pro Glu Gln Ala Lys Lys Gly
 305 310 315 320

Ser Asp Pro Leu Ser Leu Leu Gln Glu Leu Ser Leu Gly Ser Ser Pro
 325 330 335

Gly Ser Asn Gly Phe Tyr Ser Tyr Phe Lys
 340 345

<210> 120
 <211> 168
 <212> PRT
 <213> Mus musculus

<400> 120

Met Lys Gly Arg Ile Glu Leu Gly Asp Val Thr Pro His Asn Ile Lys
 1 5 10 15

Gln Leu Lys Arg Leu Asn Gln Val Ile Phe Pro Val Ser Tyr Asn Asp
 20 25 30

Lys Phe Tyr Lys Asp Val Leu Glu Val Gly Glu Leu Ala Lys Leu Ala
 35 40 45

Tyr Phe Asn Asp Ile Ala Val Gly Ala Val Cys Cys Arg Val Asp His
 50 55 60

Ser Gln Asn Gln Lys Arg Leu Tyr Ile Met Thr Leu Gly Cys Leu Ala
 65 70 75 80

Pro Tyr Arg Arg Leu Gly Ile Gly Thr Lys Met Leu Asn His Val Leu
 85 90 95

Asn Ile Cys Glu Lys Asp Gly Thr Phe Asp Asn Ile Tyr Leu His Val
 100 105 110

Gln Ile Ser Asn Glu Ser Ala Ile Asp Phe Tyr Arg Lys Phe Gly Phe
 115 120 125

Glu Ile Ile Glu Thr Lys Lys Asn Tyr Tyr Lys Arg Ile Glu Pro Ala

130 135 140

Asp Ala His Val Leu Gln Lys Asn Leu Lys Val Pro Ser Gly Gln Asn
 145 150 155 160

Ala Glu Thr Gln Lys Thr Asp Asn
 165

<210> 121
 <211> 127
 <212> PRT
 <213> Mus musculus

<400> 121

Met Ser Asp Asn Glu Asp Asn Phe Asp Gly Asp Asp Phe Asp Asp Val
 1 5 10 15

Glu Glu Asp Glu Gly Leu Asp Asp Leu Glu Asn Ala Glu Glu Glu Gly
 20 25 30

Gln Glu Asn Val Glu Ile Leu Pro Ser Gly Glu Arg Pro Gln Ala Asn
 35 40 45

Gln Lys Arg Ile Thr Thr Pro Tyr Met Thr Lys Tyr Glu Arg Ala Arg
 50 55 60

Val Leu Gly Thr Arg Ala Leu Gln Ile Ala Met Cys Ala Pro Val Met
 65 70 75 80

Val Glu Leu Glu Gly Glu Thr Asp Pro Leu Leu Ile Ala Met Lys Glu
 85 90 95

Leu Lys Ala Arg Lys Ile Pro Ile Ile Ile Arg Arg Tyr Leu Pro Asp
 100 105 110

Gly Ser Tyr Glu Asp Trp Gly Val Asp Glu Leu Ile Ile Ser Asp
 115 120 125

<210> 122
 <211> 261
 <212> PRT
 <213> Mus musculus

<400> 122

Met Ala Gly Asp Ser Glu Gln Thr Leu Gln Asn His Gln Gln Pro Asn
 1 5 10 15

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

Ser Ser Arg Pro His
260

<210> 123
<211> 1115
<212> PRT
<213> Mus musculus

<400> 123

Met Ser Lys Val Ile Gln Lys Lys Asn His Trp Thr Gly Arg Val His
1 5 10 15

Glu Cys Thr Val Lys Arg Gly Pro Gln Gly Glu Leu Gly Val Thr Val
20 25 30

Leu Gly Gly Ala Glu His Gly Glu Phe Pro Tyr Val Gly Ala Val Ala
35 40 45

Ala Ala Glu Ala Ala Gly Leu Pro Gly Gly Gly Glu Gly Pro Lys Leu
50 55 60

Ala Glu Gly Glu Leu Leu Leu Glu Val Gln Gly Val Arg Val Ser Gly
65 70 75 80

Leu Pro Arg Tyr Asp Val Leu Gly Val Ile Asp Ser Cys Lys Glu Ala
85 90 95

Val Thr Phe Lys Ala Val Arg Gln Gly Gly Arg Leu Asn Lys Asp Leu
100 105 110

Arg His Phe Leu Asn Gln Arg Phe Gln Lys Gly Ser Pro Asp His Glu
115 120 125

Leu Gln Gln Thr Ile Arg Asp Asn Leu Tyr Arg His Ala Val Pro Cys
130 135 140

Thr Thr Arg Ser Pro Arg Glu Gly Glu Val Pro Gly Val Asp Tyr Ser
145 150 155 160

Phe Leu Thr Val Lys Glu Phe Leu Asp Leu Glu Gln Ser Gly Thr Leu
165 170 175

Leu Glu Val Gly Thr Tyr Glu Gly Asn Tyr Tyr Gly Thr Pro Lys Pro
180 185 190

Pro Ser Gln Pro Val Ser Gly Lys Val Ile Thr Thr Asp Ala Leu His
 195 200 205
 Ser Leu Gln Ser Gly Ser Lys Gln Ser Thr Pro Lys Arg Thr Lys Ser
 210 215 220
 Tyr Asn Asp Met Gln Asn Ala Gly Ile Val His Pro Glu Asn Glu Glu
 225 230 235 240
 Glu Glu Asp Val Pro Glu Met Asn Ser Ser Phe Thr Ala Asp Ser Gly
 245 250 255
 Asp Gln Asp Glu His Thr Leu Gln Glu Ala Thr Leu Pro Pro Val Asn
 260 265 270
 Ser Ser Ile Leu Ala Ala Pro Ile Thr Asp Pro Ser Gln Lys Phe Pro
 275 280 285
 Gln Tyr Leu Pro Leu Ser Ala Glu Asp Asn Leu Gly Pro Leu Pro Glu
 290 295 300
 Asn Trp Glu Met Ala Tyr Thr Glu Asn Gly Glu Val Tyr Phe Ile Asp
 305 310 315 320
 His Asn Thr Lys Thr Thr Ser Trp Leu Asp Pro Arg Cys Leu Asn Lys
 325 330 335
 Gln Gln Lys Pro Leu Glu Glu Cys Glu Asp Asp Glu Gly Val His Thr
 340 345 350
 Glu Glu Leu Asp Ser Glu Leu Glu Leu Pro Ala Gly Trp Glu Lys Ile
 355 360 365
 Glu Asp Pro Val Tyr Gly Val Tyr Tyr Val Asp His Ile Asn Arg Lys
 370 375 380
 Thr Gln Tyr Glu Asn Pro Val Leu Glu Ala Lys Arg Lys Lys Gln Leu
 385 390 395 400
 Glu Gln Gln Gln Gln Gln Gln Gln Pro Gln Pro Pro Gln Pro Glu Glu
 405 410 415
 Trp Thr Glu Asp His Ala Ser Val Val Pro Pro Val Ala Pro Ser His
 420 425 430

Pro Pro Ser Asn Pro Glu Pro Ala Arg Glu Thr Pro Leu Gln Gly Lys
 435 440 445
 Pro Phe Phe Thr Arg Asn Pro Ser Glu Leu Lys Gly Lys Phe Ile His
 450 455 460
 Thr Lys Leu Arg Lys Ser Ser Arg Gly Phe Gly Phe Thr Val Val Gly
 465 470 475 480
 Gly Asp Glu Pro Asp Glu Phe Leu Gln Ile Lys Ser Leu Val Leu Asp
 485 490 495
 Gly Pro Ala Ala Leu Asp Gly Lys Met Glu Thr Gly Asp Val Ile Val
 500 505 510
 Ser Val Asn Asp Thr Cys Val Leu Gly His Thr His Ala Gln Val Val
 515 520 525
 Lys Ile Phe Gln Ser Ile Pro Ile Gly Ala Ser Val Asp Leu Glu Leu
 530 535 540
 Cys Arg Gly Tyr Pro Leu Pro Phe Asp Pro Asp Asp Pro Asn Thr Ser
 545 550 555 560
 Leu Val Thr Ser Val Ala Ile Leu Asp Lys Glu Pro Ile Ile Val Asn
 565 570 575
 Gly Gln Glu Thr Tyr Asp Ser Pro Ala Ser His Ser Ser Lys Thr Gly
 580 585 590
 Lys Val Ser Ser Met Lys Asp Ala Arg Pro Ser Ser Pro Ala Asp Val
 595 600 605
 Ala Ser Asn Ser Ser His Gly Tyr Pro Asn Asp Thr Val Ser Leu Ala
 610 615 620
 Ser Ser Ile Ala Thr Gln Pro Glu Leu Ile Thr Val His Ile Val Lys
 625 630 635 640
 Gly Pro Met Gly Phe Gly Phe Thr Ile Ala Asp Ser Pro Gly Gly Gly
 645 650 655
 Gly Gln Arg Val Lys Gln Ile Val Asp Ser Pro Arg Cys Arg Gly Leu
 660 665 670

Lys Glu Gly Asp Leu Ile Val Glu Val Asn Lys Lys Asn Val Gln Ala
 675 680 685
 Leu Thr His Asn Gln Val Val Asp Met Leu Ile Glu Cys Pro Lys Gly
 690 695 700
 Ser Glu Val Thr Leu Leu Val Gln Arg Gly Gly Leu Pro Val Pro Lys
 705 710 715 720
 Lys Ser Pro Lys Ser Pro Leu Glu Arg Lys Asp Ser Gln Asn Ser Ser
 725 730 735
 Gln His Ser Val Ser Ser His Arg Ser Leu His Thr Ala Ser Pro Ser
 740 745 750
 His Gly Ile Gln Val Leu Pro Glu Tyr Leu Pro Ala Asp Ala Pro Ala
 755 760 765
 Pro Asp Gln Thr Asp Ser Ser Gly Gln Lys Lys Pro Asp Pro Phe Lys
 770 775 780
 Ile Trp Ala Gln Ser Arg Ser Met Tyr Glu Asn Arg Leu Pro Asp Tyr
 785 790 795 800
 Gln Glu Gln Asp Ile Phe Leu Trp Arg Lys Glu Thr Gly Phe Gly Phe
 805 810 815
 Arg Ile Leu Gly Gly Asn Glu Pro Gly Glu Pro Ile Tyr Ile Gly His
 820 825 830
 Ile Val Pro Leu Gly Ala Ala Asp Thr Asp Gly Arg Leu Arg Ser Gly
 835 840 845
 Asp Glu Leu Ile Cys Val Asp Gly Thr Pro Val Ile Gly Lys Ser His
 850 855 860
 Gln Leu Val Val Gln Leu Met Gln Gln Ala Ala Lys Gln Gly His Val
 865 870 875 880
 Asn Leu Thr Val Arg Arg Lys Val Val Phe Ala Val Pro Lys Ala Glu
 885 890 895
 Asn Glu Val Pro Ser Pro Ala Ser Ser His His Ser Ser Asn Gln Pro
 900 905 910

Ala Ser Leu Thr Glu Glu Lys Arg Thr Pro Gln Gly Ser Gln Asn Ser
 915 920 925
 Leu Asn Thr Val Ser Ser Gly Ser Gly Ser Thr Ser Gly Ile Gly Ser
 930 935 940
 Gly Gly Gly Gly Gly Ser Gly Val Val Ser Ala Val Leu Gln Pro Tyr
 945 950 955 960
 Asp Val Glu Ile Arg Arg Gly Glu Asn Glu Gly Phe Gly Phe Val Ile
 965 970 975
 Val Ser Ser Val Ser Arg Pro Glu Ala Gly Thr Thr Phe Glu Ser Ser
 980 985 990
 Asn Ala Thr Leu Leu Thr Asn Ala Glu Lys Ile Ala Thr Ile Thr Thr
 995 1000 1005
 Thr His Ala Pro Ser Gln Gln Gly Thr Gln Glu Thr Arg Thr Thr
 1010 1015 1020
 Thr Lys Pro Lys Gln Asp Ser Gln Phe Glu Phe Lys Gly Pro Gln
 1025 1030 1035
 Ala Ala Gln Glu Gln Asp Phe Tyr Thr Val Glu Leu Glu Arg Gly
 1040 1045 1050
 Ala Lys Gly Phe Gly Phe Ser Leu Arg Gly Gly Arg Glu Tyr Asn
 1055 1060 1065
 Met Asp Leu Tyr Val Leu Arg Leu Ala Glu Asp Gly Pro Ala Glu
 1070 1075 1080
 Arg Cys Gly Lys Met Arg Ile Gly Asp Glu Ile Leu Glu Ile Asn
 1085 1090 1095
 Gly Glu Thr Thr Lys Asn Met Lys His Ser Arg Ala Ile Glu Leu
 1100 1105 1110
 Ile Lys
 1115

<210> 124
 <211> 375
 <212> PRT
 <213> Mus musculus

<400> 124

Met Ala Ser Lys Pro Glu Lys Arg Val Ala Ser Ser Val Phe Ile Thr
 1 5 10 15

Leu Ala Pro Pro Arg Arg Asp Val Ala Val Ser Glu Glu Val Gly Gln
 20 25 30

Ala Ala Cys Glu Ala Arg Arg Ala Arg Pro Trp Glu Met Leu Pro Thr
 35 40 45

Lys Thr Pro Gly Ala Ala Val Gly Arg Ser Pro Lys Thr Trp Thr Pro
 50 55 60

Ser Gly Lys Thr Asn Ala Ser Leu Ser Gly Val Thr Pro Gln Leu Ser
 65 70 75 80

Asn Gly Gly Cys Ser Leu Pro Pro Pro Ser Leu Asn Glu Glu Asp Leu
 85 90 95

Asp Leu Pro Pro Pro Pro Pro Pro Ser Ala Tyr Leu Pro Leu Pro
 100 105 110

Glu Glu Glu Pro Pro Val Leu Pro Gly Lys Ser Leu Ile Ser Asp Leu
 115 120 125

Glu Gln Leu His Leu Pro Pro Pro Pro Pro Pro Pro Pro Gln Ala
 130 135 140

Pro Ser Lys Gly Ser Ser Val His Pro Pro Pro Gly His Ala Arg Pro
 145 150 155 160

Ser Glu Glu Glu Leu Pro Pro Pro Pro Glu Glu Pro Val Thr Leu Pro
 165 170 175

Glu Arg Glu Val Ser Thr Asp Val Cys Gly Phe Cys His Lys Pro Val
 180 185 190

Ser Pro Arg Glu Leu Ala Val Glu Ala Met Lys Arg Gln Tyr His Ala
 195 200 205

Gln Cys Phe Thr Cys Arg Thr Cys Arg Arg Gln Leu Ala Gly Gln Arg
 210 215 220

Phe Tyr Gln Lys Asp Gly Arg Pro Leu Cys Glu Pro Cys Tyr Gln Asp

<210>	125
<211>	610
<212>	PRT
<213>	Mus musculus
<400>	125

Met Glu Arg Pro His Gln Asp Ala Ser Leu Ser Lys Lys Asp Ala Cys
1 5 10 15

Thr Gln Thr Tyr Pro Pro Arg Arg Ile Arg His Ala Gln Val Gln
20 25 30

Asp Ala Gly Gln Leu Lys Leu Ser Ile Asp Ala Gln Asp Arg Val Leu
35 40 45

Leu Pro His Ile Ile Glu Gly Lys Gly Leu Met Ser Arg Glu Pro Gly
50 55 60

Ile Cys Asp Pro Tyr Val Lys Val Ser Leu Ile Pro Glu Asp Ser Gln
 65 70 75 80
 Leu Pro Cys Gln Thr Thr Gln Ile Ile Pro Asp Cys Arg Asp Pro Ala
 85 90
 Phe His Glu His Phe Phe Phe Pro Val Pro Glu Glu Gly Asp Gln Lys
 100 105 110
 Arg Leu Leu Val Thr Val Trp Asn Arg Ala Ser Glu Thr Arg Gln His
 115 120 125
 Thr Leu Ile Gly Cys Met Ser Phe Gly Val Arg Ser Leu Leu Thr Pro
 130 135 140
 Asp Lys Glu Ile Ser Gly Trp Tyr Tyr Leu Leu Gly Glu Asp Leu Gly
 145 150 155 160
 Arg Thr Lys His Leu Lys Val Ala Arg Arg Arg Leu Gln Pro Leu Arg
 165 170 175
 Asp Met Leu Leu Arg Met Pro Gly Glu Gly Asp Pro Glu Asn Gly Glu
 180 185 190
 Lys Leu Gln Ile Thr Ile Arg Arg Gly Lys Asp Gly Phe Gly Phe Thr
 195 200 205
 Ile Cys Cys Asp Ser Pro Val Arg Val Gln Ala Val Asp Ser Gly Gly
 210 215 220
 Pro Ala Glu Arg Ala Gly Leu Gln Gln Leu Asp Thr Val Leu Gln Leu
 225 230 235 240
 Asn Glu Arg Pro Val Glu His Trp Lys Cys Val Glu Leu Ala His Glu
 245 250 255
 Ile Arg Ser Cys Pro Ser Glu Ile Ile Leu Leu Val Trp Arg Val Val
 260 265 270
 Pro Gln Ile Lys Pro Gly Pro Asp Gly Gly Val Leu Arg Arg Ala Ser
 275 280 285
 Cys Lys Ser Thr His Asp Leu Leu Ser Pro Pro Asn Lys Arg Glu Lys
 290 295 300

Asn Cys Thr His Gly Ala Pro Val Arg Pro Glu Gln Arg His Ser Cys
 305 310 315 320
 His Leu Val Cys Asp Ser Ser Asp Gly Leu Leu Leu Gly Gly Trp Glu
 325 330 335
 Arg Tyr Thr Glu Val Gly Lys Arg Ser Gly Gln His Thr Leu Pro Ala
 340 345 350
 Leu Ser Arg Thr Thr Thr Pro Thr Asp Pro Asn Tyr Ile Ile Leu Ala
 355 360 365
 Pro Leu Asn Pro Gly Ser Gln Leu Leu Arg Pro Val Tyr Gln Glu Asp
 370 375 380
 Thr Ile Pro Glu Glu Pro Gly Thr Thr Thr Lys Gly Lys Ser Tyr Thr
 385 390 395 400
 Gly Leu Gly Lys Lys Ser Arg Leu Met Lys Thr Val Gln Thr Met Lys
 405 410 415
 Gly His Ser Asn Tyr Gln Asp Cys Ser Ala Leu Arg Pro His Ile Pro
 420 425 430
 His Ser Ser Tyr Gly Thr Tyr Val Thr Leu Ala Pro Lys Val Leu Val
 435 440 445
 Phe Pro Val Phe Val Gln Pro Leu Asp Leu Cys Asn Pro Ala Arg Thr
 450 455 460
 Leu Leu Leu Ser Glu Glu Leu Leu Leu Tyr Glu Gly Arg Asn Lys Thr
 465 470 475 480
 Ser Gln Val Thr Leu Phe Ala Tyr Ser Asp Leu Leu Leu Phe Thr Lys
 485 490 495
 Glu Glu Glu Pro Gly Arg Cys Asp Val Leu Arg Asn Pro Leu Tyr Leu
 500 505 510
 Gln Ser Val Lys Leu Gln Glu Gly Ser Ser Glu Asp Leu Lys Phe Cys
 515 520 525
 Val Leu Tyr Leu Ala Glu Lys Ala Glu Cys Leu Phe Thr Leu Glu Ala
 530 535 540

His Ser Gln Glu Gln Lys Lys Arg Val Cys Trp Cys Leu Ser Glu Asn
545 550 555 560

Ile Ala Lys Gln Gln Gln Leu Ala Ala Pro Pro Thr Glu Arg Lys Lys
565 570 575

Leu His Pro Tyr Gly Ser Leu Gln Gln Glu Met Gly Pro Val Thr Ser
580 585 590

Ile Ser Ala Thr Gln Asp Arg Ser Phe Thr Ser Ser Gly Gln Thr Leu
595 600 605

Ile Gly
610

<210> 126
<211> 1354
<212> PRT
<213> Mus musculus

<400> 126

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

Glu Ala Ser Glu Phe Asp Glu Trp Glu Pro Glu Gly Thr Ala Thr Leu
20 25 30

Gly Gly Pro Val Thr Ala Ile Ile Pro Thr Trp Gln Ala Leu Thr Thr
35 40 45

Leu Asp Leu Ser His Asn Ser Ile Cys Glu Ile Asp Glu Ser Val Lys
50 55 60

Leu Ile Pro Lys Ile Glu Tyr Leu Asp Leu Ser His Asn Gly Leu Arg
65 70 75 80

Val Val Asp Asn Leu Gln His Leu Tyr Asn Leu Val His Leu Asp Leu
85 90 95

Ser Tyr Asn Lys Leu Ser Ser Leu Glu Gly Val His Thr Lys Leu Gly
100 105 110

Asn Val Lys Thr Leu Asn Leu Ala Gly Asn Phe Leu Glu Ser Leu Ser
115 120 125

Gly Leu His Lys Leu Tyr Ser Leu Val Asn Val Asp Leu Arg Asp Asn
 130 135 140
 Arg Ile Glu Gln Leu Asp Glu Val Lys Ser Ile Gly Ser Leu Pro Cys
 145 150 155 160
 Leu Glu Arg Leu Thr Leu Leu Asn Asn Pro Leu Ser Ile Ile Pro Asp
 165 170 175
 Tyr Arg Thr Lys Val Leu Ser Gln Phe Gly Glu Arg Ala Ser Glu Ile
 180 185 190
 Cys Leu Asp Asp Val Ala Thr Thr Glu Lys Glu Leu Asp Thr Val Glu
 195 200 205
 Val Leu Lys Ala Ile Gln Lys Ala Lys Asp Val Lys Ser Lys Leu Ser
 210 215 220
 Asn Thr Glu Lys Lys Ala Gly Glu Asp Phe Arg Leu Pro Pro Ala Pro
 225 230 235 240
 Cys Ile Arg Pro Gly Gly Ser Pro Pro Ala Ala Pro Ala Ser Ala Ser
 245 250 255
 Leu Pro Gln Pro Ile Leu Ser Asn Gln Gly Ile Met Phe Val Gln Glu
 260 265 270
 Glu Ala Leu Ala Ser Ser Leu Ser Ser Thr Asp Ser Leu Pro Pro Glu
 275 280 285
 Asp His Arg Pro Ile Ala Arg Ala Cys Ser Asp Ser Leu Glu Ser Ile
 290 295 300
 Pro Ala Gly Gln Val Ala Ser Asp Asp Leu Arg Asp Val Pro Gly Ala
 305 310 315 320
 Val Gly Gly Val Ser Pro Asp His Ala Glu Pro Glu Val Gln Val Val
 325 330 335
 Pro Gly Ser Gly Gln Ile Ile Phe Leu Pro Phe Thr Cys Ile Gly Tyr
 340 345 350
 Thr Ala Thr Asn Gln Asp Phe Ile Gln Arg Leu Ser Thr Leu Ile Arg
 355 360 365

Gln Ala Ile Glu Arg Gln Leu Pro Ala Trp Ile Glu Ala Ala Asn Gln
 370 375 380
 Arg Glu Glu Ala His Gly Glu Gln Gly Glu Glu Glu Glu Glu Glu
 385 390 395 400
 Glu Glu Glu Asp Val Ala Glu Asn Arg Tyr Phe Glu Met Gly Pro Pro
 405 410 415
 Asp Ala Glu Glu Glu Glu Gly Ser Gly Gln Gly Glu Glu Asp Glu Glu
 420 425 430
 Asp Glu Asp Glu Glu Ala Glu Glu Glu Arg Leu Ala Leu Glu Trp Ala
 435 440 445
 Leu Gly Ala Asp Glu Asp Phe Leu Leu Glu His Ile Arg Ile Leu Lys
 450 455 460
 Val Leu Trp Cys Phe Leu Ile His Val Gln Gly Ser Ile Arg Gln Phe
 465 470 475 480
 Ala Ala Cys Leu Val Leu Thr Asp Phe Gly Ile Ala Val Phe Glu Ile
 485 490 495
 Pro His Gln Glu Ser Arg Gly Ser Ser Gln His Ile Leu Ser Ser Leu
 500 505 510
 Arg Phe Val Phe Cys Phe Pro His Gly Asp Leu Thr Glu Phe Gly Phe
 515 520 525
 Leu Met Pro Glu Leu Cys Leu Val Leu Lys Val Arg His Ser Glu Asn
 530 535 540
 Thr Leu Phe Ile Ile Ser Asp Ala Ala Asn Leu His Glu Phe His Ala
 545 550 555 560
 Asp Leu Arg Ser Cys Phe Ala Pro Gln His Met Ala Met Leu Cys Ser
 565 570 575
 Pro Ile Leu Tyr Gly Ser His Thr Thr Leu Gln Glu Phe Leu Arg Gln
 580 585 590
 Leu Leu Thr Phe Tyr Lys Val Ala Gly Gly Ser Gln Glu Arg Ser Gln
 595 600 605

Gly Cys Phe Pro Val Tyr Leu Val Tyr Ser Asp Lys Arg Met Val Gln
 610 615 620
 Thr Pro Ala Gly Asp Tyr Ser Gly Asn Ile Glu Trp Ala Ser Cys Thr
 625 630 635 640
 Leu Cys Ser Ala Val Arg Arg Ser Cys Cys Ala Pro Ser Glu Ala Val
 645 650 655
 Lys Ser Ala Ala Ile Pro Tyr Trp Leu Leu Leu Thr Ser Gln His Leu
 660 665 670
 Asn Val Ile Lys Ala Asp Phe Asn Pro Met Pro Asn Arg Gly Thr His
 675 680 685
 Asn Cys Arg Asn Arg Asn Ser Phe Lys Leu Ser Arg Val Pro Leu Ser
 690 695 700
 Thr Val Leu Leu Asp Pro Thr Arg Ser Cys Thr Gln Pro Arg Gly Ala
 705 710 715 720
 Phe Ala Asp Gly His Val Leu Glu Leu Leu Val Gly Tyr Arg Phe Val
 725 730 735
 Thr Ala Ile Phe Val Leu Pro His Glu Lys Phe His Phe Leu Arg Val
 740 745 750
 Tyr Asn Gln Leu Arg Ala Ser Leu Gln Asp Leu Lys Thr Val Val Ile
 755 760 765
 Ser Lys Asn Pro Ser Ala Lys Pro Arg Asn Gln Pro Ala Lys Ser Arg
 770 775 780
 Ala Ser Ala Glu Gln Arg Leu Gln Glu Thr Pro Ala Asp Ala Pro Ala
 785 790 795 800
 Pro Ala Ala Val Pro Pro Thr Ala Ser Ala Pro Ala Pro Ala Glu Ala
 805 810 815
 Leu Ala Pro Asp Leu Ala Pro Val Gln Ala Pro Gly Glu Asp Arg Gly
 820 825 830
 Leu Thr Ser Ala Glu Ala Pro Ala Ala Ala Glu Ala Pro Ala Ala Ala
 835 840 845

Glu Ala Pro Ala Ala Ala Glu Ala Pro Ala Ala Ala Glu Ala Pro Ala
 850 855 860
 Ala Ala Glu Ala Pro Ala Ala Ala Glu Ala Pro Ala Pro Ala Glu Ala
 865 870 875 880
 Pro Ala Ala Ala Glu Ala Pro Ala Ala Ala Glu Ala Pro Ala Ala Ala
 885 890 895
 Glu Ala Pro Ala Ala Ala Glu Ala Pro Ala Ser Ala Glu Ala Pro Ala
 900 905 910
 Pro Asn Gln Ala Pro Ala Pro Ala Arg Gly Pro Ala Pro Ala Arg Gly
 915 920 925
 Pro Ala Pro Ala Gly Gly Pro Ala Pro Ala Gly Gly Pro Ala Pro Ala
 930 935 940
 Glu Ala Leu Ala Gln Ala Glu Val Pro Ala Gln Tyr Pro Ser Glu Arg
 945 950 955 960
 Leu Ile Gln Ser Thr Ser Glu Glu Asn Gln Ile Pro Ser His Leu Pro
 965 970 975
 Val Cys Pro Ser Leu Gln His Ile Ala Arg Leu Arg Gly Arg Ala Ile
 980 985 990
 Ile Asp Leu Phe His Asn Ser Ile Ala Glu Val Glu Asn Glu Glu Leu
 995 1000 1005
 Arg His Leu Leu Trp Ser Ser Val Val Phe Tyr Gln Thr Pro Gly
 1010 1015 1020
 Leu Glu Val Thr Ala Cys Val Leu Leu Ser Ser Lys Ala Val Tyr
 1025 1030 1035
 Phe Ile Leu His Asp Gly Leu Arg Arg Tyr Phe Ser Glu Pro Leu
 1040 1045 1050
 Gln Asp Phe Trp His Gln Lys Asn Thr Asp Tyr Asn Asn Ser Pro
 1055 1060 1065
 Phe His Val Ser Gln Cys Phe Val Leu Lys Leu Ser Asp Leu Gln
 1070 1075 1080

Ser Val Asn Val Gly Leu Phe Asp Gln Tyr Phe Arg Leu Thr Gly
 1085 1090 1095
 Ser Ser Pro Thr Gln Val Val Thr Cys Leu Thr Arg Asp Ser Tyr
 1100 1105 1110
 Leu Thr His Cys Phe Leu Gln His Leu Met Leu Val Leu Ser Ser
 1115 1120 1125
 Leu Glu Arg Thr Pro Ser Pro Glu Pro Val Asp Lys Asp Phe Tyr
 1130 1135 1140
 Ser Glu Phe Gly Asp Lys Asn Thr Gly Lys Met Glu Asn Tyr Glu
 1145 1150 1155
 Leu Ile His Ser Ser Arg Val Lys Phe Thr Tyr Pro Ser Glu Glu
 1160 1165 1170
 Glu Val Gly Asp Leu Thr Tyr Ile Val Ala Gln Lys Met Ala Asp
 1175 1180 1185
 Pro Ala Lys Asn Pro Ala Leu Ser Ile Leu Leu Tyr Ile Gln Ala
 1190 1200
 Phe Gln Val Val Thr Pro His Leu Gly Arg Gly Arg Gly Pro Leu
 1205 1210 1215
 Arg Pro Lys Thr Leu Leu Leu Thr Ser Ala Glu Ile Phe Leu Leu
 1220 1225 1230
 Asp Glu Asp Tyr Ile His Tyr Pro Leu Pro Glu Phe Ala Lys Glu
 1235 1240 1245
 Pro Pro Gln Arg Asp Arg Tyr Arg Leu Asp Asp Gly Arg Arg Val
 1250 1255 1260
 Arg Asp Leu Asp Arg Val Leu Met Gly Tyr Tyr Pro Tyr Pro Gln
 1265 1270 1275
 Ala Leu Thr Leu Val Phe Asp Asp Thr Gln Gly His Asp Leu Met
 1280 1285 1290
 Gly Ser Val Thr Leu Asp His Phe Gly Glu Met Pro Gly Gly Pro
 1295 1300 1305

Gly Arg Val Gly Gln Gly Arg Glu Val Gln Trp Gln Val Phe Val
 1310 1315 1320

Pro Ser Ala Glu Ser Arg Glu Lys Leu Ile Ser Leu Leu Ala Arg
 1325 1330 1335

Gln Trp Glu Ala Leu Cys Gly Arg Glu Leu Pro Val Glu Leu Thr
 1340 1345 1350

Gly

<210> 127
 <211> 1118
 <212> PRT
 <213> Mus musculus

<400> 127

Met Lys Glu Ile Cys Arg Ile Cys Ala Arg Glu Leu Cys Gly Asn Gln
 1 5 10 15

Arg Arg Trp Ile Phe His Thr Ala Ser Lys Leu Asn Leu Gln Val Leu
 20 25 30

Leu Ser His Val Leu Gly Lys Asp Val Ser Arg Asp Gly Lys Ala Glu
 35 40 45

Phe Ala Cys Ser Lys Cys Ala Phe Met Leu Asp Arg Ile Tyr Arg Phe
 50 55 60

Asp Thr Val Ile Ala Arg Ile Glu Ala Leu Ser Leu Glu Arg Leu Gln
 65 70 75 80

Lys Leu Leu Leu Glu Lys Asp Arg Leu Lys Phe Cys Ile Ala Ser Met
 85 90 95

Tyr Arg Lys Asn Asn Asp Asp Ser Gly Glu Glu Asn Lys Ala Gly Ser
 100 105 110

Gly Thr Val Asp Ile Ser Gly Leu Pro Asp Met Arg Tyr Ala Ala Leu
 115 120 125

Leu Gln Glu Asp Phe Ala Tyr Ser Gly Phe Glu Cys Trp Val Glu Asn
 130 135 140

Glu Asp Gln Ile Asn Asp Ser His Ser Cys His Ala Ser Glu Gly Pro
 145 150 155 160
 Gly Asn Arg Pro Arg Arg Cys Arg Gly Cys Ala Ala Leu Arg Val Ala
 165 170
 Asp Ser Asp Tyr Glu Ala Ile Cys Lys Val Pro Arg Lys Val Ala Arg
 180 185 190
 Ser Ile Ser Tyr Ala Pro Ser Ser Arg Trp Ser Thr Ser Ile Cys Thr
 195 200 205
 Glu Glu Pro Ala Leu Ser Glu Val Gly Pro Pro Asp Leu Ala Ser Thr
 210 215 220
 Lys Val Pro Pro Asp Gly Glu Ser Met Glu Glu Gly Thr Pro Gly Ser
 225 230 235 240
 Ser Val Glu Ser Leu Asp Ala Ser Val Gln Ala Ser Pro Pro Gln Gln
 245 250 255
 Lys Asp Glu Glu Thr Glu Arg Ser Ala Lys Glu Leu Val Lys Cys Asp
 260 265 270
 Tyr Cys Ser Asp Glu Gln Ala Pro Gln His Leu Cys Asn His Lys Leu
 275 280 285
 Glu Leu Ala Leu Ser Met Ile Lys Gly Leu Asp Tyr Lys Pro Ile Gln
 290 295 300
 Ser Pro Arg Gly Ser Lys Leu Pro Ile Pro Val Lys Ser Ile Leu Pro
 305 310 315 320
 Gly Ala Lys Pro Gly His Ile Leu Thr Asn Gly Val Ser Ser Ser Phe
 325 330 335
 Leu Asn Arg Pro Leu Lys Pro Leu Tyr Arg Thr Pro Val Ser Tyr Pro
 340 345 350
 Trp Glu Ile Ser Asp Gly Gln Glu Leu Trp Asp Asp Leu Cys Asp Glu
 355 360 365
 Tyr Leu Pro Ile Gly Phe Gln Pro Val Pro Lys Gly Leu Pro Thr Gln
 370 375 380

Gln Lys Pro Asp Leu His Glu Thr Pro Thr Thr Gln Pro Pro Val Ser
 385 390 395 400
 Glu Ser His Leu Ala Glu Leu Gln Asp Lys Ile Gln Gln Thr Glu Ala
 405 410 415
 Thr Asn Lys Ile Leu Gln Glu Lys Leu Asn Asp Leu Ser Cys Glu Leu
 420 425 430
 Lys Ser Ala Gln Glu Ser Ser Gln Lys Gln Asp Thr Thr Ile Gln Ser
 435 440 445
 Leu Lys Glu Met Leu Lys Ser Arg Glu Ser Glu Thr Glu Glu Leu Tyr
 450 455 460
 Gln Val Ile Glu Gly Gln Asn Asp Thr Met Ala Lys Leu Arg Glu Met
 465 470 475 480
 Leu His Gln Ser Gln Leu Gly Gln Leu His Ser Ser Glu Gly Ile Ala
 485 490 495
 Pro Ala Gln Gln Gln Val Ala Leu Leu Asp Leu Gln Ser Ala Leu Phe
 500 505 510
 Cys Ser Gln Leu Glu Ile Gln Arg Leu Gln Arg Leu Val Arg Gln Lys
 515 520 525
 Glu Arg Gln Leu Ala Asp Gly Lys Arg Cys Val Gln Leu Val Glu Ala
 530 535 540
 Ala Ala Gln Glu Arg Glu His Gln Lys Glu Ala Ala Trp Lys His Asn
 545 550 555 560
 Gln Glu Leu Arg Lys Ala Leu Gln His Leu Gln Gly Glu Leu His Ser
 565 570 575
 Lys Ser Gln Gln Leu His Val Leu Glu Ala Glu Lys Tyr Asn Glu Ile
 580 585 590
 Arg Thr Gln Gly Gln Asn Ile Gln His Leu Ser His Ser Leu Ser His
 595 600 605
 Lys Glu Gln Leu Ile Gln Glu Leu Gln Glu Leu Leu Gln Tyr Arg Asp
 610 615 620

Asn Ala Asp Lys Thr Leu Asp Thr Asn Glu Val Phe Leu Glu Lys Leu
 625 630 635 640
 Arg Gln Arg Ile Gln Asp Arg Ala Val Ala Leu Glu Arg Val Ile Asp
 645 650 655
 Glu Lys Phe Ser Ala Leu Glu Glu Lys Asp Lys Glu Leu Arg Gln Leu
 660 665 670
 Arg Leu Ala Val Arg Asp Arg Asp His Asp Leu Glu Arg Leu Arg Cys
 675 680 685
 Val Leu Ser Ala Asn Glu Ala Thr Met Gln Ser Met Glu Ser Leu Leu
 690 695 700
 Arg Ala Arg Gly Leu Glu Val Glu Gln Leu Thr Ala Thr Cys Gln Asn
 705 710 715 720
 Leu Gln Trp Leu Lys Glu Glu Leu Glu Thr Lys Phe Gly His Trp Gln
 725 730 735
 Lys Glu Gln Glu Ser Ile Ile Gln Gln Leu Gln Thr Ser Leu His Asp
 740 745 750
 Arg Asn Lys Glu Val Glu Asp Leu Ser Ala Thr Leu Leu Cys Lys Leu
 755 760 765
 Gly Pro Gly Gln Ser Glu Val Ala Glu Glu Leu Cys Gln Arg Leu Gln
 770 775 780
 Arg Lys Glu Arg Met Leu Gln Asp Leu Leu Ser Asp Arg Asn Lys Gln
 785 790 795 800
 Ala Val Glu His Glu Met Glu Ile Gln Gly Leu Leu Gln Ser Met Gly
 805 810 815
 Thr Arg Glu Gln Glu Arg Gln Ala Ala Ala Glu Lys Met Val Gln Ala
 820 825 830
 Phe Met Glu Arg Asn Ser Glu Leu Gln Ala Leu Arg Gln Tyr Leu Gly
 835 840 845
 Gly Lys Glu Leu Met Thr Ser Ser Gln Thr Phe Ile Ser Asn Gln Pro
 850 855 860

Ala Gly Val Thr Ser Ile Gly Pro His His Gly Glu Gln Thr Asp Gln
 865 870 875 880
 Gly Ser Met Gln Met Pro Ser Arg Asp Asp Ser Thr Ser Leu Thr Ala
 885 890 895
 Arg Glu Glu Ala Ser Ile Pro Arg Ser Thr Leu Gly Asp Ser Asp Thr
 900 905 910
 Val Ala Gly Leu Glu Lys Glu Leu Ser Asn Ala Lys Glu Glu Leu Glu
 915 920 925
 Leu Met Ala Lys Lys Glu Arg Glu Ser Gln Met Glu Leu Ser Ala Leu
 930 935 940
 Gln Ser Met Met Ala Met Gln Glu Glu Glu Leu Gln Val Gln Ala Ala
 945 950 955 960
 Asp Leu Glu Ser Leu Thr Arg Asn Val Gln Ile Lys Glu Asp Leu Ile
 965 970 975
 Lys Asp Leu Gln Met Gln Leu Val Asp Pro Glu Asp Ile Pro Ala Met
 980 985 990
 Glu Arg Leu Thr Gln Glu Val Leu Leu Leu Arg Glu Lys Val Ala Ser
 995 1000 1005
 Val Glu Pro Gln Gly Gln Glu Val Ser Gly Asn Lys Arg Gln Gln
 1010 1015 1020
 Leu Leu Leu Met Leu Glu Gly Leu Val Asp Glu Arg Ser Arg Leu
 1025 1030 1035
 Asn Glu Ala Leu Gln Ala Glu Arg Gln Leu Tyr Ser Ser Leu Val
 1040 1045 1050
 Lys Phe His Ala Gln Pro Glu Asn Ser Glu Arg Asp Gly Thr Leu
 1055 1060 1065
 Gln Val Glu Leu Glu Gly Ala Gln Val Leu Arg Thr Arg Leu Glu
 1070 1075 1080
 Glu Val Leu Gly Arg Ser Leu Glu Arg Leu Ser Arg Leu Glu Ser
 1085 1090 1095

Leu Ala Ala Ile Gly Gly Gly Glu Leu Glu Ser Val Gln Ala Arg
 1100 1105 1110

His Lys His Ala Phe
 1115

<210> 128
 <211> 326
 <212> PRT
 <213> Mus musculus

<400> 128

Met Glu Lys Asp Ser Leu Ser Arg Ala Asp Gln Gln Tyr Glu Cys Val
 1 5 10 15

Ala Glu Ile Gly Glu Gly Ala Tyr Gly Lys Val Phe Lys Ala Arg Asp
 20 25 30

Leu Lys Asn Gly Gly Arg Phe Val Ala Leu Lys Arg Val Arg Val Gln
 35 40 45

Thr Ser Glu Glu Gly Met Pro Leu Ser Thr Ile Arg Glu Val Ala Val
 50 55 60

Leu Arg His Leu Glu Thr Phe Glu His Pro Asn Val Val Arg Leu Phe
 65 70 75 80

Asp Val Cys Thr Val Ser Arg Thr Asp Arg Glu Thr Lys Leu Thr Leu
 85 90 95

Val Phe Glu His Val Asp Gln Asp Leu Thr Thr Tyr Leu Asp Lys Val
 100 105 110

Pro Glu Pro Gly Val Pro Thr Glu Thr Ile Lys Asp Met Met Phe Gln
 115 120 125

Leu Leu Arg Gly Leu Asp Phe Leu His Ser His Arg Val Val His Arg
 130 135 140

Asp Leu Lys Pro Gln Asn Ile Leu Val Thr Ser Ser Gly Gln Ile Lys
 145 150 155 160

Leu Ala Asp Phe Gly Leu Ala Arg Ile Tyr Ser Phe Gln Met Ala Leu
 165 170 175

Thr Ser Val Val Val Thr Leu Trp Tyr Arg Ala Pro Glu Val Leu Leu

180 185 190
 Gln Ser Ser Tyr Ala Thr Pro Val Asp Leu Trp Ser Val Gly Cys Ile
 195 200 205
 Phe Ala Glu Met Phe Arg Arg Lys Pro Leu Phe Arg Gly Ser Ser Asp
 210 215 220
 Val Asp Gln Leu Gly Lys Ile Leu Asp Ile Ile Gly Leu Pro Gly Glu
 225 230 235 240
 Glu Asp Trp Pro Arg Asp Val Ala Leu Pro Arg Gln Ala Phe His Ser
 245 250 255
 Lys Ser Ala Gln Pro Ile Glu Lys Phe Val Thr Asp Ile Asp Glu Leu
 260 265 270
 Gly Lys Asp Leu Leu Leu Lys Cys Leu Thr Phe Asn Pro Ala Lys Arg
 275 280 285
 Ile Ser Ala Tyr Gly Ala Leu Asn His Pro Tyr Phe Gln Asp Leu Glu
 290 295 300
 Arg Tyr Lys Asp Asn Leu Asn Ser His Leu Pro Ser Asn Gln Ser Thr
 305 310 315 320
 Ser Glu Leu Asn Thr Ala
 325

<210> 129
 <211> 560
 <212> PRT
 <213> Mus musculus

<400> 129

Met Ser Thr Glu Arg Thr Ser Trp Thr Asn Leu Ser Thr Ile Gln Lys
 1 5 10 15
 Ile Ala Leu Gly Leu Gly Ile Pro Ala Ser Ala Thr Val Ala Tyr Ile
 20 25 30
 Leu Tyr Arg Arg Tyr Arg Glu Ser Arg Glu Glu Arg Leu Thr Phe Val
 35 40 45
 Gly Glu Asp Asp Ile Glu Ile Glu Met Arg Val Pro Gln Glu Ala Val
 50 55 60

Lys Leu Ile Ile Gly Arg Gln Gly Ala Asn Ile Lys Gln Leu Arg Lys
 65 70 75 80
 Gln Thr Gly Ala Arg Ile Asp Val Asp Thr Glu Asp Val Gly Asp Glu
 85 90 95
 Arg Val Leu Leu Ile Ser Gly Phe Pro Val Gln Val Cys Lys Ala Lys
 100 105 110
 Ala Ala Ile His Gln Ile Leu Thr Glu Asn Thr Pro Val Phe Glu Gln
 115 120 125
 Leu Ser Val Pro Gln Arg Ser Val Gly Arg Ile Ile Gly Arg Gly Gly
 130 135 140
 Glu Thr Ile Arg Ser Ile Cys Lys Ala Ser Gly Ala Lys Ile Thr Cys
 145 150 155 160
 Asp Lys Glu Ser Glu Gly Thr Leu Leu Leu Ser Arg Leu Ile Lys Ile
 165 170 175
 Ser Gly Thr Gln Lys Glu Val Ala Ala Ala Lys His Leu Ile Leu Glu
 180 185 190
 Lys Val Ser Glu Asp Glu Glu Leu Arg Lys Arg Ile Ala His Ser Ala
 195 200 205
 Glu Thr Arg Val Pro Arg Lys Gln Pro Ile Ser Val Arg Arg Glu Glu
 210 215 220
 Val Thr Glu Pro Gly Gly Ala Gly Glu Ala Ala Leu Trp Lys Asn Thr
 225 230 235 240
 Asn Ser Ser Met Gly Pro Ala Thr Pro Leu Glu Val Pro Leu Arg Lys
 245 250 255
 Gly Gly Gly Asp Met Val Val Val Gly Pro Lys Glu Gly Ser Trp Glu
 260 265 270
 Lys Pro Asn Asp Asp Ser Phe Gln Asn Ser Gly Ala Gln Ser Ser Pro
 275 280 285
 Glu Thr Ser Met Phe Glu Ile Pro Ser Pro Asp Phe Ser Phe His Ala
 290 295 300

Asp Glu Tyr Leu Glu Val Tyr Val Ser Ser Ser Glu His Pro Asn His
 305 310 315 320
 Phe Trp Ile Gln Ile Ile Gly Ser Arg Ser Leu Gln Leu Asp Lys Leu
 325 330 335
 Val Ser Glu Met Thr Gln His Tyr Glu Asn Ser Leu Pro Glu Asp Leu
 340 345 350
 Thr Val His Val Gly Asp Ile Val Ala Ala Pro Leu Ser Thr Asn Gly
 355 360 365
 Ser Trp Tyr Arg Ala Arg Val Leu Gly Thr Leu Glu Asn Gly Asn Leu
 370 375 380
 Asp Leu Tyr Phe Val Asp Phe Gly Asp Asn Gly Asp Cys Ala Leu Lys
 385 390 395 400
 Asp Leu Arg Ala Leu Arg Ser Asp Phe Leu Ser Leu Pro Phe Gln Ala
 405 410 415
 Ile Glu Cys Ser Leu Ala Arg Ile Ala Pro Thr Gly Glu Glu Trp Glu
 420 425 430
 Glu Glu Ala Leu Asp Glu Phe Asp Arg Leu Thr His Cys Ala Asp Trp
 435 440 445
 Lys Pro Leu Val Ala Lys Ile Ser Ser Tyr Val Gln Thr Gly Ile Ser
 450 455 460
 Thr Trp Pro Lys Ile Tyr Leu Tyr Asp Thr Ser Asp Glu Lys Lys Leu
 465 470 475 480
 Asp Ile Gly Leu Glu Leu Val Arg Lys Gly Tyr Ala Val Glu Leu Pro
 485 490 495
 Glu Asp Met Glu Glu Asn Arg Thr Val Pro Asn Met Leu Lys Asp Met
 500 505 510
 Ala Thr Glu Thr Asp Asp Ser Leu Ala Ser Ile Leu Thr Glu Thr Lys
 515 520 525
 Lys Ser Pro Glu Glu Met Pro His Thr Leu Ser Cys Leu Ser Leu Ser
 530 535 540

Glu Ala Ala Ser Met Ser Gly Asp Asp Asn Leu Glu Asp Asp Leu Phe
 545 550 555 560

<210> 130
 <211> 429
 <212> PRT
 <213> Mus musculus

<400> 130

Met Arg Gly Pro Glu Leu Gly Pro Glu Thr Ser Met Glu Gly Asp Val
 1 5 10 15

Leu Asp Thr Leu Glu Ala Leu Gly Tyr Lys Gly Pro Leu Leu Glu Glu
 20 25 30

Gln Ala Leu Ser Lys Ala Ala Glu Gly Gly Leu Ser Ser Pro Glu Phe
 35 40 45

Ser Glu Leu Cys Ile Trp Leu Gly Ser Gln Ile Lys Ser Leu Cys Asn
 50 55 60

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

Gln Leu Glu Ile Ser Gly Phe Leu Lys Glu Met Ala Cys Pro Tyr Ser
 85 90 95

Val Leu Val Ser Gly Asp Ile Lys Glu Arg Leu Thr Lys Lys Asp Asp
 100 105 110

Cys Leu Lys Leu Leu Leu Phe Leu Ser Thr Glu Leu Gln Ala Leu Gln
 115 120 125

Ile Leu Gln Lys Lys Lys His Lys Asn Ser Gln Leu Asp Lys Asn Ser
 130 135 140

Glu Ile Cys Gln Glu Val Gln Ala Val Cys Asp Ala Leu Gly Val Pro
 145 150 155 160

Lys Ser Asp Thr Ser Asp Ile Pro Leu Leu Leu Ser Gln Val Glu Ser
 165 170 175

Lys Val Lys Asp Ile Leu Cys Arg Val Gln Lys Asn His Val Gly Lys
 180 185 190

Pro Leu Leu Lys Val Asp Leu Ser Ser Glu Gln Ala Glu Lys Leu Glu
 195 200 205
 Arg Ile Asn Asp Ala Leu Ser Cys Glu Tyr Glu Cys Arg Arg Arg Met
 210 215 220
 Leu Met Lys Arg Leu Asp Val Thr Val Gln Ser Phe Gly Trp Ser Asp
 225 230 235 240
 Arg Ala Lys Ala Lys Thr Asp Asn Ile Ala Arg Ile Tyr Gln Pro Lys
 245 250 255
 Arg Tyr Ala Leu Ser Pro Lys Thr Thr Val Thr Leu Ala His Leu Leu
 260 265 270
 Ala Ala Arg Glu Asp Leu Ser Lys Ile Ile Arg Thr Ser Ser Gly Ile
 275 280 285
 Ser Arg Glu Lys Thr Ala Cys Ala Ile Asn Lys Val Leu Met Gly Arg
 290 295 300
 Val Pro Asp Arg Gly Gly Arg Pro Asn Glu Ile Glu Pro Pro Pro Pro
 305 310 315 320
 Glu Met Pro Pro Trp Gln Lys Arg Gln Glu Gly Gly Gly Arg Gly Gly
 325 330 335
 Trp Gly Gly Gly Gly Gly Gly Arg Gly Gly Gly Gly Gly Gly Arg Gly
 340 345 350
 Gly Trp Gly Gly Gly Gly Gly Trp Gly Gly Gly Gly Gly Ser Gly Gly
 355 360 365
 Gly Trp Gly Gly Ser Gly Gly Gly Gly Gly Gly Arg Gly Gly Phe Gln
 370 375 380
 Gly Arg Gly Asp Tyr Gly Gly Arg Gly Asp Tyr Gly Gly Arg Gly Gly
 385 390 395 400
 Tyr Gly Gly Arg Gly Gly Tyr Gly Gly Arg Gly Tyr Gly Asp Pro Tyr
 405 410 415
 Gly Gly Gly Gly Gly Gly Gly Gly Tyr Arg Arg Tyr
 420 425

<210> 131
 <211> 93
 <212> PRT
 <213> Mus musculus

<400> 131

Met Cys Gly Pro Asn Ala Asn Ala Pro Gln Thr Thr Val Lys Ala His
 1 5 10 15

Thr Ile Glu Trp His Cys Pro Ala Gly His Cys Trp His Pro Thr Asn
 20 25 30

Ser Pro His Arg Pro Thr Leu Glu Pro Gly Gln Ser Tyr Gly Pro Ser
 35 40 45

Leu Val Val Cys Trp Ser Leu Pro Pro His Gln Arg Ser Leu Ser Leu
 50 55 60

His Ser Glu Arg Asn Val Val Thr Ser Arg Cys Pro Ala Leu Ser Leu
 65 70 75 80

Ala Pro Phe Leu His Asp Leu Lys Leu Asn Arg Leu Pro
 85 90

<210> 132
 <211> 123
 <212> PRT
 <213> Mus musculus

<400> 132

Met Val Ala Trp Leu Trp Lys Val Leu Met Gly Val Gly Leu Phe Ala
 1 5 10 15

Leu Thr His Ala Ala Phe Ser Ala Ala Gln His Arg Ser His Ala Arg
 20 25 30

Leu Thr Glu Lys Lys Tyr Glu Pro Leu Pro Ala Asp Ile Val Leu Gln
 35 40 45

Thr Leu Leu Ala Phe Ala Leu Thr Cys Tyr Gly Val Val His Thr Ala
 50 55 60

Gly Asp Phe Arg Asp Arg Asp Ala Thr Ser Glu Leu Lys Asp Met Thr
 65 70 75 80

Phe Asp Thr Leu Arg Asn Arg Pro Ser Phe Tyr Val Phe His Arg Ser

85 90 95
 Gly Tyr Arg Leu Phe Gln Arg Pro Asp Ser Thr His Ser Ser Asn Leu
 100 105 110
 Ser Ala Ser Ser Ser Asp Leu Pro Leu Lys Phe
 115 120
 <210> 133
 <211> 820
 <212> PRT
 <213> Mus musculus
 <400> 133
 Met Ala Ala Gly Lys Phe Ala Ser Leu Pro Arg Asn Met Pro Val Asn
 1 5 10 15
 His Gln Phe Pro Leu Ala Ser Ser Met Asp Leu Leu Ser Ser Lys Ser
 20 25 30
 Pro Leu Ala Glu Arg Arg Thr Asp Ala Tyr Gln Asp Val Ser Ile His
 35 40 45
 Gly Thr Leu Pro Arg Lys Lys Lys Gly Pro Pro Ser Ile Arg Ser Cys
 50 55 60
 Asp Asn Ala Gly His Ser Lys Ser Pro Arg Gln Ser Ser Pro Leu Thr
 65 70 75 80
 Gln Asp Ile Ile Gln Glu Asn Pro Leu Gln Asp Arg Lys Gly Glu Asn
 85 90 95
 Phe Ile Phe Arg Asp Pro Tyr Leu Leu Asp Pro Thr Leu Glu Tyr Val
 100 105 110
 Lys Phe Ser Lys Glu Arg His Ile Met Asp Arg Thr Pro Glu Arg Leu
 115 120 125
 Lys Lys Glu Leu Glu Glu Glu Leu Leu Leu Ser Ser Glu Asp Leu Arg
 130 135 140
 Ser His Ala Trp Tyr His Gly Arg Ile Pro Arg Gln Val Ser Glu Asn
 145 150 155 160
 Leu Val Gln Arg Asp Gly Asp Phe Leu Val Arg Asp Ser Leu Ser Ser
 165 170 175

Pro Gly Asn Phe Val Leu Thr Cys Gln Trp Lys Asn Leu Ala Gln His
 180 185 190
 Phe Lys Ile Asn Arg Thr Val Leu Arg Leu Ser Glu Ala Tyr Ser Arg
 195 200 205
 Val Gln Tyr Gln Phe Glu Met Glu Ser Phe Asp Ser Ile Pro Gly Leu
 210 215 220
 Val Arg Cys Tyr Val Gly Asn Arg Arg Pro Ile Ser Gln Gln Ser Gly
 225 230 235 240
 Ala Ile Ile Phe Gln Pro Ile Asn Arg Thr Val Pro Leu Trp Cys Leu
 245 250 255
 Glu Glu Arg Tyr Gly Thr Ser Pro Gly Arg Gly Arg Glu Gly Ser Leu
 260 265 270
 Ala Glu Gly Arg Pro Asp Val Val Lys Arg Leu Ser Leu Thr Thr Gly
 275 280 285
 Ser Ser Ile Gln Ala Arg Glu His Ser Leu Pro Arg Gly Asn Leu Leu
 290 295 300
 Arg Asn Lys Glu Lys Ser Gly Ser Gln Pro Ala Cys Leu Asp His Val
 305 310 315 320
 Gln Asp Arg Lys Ala Leu Thr Leu Lys Ala His Gln Ser Glu Ser His
 325 330 335
 Leu Pro Ile Gly Cys Lys Leu Pro Pro Gln Ser Pro Ser Met Asp Thr
 340 345 350
 Ser Pro Cys Pro Ser Ser Pro Val Phe Arg Thr Gly Ser Glu Pro Thr
 355 360 365
 Leu Ser Pro Ala Leu Val Arg Arg Phe Ser Ser Asp Ala Arg Thr Gly
 370 375 380
 Glu Ala Leu Arg Gly Ser Asp Ser Gln Leu Cys Pro Lys Pro Pro Pro
 385 390 395 400
 Lys Pro Cys Lys Val Pro Phe Leu Lys Thr Pro Pro Ser Pro Ser Pro
 405 410 415

Trp Leu Thr Ser Glu Ala Asn Tyr Cys Glu Leu Asn Pro Ala Phe Ala
 420 425 430
 Val Gly Cys Asp Arg Gly Ala Lys Leu Pro Met Gln Ala His Asp Ser
 435 440 445
 His Glu Met Leu Leu Thr Ala Lys Gln Asn Gly Pro Ser Gly Pro Arg
 450 455 460
 Asn Ser Gly Ile Asn Tyr Met Ile Leu Asp Gly Asp Asp Gln Ala Arg
 465 470 475 480
 His Trp Asp Pro Leu Ala Val Gln Thr Asp Glu Gly Gln Glu Asp Lys
 485 490 495
 Thr Lys Phe Val Pro Pro Leu Met Glu Thr Val Ser Ser Phe Arg Pro
 500 505 510
 Asn Asp Phe Glu Ser Lys Leu Leu Pro Pro Glu Asn Lys Pro Leu Glu
 515 520 525
 Thr Ala Met Leu Lys His Ala Lys Glu Leu Phe Thr Asn His Asp Ala
 530 535 540
 Arg Val Ile Ala Gln His Met Leu Ser Val Asp Cys Lys Val Ala Arg
 545 550 555 560
 Ile Leu Glu Val Ser Glu Asp Arg Lys Arg Ser Met Gly Val Ser Ser
 565 570 575
 Gly Leu Glu Leu Ile Thr Leu Pro His Gly Arg Gln Leu Arg Leu Asp
 580 585 590
 Ile Ile Glu Arg His Asn Thr Met Ala Ile Gly Ile Ala Val Asp Ile
 595 600 605
 Leu Gly Cys Thr Gly Thr Leu Glu Asn Arg Ala Gly Thr Leu Asn Lys
 610 615 620
 Ile Ile Gln Val Ala Val Glu Leu Lys Asp Ala Met Gly Asp Leu Tyr
 625 630 635 640
 Ala Phe Ser Ala Ile Met Lys Ala Leu Glu Met Pro Gln Ile Thr Arg
 645 650 655

Leu Glu Lys Thr Trp Thr Ala Leu Arg His His Tyr Thr Gln Thr Ala
660 665 670

Ile Leu Tyr Glu Lys Gln Leu Lys Pro Phe Ser Lys Ile Leu His Glu
675 680 685

Gly Arg Glu Ser Thr Tyr Val Pro Ala Ser Asn Val Ser Val Pro Leu
690 695 700

Leu Met Pro Leu Val Thr Leu Met Glu Arg Gln Ala Val Thr Phe Glu
705 710 715 720

Gly Thr Asp Met Trp Glu Asn Asn Asp Glu Ser Cys Glu Ile Leu Leu
725 730 735

Asn His Leu Ala Thr Ala Arg Phe Met Ala Glu Ala Ser Glu Ser Tyr
740 745 750

Arg Met Asn Ala Glu Arg Ile Leu Ala Asp Phe Gln Pro Asp Glu Glu
755 760 765

Met Thr Glu Ile Leu Arg Thr Glu Phe Gln Met Arg Leu Leu Trp Gly
770 775 780

Ser Lys Gly Ala Glu Val Asn Gln Asn Glu Arg Tyr Asp Lys Phe Asn
785 790 795 800

Gln Ile Leu Thr Ala Leu Ser Arg Lys Leu Glu Pro Pro Ser Gly Lys
805 810 815

Gln Ala Glu Leu
820

<210> 134

<211> 849

<212> PRT

<213> Mus musculus

<400> 134

Met His Lys His Gln His Cys Cys Lys Cys Pro Glu Cys Tyr Glu Val
1 5 10 15

Thr Arg Leu Ala Ala Leu Arg Arg Leu Glu Pro Pro Gly Tyr Gly Asp
20 25 30

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

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

Ser Leu Arg Thr Ser Glu Lys Arg Ser Leu Tyr Val Arg Ala Leu Phe
 515 520 525
 Asp Tyr Asp Arg Thr Arg Asp Ser Cys Leu Pro Ser Gln Gly Leu Ser
 530 535 540
 Phe Ser Tyr Gly Asp Ile Leu His Val Ile Asn Ala Ser Asp Asp Glu
 545 550 555 560
 Trp Trp Gln Ala Arg Leu Val Thr Pro His Gly Glu Ser Glu Gln Ile
 565 570 575
 Gly Val Ile Pro Ser Lys Lys Arg Val Glu Lys Lys Glu Arg Ala Arg
 580 585 590
 Leu Lys Thr Val Lys Phe His Ala Arg Thr Gly Met Ile Glu Ser Asn
 595 600 605
 Arg Asp Phe Pro Gly Leu Ser Asp Asp Tyr Tyr Gly Ala Lys Asn Leu
 610 615 620
 Lys Gly Val Thr Ser Asn Thr Ser Asp Ser Glu Ser Ser Ser Lys Gly
 625 630 635 640
 Gln Glu Asp Ala Ile Leu Ser Tyr Glu Pro Val Thr Arg Gln Glu Ile
 645 650 655
 His Tyr Ala Arg Pro Val Ile Ile Leu Gly Pro Met Lys Asp Arg Val
 660 665 670
 Asn Asp Asp Leu Ile Ser Glu Phe Pro His Lys Phe Gly Ser Cys Val
 675 680 685
 Pro His Thr Thr Arg Pro Arg Arg Asp Asn Glu Val Asp Gly Gln Asp
 690 695 700
 Tyr His Phe Val Val Ser Arg Glu Gln Met Glu Lys Asp Ile Gln Asp
 705 710 715 720
 Asn Lys Phe Ile Glu Ala Gly Gln Phe Asn Asp Asn Leu Tyr Gly Thr
 725 730 735
 Ser Ile Gln Ser Val Arg Ala Val Ala Glu Arg Gly Lys His Cys Ile
 740 745 750

Leu Asp Val Ser Gly Asn Ala Ile Lys Arg Leu Gln Gln Ala Gln Leu
755 760 765

Tyr Pro Ile Ala Ile Phe Ile Lys Pro Lys Ser Ile Glu Ala Leu Met
770 775 780

Glu Met Asn Arg Arg Gln Thr Tyr Glu Gln Ala Asn Lys Ile Phe Asp
785 790 795 800

Lys Ala Met Lys Leu Glu Gln Glu Phe Gly Glu Tyr Phe Thr Ala Ile
805 810 815

Val Gln Gly Asp Ser Leu Glu Glu Ile Tyr Asn Lys Ile Lys Gln Ile
820 825 830

Ile Glu Asp Gln Ser Gly His Tyr Ile Trp Val Pro Ser Pro Glu Lys
835 840 845

Leu

<210> 135
<211> 59
<212> PRT
<213> Mus musculus

<400> 135

Met Arg Gln Leu Lys Gly Lys Pro Lys Lys Glu Thr Ser Lys Asp Lys
1 5 10 15

Lys Glu Arg Lys Gln Ala Met Gln Glu Ala Arg Gln Gln Ile Thr Thr
20 25 30

Val Val Leu Pro Thr Leu Ala Val Val Val Leu Leu Ile Val Val Phe
35 40 45

Val Tyr Val Ala Thr Arg Pro Ala Val Thr Glu
50 55

<210> 136
<211> 683
<212> PRT
<213> Mus musculus

<400> 136

Met Thr Met Gln Pro Ala Ile Gln Val Trp Phe Gly Glu Asp Leu Pro

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

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

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

<210> 137
 <211> 115
 <212> PRT
 <213> Mus musculus

<400> 137

Met Gly Lys Arg Asp Asn Arg Val Ala Tyr Met Asn Pro Ile Ala Met
 1 5 10 15

Ala Arg Ser Arg Gly Pro Ile Gln Ser Ser Gly Pro Thr Ile Gln Asp
20 25 30

Tyr Leu Asn Arg Pro Arg Pro Thr Trp Glu Glu Val Lys Glu Gln Leu
35 40 45

Glu Lys Lys Lys Lys Gly Ser Lys Ala Leu Ala Glu Phe Glu Glu Lys
50 55 60

Met Asn Glu Asn Trp Lys Lys Glu Leu Glu Lys His Arg Glu Lys Leu
65 70 75 80

Leu Ser Gly Asn Glu Ser Ser Ser Lys Lys Arg Gln Lys Lys Lys Lys
85 90 95

Glu Lys Lys Lys Ser Gly Arg Val Ser Lys Ser Phe Leu Phe Ser Lys
100 105 110

Cys Tyr Ser
115

<210> 138
<211> 343
<212> PRT
<213> Mus musculus

<400> 138

Met Glu Val Ser Cys Gly Gln Ala Glu Ser Ser Glu Lys Pro Asn Ala
1 5 10 15

Glu Asp Met Thr Ser Lys Asp Tyr Tyr Phe Asp Ser Tyr Ala His Phe
20 25 30

Gly Ile His Glu Glu Met Leu Lys Asp Glu Val Arg Thr Leu Thr Tyr
35 40 45

Arg Asn Ser Met Phe His Asn Arg His Leu Phe Lys Asp Lys Val Val
50 55 60

Leu Asp Val Gly Ser Gly Thr Gly Ile Leu Cys Met Phe Ala Ala Lys
65 70 75 80

Ala Gly Ala Arg Lys Val Ile Gly Ile Glu Cys Ser Ser Ile Ser Asp
85 90 95

Tyr Ala Val Lys Ile Val Lys Ala Asn Lys Leu Asp His Val Val Thr
 100 105 110
 Ile Ile Lys Gly Lys Val Glu Glu Val Glu Leu Pro Val Glu Lys Val
 115 120 125
 Asp Ile Ile Ile Ser Glu Trp Met Gly Tyr Cys Leu Phe Tyr Glu Ser
 130 135 140
 Met Leu Asn Thr Val Leu His Ala Arg Asp Lys Trp Leu Ala Pro Asp
 145 150 155 160
 Gly Leu Ile Phe Pro Asp Arg Ala Thr Leu Tyr Val Thr Ala Ile Glu
 165 170 175
 Asp Arg Gln Tyr Lys Asp Tyr Lys Ile His Trp Trp Glu Asn Val Tyr
 180 185 190
 Gly Phe Asp Met Ser Cys Ile Lys Asp Val Ala Ile Lys Glu Pro Leu
 195 200 205
 Val Asp Val Val Asp Pro Lys Gln Leu Val Thr Asn Ala Cys Leu Ile
 210 215 220
 Lys Glu Val Asp Ile Tyr Thr Val Lys Val Glu Asp Leu Thr Phe Thr
 225 230 235 240
 Ser Pro Phe Cys Leu Gln Val Lys Arg Asn Asp Tyr Val His Ala Leu
 245 250 255
 Val Ala Tyr Phe Asn Ile Glu Phe Thr Arg Cys His Lys Arg Thr Gly
 260 265 270
 Phe Ser Thr Ser Pro Glu Ser Pro Tyr Thr His Trp Lys Gln Thr Val
 275 280 285
 Phe Tyr Met Glu Asp Tyr Leu Thr Val Lys Thr Gly Glu Glu Ile Phe
 290 295 300
 Gly Thr Ile Gly Met Arg Pro Asn Ala Lys Asn Asn Arg Asp Leu Asp
 305 310 315 320
 Phe Thr Ile Asp Leu Asp Phe Lys Gly Gln Leu Cys Glu Leu Ser Cys
 325 330 335

Ser Thr Asp Tyr Arg Met Arg
340

<210> 139

<211> 97

<212> PRT

<213> Mus musculus

<400> 139

Met Ser Ser Ala Pro Asp Pro Pro Thr Val Lys Lys Glu Pro Leu Lys
1 5 10 15

Glu Lys Asn Phe Glu Asn Pro Gly Leu Arg Gly Ala His Thr Thr Thr
20 25 30

Leu Phe Arg Ala Val Asn Pro Glu Leu Phe Ile Lys Pro Asn Lys Pro
35 40 45

Val Met Ala Phe Gly Leu Val Thr Leu Ser Leu Cys Val Ala Tyr Ile
50 55 60

Gly Tyr Leu His Ala Thr Gln Glu Asn Arg Lys Asp Leu Tyr Glu Ala
65 70 75 80

Ile Asp Ser Glu Gly His Arg Tyr Met Arg Arg Lys Thr Ser Lys Trp
85 90 95

Asp

<210> 140

<211> 393

<212> PRT

<213> Mus musculus

<400> 140

Met Gly Ala Ala Ala Trp Ala Pro Pro His Leu Leu Leu Arg Ala Ser
1 5 10 15

Phe Leu Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Arg Ser Ala Gly
20 25 30

Ser Trp Asp Leu Ala Gly Tyr Leu Leu Tyr Cys Pro Cys Met Gly Arg
35 40 45

Phe Gly Asn Gln Ala Asp His Phe Leu Gly Ser Leu Ala Phe Ala Lys

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

290 295 300
 Ala Leu Asn Ala Arg Ser Val Tyr Ile Ala Thr Asp Ser Glu Ser Tyr
 305 310 315 320
 Val Ser Glu Ile Gln Gln Leu Phe Lys Asp Lys Val Arg Val Val Ser
 325 330 335
 Leu Lys Pro Glu Val Ala Gln Ile Asp Leu Tyr Ile Leu Gly Gln Ala
 340 345 350
 Asp His Phe Ile Gly Asn Cys Val Ser Ser Phe Thr Ala Phe Val Lys
 355 360 365
 Arg Glu Arg Asp Leu His Gly Arg Gln Ser Ser Phe Phe Gly Met Asp
 370 375 380
 Arg Pro Ser Gln Leu Arg Asp Glu Phe
 385 390
 <210> 141
 <211> 1658
 <212> PRT
 <213> Mus musculus
 <400> 141
 Met Met Ala Gln Phe Pro Thr Ala Met Asn Gly Gly Pro Asn Met Trp
 1 5 10 15
 Ala Ile Thr Ser Glu Glu Arg Thr Lys His Asp Lys Gln Phe Asp Asn
 20 25 30
 Leu Lys Pro Ser Gly Gly Tyr Ile Thr Gly Asp Gln Ala Arg Thr Phe
 35 40 45
 Phe Leu Gln Ser Gly Leu Pro Ala Pro Val Leu Ala Glu Ile Trp Ala
 50 55 60
 Leu Ser Asp Leu Asn Lys Asp Gly Lys Met Asp Gln Gln Glu Phe Ser
 65 70 75 80
 Ile Ala Met Lys Leu Ile Lys Leu Lys Leu Gln Gly Gln Gln Leu Pro
 85 90 95
 Val Val Leu Pro Pro Ile Met Lys Gln Pro Pro Met Phe Ser Pro Leu
 100 105 110

Ile Ser Ala Arg Phe Gly Met Gly Ser Met Pro Asn Leu Ser Ile His
 115 120 125
 Gln Pro Leu Pro Pro Val Ala Pro Ile Ala Thr Pro Leu Ser Ser Ala
 130 135 140
 Thr Ser Gly Thr Ser Ile Pro Pro Leu Met Met Pro Ala Pro Leu Val
 145 150 155 160
 Pro Ser Val Ser Thr Ser Ser Leu Pro Asn Gly Thr Ala Ser Leu Ile
 165 170 175
 Gln Pro Leu Ser Ile Pro Tyr Ser Ser Ser Thr Leu Pro His Ala Ser
 180 185 190
 Ser Tyr Ser Leu Met Met Gly Gly Phe Gly Gly Ala Ser Ile Gln Lys
 195 200 205
 Ala Gln Ser Leu Ile Asp Leu Gly Ser Ser Ser Ser Thr Ser Ser Thr
 210 215 220
 Ala Ser Leu Ser Gly Asn Ser Pro Lys Thr Gly Thr Ser Glu Trp Ala
 225 230 235 240
 Val Pro Gln Pro Ser Arg Leu Lys Tyr Arg Gln Lys Phe Asn Ser Leu
 245 250 255
 Asp Lys Gly Met Ser Gly Tyr Leu Ser Gly Phe Gln Ala Arg Asn Ala
 260 265 270
 Leu Leu Gln Ser Asn Leu Ser Gln Thr Gln Leu Ala Thr Ile Trp Thr
 275 280 285
 Leu Ala Asp Ile Asp Gly Asp Gly Gln Leu Lys Ala Glu Glu Phe Ile
 290 295 300
 Leu Ala Met His Leu Thr Asp Met Ala Lys Ala Gly Gln Pro Leu Pro
 305 310 315 320
 Leu Thr Leu Pro Pro Glu Leu Val Pro Pro Ser Phe Arg Gly Gly Lys
 325 330 335
 Gln Val Asp Ser Val Asn Gly Thr Leu Pro Ser Tyr Gln Lys Thr Gln
 340 345 350

Glu Glu Glu Pro Gln Lys Lys Leu Pro Val Thr Phe Glu Asp Lys Arg
 355 360 365
 Lys Ala Asn Tyr Glu Arg Gly Asn Met Glu Leu Glu Lys Arg Arg Gln
 370 375 380
 Val Leu Met Glu Gln Gln Gln Arg Glu Ala Glu Arg Lys Ala Gln Lys
 385 390 395 400
 Glu Lys Glu Glu Trp Glu Arg Lys Gln Arg Glu Leu Gln Glu Gln Glu
 405 410 415
 Trp Lys Lys Gln Leu Glu Leu Glu Lys Arg Leu Glu Lys Gln Arg Glu
 420 425 430
 Leu Glu Arg Gln Arg Glu Glu Glu Arg Arg Lys Glu Ile Glu Arg Arg
 435 440 445
 Glu Ala Ala Lys Gln Glu Leu Glu Arg Gln Arg Arg Leu Glu Trp Glu
 450 455 460
 Arg Leu Arg Arg Gln Glu Leu Leu Ser Gln Lys Thr Arg Glu Gln Glu
 465 470 475 480
 Asp Ile Val Arg Leu Ser Ser Arg Lys Lys Ser Leu His Leu Glu Leu
 485 490 495
 Glu Ala Val Asn Gly Lys His Gln Gln Ile Ser Gly Arg Leu Gln Asp
 500 505 510
 Val Gln Ile Arg Lys Gln Thr Gln Lys Thr Glu Leu Glu Val Leu Asp
 515 520 525
 Lys Gln Cys Asp Leu Glu Ile Met Glu Ile Lys Gln Leu Gln Gln Glu
 530 535 540
 Leu Lys Glu Tyr Gln Asn Lys Leu Ile Tyr Leu Val Pro Glu Lys Gln
 545 550 555 560
 Leu Leu Asn Glu Arg Ile Lys Asn Met Gln Leu Ser Asn Thr Pro Asp
 565 570 575
 Ser Gly Ile Ser Leu Leu His Lys Lys Ser Ser Glu Lys Glu Glu Leu
 580 585 590

Cys Gln Arg Leu Lys Glu Gln Leu Asp Ala Leu Glu Lys Glu Thr Ala
 595 600 605
 Ser Lys Leu Ser Glu Met Asp Ser Phe Asn Asn Gln Leu Lys Glu Leu
 610 615 620
 Arg Glu Ser Tyr Asn Thr Gln Gln Leu Ala Leu Glu Gln Leu His Lys
 625 630 635 640
 Ile Lys Arg Asp Lys Leu Lys Glu Ile Glu Arg Lys Arg Leu Glu Gln
 645 650 655
 Ile Gln Lys Lys Lys Leu Glu Asp Glu Ala Ala Arg Lys Ala Lys Gln
 660 665 670
 Gly Lys Glu Asn Leu Trp Arg Glu Ser Ile Arg Lys Glu Glu Glu Glu
 675 680 685
 Lys Gln Lys Arg Leu Gln Glu Glu Lys Ser Gln Asp Lys Thr Gln Glu
 690 695 700
 Glu Glu Arg Lys Ala Glu Ala Lys Gln Ser Glu Thr Ala Ser Ala Leu
 705 710 715 720
 Val Asn Tyr Arg Ala Leu Tyr Pro Phe Glu Ala Arg Asn His Asp Glu
 725 730 735
 Met Ser Phe Ser Ser Gly Asp Ile Ile Gln Val Asp Glu Lys Thr Val
 740 745 750
 Gly Glu Pro Gly Trp Leu Tyr Gly Ser Phe Gln Gly Lys Phe Gly Trp
 755 760 765
 Phe Pro Cys Asn Tyr Val Glu Lys Val Leu Ser Ser Glu Lys Ala Leu
 770 775 780
 Ser Pro Lys Lys Ala Leu Leu Pro Pro Thr Val Ser Leu Ser Ala Thr
 785 790 795 800
 Ser Thr Ser Ser Gln Pro Pro Ala Ser Val Thr Asp Tyr His Asn Val
 805 810 815
 Ser Phe Ser Asn Leu Thr Val Asn Thr Thr Trp Gln Gln Lys Ser Ala
 820 825 830

Phe Thr Arg Thr Val Ser Pro Gly Ser Val Ser Pro Ile His Gly Gln
 835 840 845

Gly Gln Ala Val Glu Asn Leu Lys Ala Gln Ala Leu Cys Ser Trp Thr
 850 855 860

Ala Lys Lys Glu Asn His Leu Asn Phe Ser Lys His Asp Val Ile Thr
 865 870 875 880

Val Leu Glu Gln Gln Glu Asn Trp Trp Phe Gly Glu Val His Gly Gly
 885 890 895

Arg Gly Trp Phe Pro Lys Ser Tyr Val Lys Leu Ile Pro Gly Asn Glu
 900 905 910

Val Gln Arg Gly Glu Pro Glu Ala Leu Tyr Ala Ala Val Thr Lys Lys
 915 920 925

Pro Thr Ser Thr Ala Tyr Pro Val Thr Ser Thr Ala Tyr Pro Val Gly
 930 935 940

Glu Asp Tyr Ile Ala Leu Tyr Ser Tyr Ser Ser Val Glu Pro Gly Asp
 945 950 955 960

Leu Thr Phe Thr Glu Gly Glu Glu Ile Leu Val Thr Gln Lys Asp Gly
 965 970 975

Glu Trp Trp Thr Gly Ser Ile Gly Glu Arg Thr Gly Ile Phe Pro Ser
 980 985 990

Asn Tyr Val Arg Pro Lys Asp Gln Glu Asn Phe Gly Asn Ala Ser Lys
 995 1000 1005

Ser Gly Ala Ser Asn Lys Lys Pro Glu Ile Ala Gln Val Thr Ser
 1010 1015 1020

Ala Tyr Ala Ala Ser Gly Thr Glu Gln Leu Ser Leu Ala Pro Gly
 1025 1030 1035

Gln Leu Ile Leu Ile Leu Lys Lys Asn Thr Ser Gly Trp Trp Gln
 1040 1045 1050

Gly Glu Leu Gln Ala Arg Gly Lys Lys Arg Gln Lys Gly Trp Phe
 1055 1060 1065

Pro Ala Ser His Val Lys Leu Leu Gly Pro Ser Ser Glu Arg Thr
 1070 1075 1080
 Met Pro Thr Phe His Ala Val Cys Gln Val Ile Ala Met Tyr Asp
 1085 1090 1095
 Tyr Met Ala Asn Asn Glu Asp Glu Leu Asn Phe Ser Lys Gly Gln
 1100 1105 1110
 Leu Ile Asn Val Met Asn Lys Asp Asp Pro Asp Trp Trp Gln Gly
 1115 1120 1125
 Glu Thr Asn Gly Leu Thr Gly Leu Phe Pro Ser Asn Tyr Val Lys
 1130 1135 1140
 Met Thr Thr Asp Ser Asp Pro Ser Gln Gln Trp Cys Ala Asp Leu
 1145 1150 1155
 Gln Ala Leu Asp Thr Met Gln Pro Thr Glu Arg Lys Arg Gln Gly
 1160 1165 1170
 Tyr Ile His Glu Leu Ile Gln Thr Glu Glu Arg Tyr Met Asp Asp
 1175 1180 1185
 Leu Gln Leu Val Ile Glu Val Phe Gln Lys Arg Met Ala Glu Ser
 1190 1195 1200
 Gly Phe Leu Thr Glu Ala Asp Met Ala Leu Ile Phe Val Asn Trp
 1205 1210 1215
 Lys Glu Leu Ile Met Ser Asn Thr Lys Leu Leu Arg Ala Leu Arg
 1220 1225 1230
 Val Arg Lys Lys Thr Gly Gly Glu Lys Met Pro Val Gln Met Ile
 1235 1240 1245
 Gly Asp Ile Leu Ala Ala Glu Leu Ser His Met Gln Ala Tyr Ile
 1250 1255 1260
 Arg Phe Cys Ser Cys Gln Leu Asn Gly Ala Thr Leu Leu Gln Gln
 1265 1270 1275
 Lys Thr Asp Glu Asp Thr Asp Phe Lys Glu Phe Leu Lys Lys Leu
 1280 1285 1290

Ala Ser Asp Pro Arg Cys Lys Gly Met Pro Leu Ser Ser Phe Leu
 1295 1300 1305
 Leu Lys Pro Met Gln Arg Ile Thr Arg Tyr Pro Leu Leu Ile Arg
 1310 1315 1320
 Ser Ile Leu Glu Asn Thr Pro Gln Ser His Val Asp His Ser Ser
 1325 1330 1335
 Leu Lys Leu Ala Leu Glu Arg Ala Glu Glu Leu Cys Ser Gln Val
 1340 1345 1350
 Asn Glu Gly Val Arg Glu Lys Glu Asn Ser Asp Arg Leu Glu Trp
 1355 1360 1365
 Ile Gln Ala His Val Gln Cys Glu Gly Leu Ala Glu Gln Leu Ile
 1370 1375 1380
 Phe Asn Ser Leu Thr Asn Cys Leu Gly Pro Arg Lys Leu Leu His
 1385 1390 1395
 Ser Gly Lys Leu Tyr Lys Thr Lys Ser Asn Lys Glu Leu His Ala
 1400 1405 1410
 Phe Leu Phe Asn Asp Phe Leu Leu Leu Thr Tyr Leu Val Arg Gln
 1415 1420 1425
 Phe Ala Ala Ala Ser Gly His Glu Lys Leu Phe Asn Ser Lys Ser
 1430 1435 1440
 Ser Ala Gln Phe Arg Met Tyr Lys Thr Pro Ile Phe Leu Asn Glu
 1445 1450 1455
 Val Leu Val Lys Leu Pro Thr Asp Pro Ser Ser Asp Glu Pro Val
 1460 1465 1470
 Phe His Ile Ser His Ile Asp Arg Val Tyr Thr Leu Arg Thr Asp
 1475 1480 1485
 Asn Ile Asn Glu Arg Thr Ala Trp Val Gln Lys Ile Lys Gly Ala
 1490 1495 1500
 Ser Glu Gln Tyr Ile Asp Thr Glu Lys Lys Lys Arg Glu Lys Ala
 1505 1510 1515

Tyr Gln Ala Arg Ser Gln Lys Thr Ser Gly Ile Gly Arg Leu Met
1520 1525 1530

Val His Val Ile Glu Ala Thr Glu Leu Lys Ala Cys Lys Pro Asn
1535 1540 1545

Gly Lys Ser Asn Pro Tyr Cys Glu Val Ser Met Gly Ser Gln Ser
1550 1555 1560

Tyr Thr Thr Arg Thr Leu Gln Asp Thr Leu Asn Pro Lys Trp Asn
1565 1570 1575

Phe Asn Cys Gln Phe Phe Ile Lys Asp Leu Tyr Gln Asp Val Leu
1580 1585 1590

Cys Leu Thr Met Phe Asp Arg Asp Gln Phe Ser Pro Asp Asp Phe
1595 1600 1605

Leu Gly Arg Thr Glu Val Pro Val Ala Lys Ile Arg Thr Glu Gln
1610 1615 1620

Glu Ser Lys Gly Pro Thr Thr Arg Arg Leu Leu Leu His Glu Val
1625 1630 1635

Pro Thr Gly Glu Val Trp Val Arg Phe Asp Leu Gln Leu Phe Glu
1640 1645 1650

Gln Lys Thr Leu Leu
1655

<210> 142

<211> 227

<212> PRT

<213> Mus musculus

<400> 142

Met Thr Gln Ser Cys Thr Met Ala Ser Thr Lys Pro Leu Ser Arg Phe
1 5 10 15

Trp Glu Trp Gly Lys Asn Ile Val Cys Val Gly Arg Asn Tyr Ala Asp
20 25 30

His Val Lys Glu Met Arg Ser Thr Val Leu Ser Glu Pro Val Leu Phe
35 40 45

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

<210> 143
 <211> 207
 <212> PRT
 <213> Mus musculus

<220>
 <221> misc_feature
 <222> (40)..(40)
 <223> Xaa can be any naturally occurring amino acid

<400> 143

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

<210> 144

<211> 741

<212> PRT

<213> Mus musculus

<400> 144

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

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

Ser Ser Ala Ser Ser Ser Phe Ser Glu Glu Gly Ala Val Gly Tyr Ser
 485 490 495
 Ser Asp Ser Glu Thr Leu Asp Leu Glu Glu Ala Glu Gly Ala Val Gly
 500 505 510
 Tyr Gln Pro Glu Tyr Ser Lys Phe Cys Arg Met Ser Tyr Gln Asp Pro
 515 520 525
 Ser Gln Leu Ser Cys Leu Pro Tyr Leu Glu His Val Gly His Asn His
 530 535 540
 Thr Tyr Asn Met Ala Pro Ser Ala Leu Asp Ser Ala Asp Leu Pro Pro
 545 550 555 560
 Pro Ser Thr Leu Lys Lys Gly Ser Lys Glu Lys Gln Ala Asp Phe Leu
 565 570 575
 Asp Lys Gln Met Ser Arg Asp Glu His Arg Ala Arg Ala Met Lys Ile
 580 585 590
 Pro Phe Thr Asn Asp Lys Ile Ile Asn Leu Pro Val Glu Glu Phe Asn
 595 600 605
 Glu Leu Leu Ser Lys Tyr Gln Leu Ser Glu Ala Gln Leu Ser Leu Ile
 610 615 620
 Arg Asp Ile Arg Arg Arg Gly Lys Asn Lys Met Ala Ala Gln Asn Cys
 625 630 635 640
 Arg Lys Arg Lys Leu Asp Thr Ile Leu Asn Leu Glu Arg Asp Val Glu
 645 650 655
 Asp Leu Gln Arg Asp Lys Ala Arg Leu Leu Arg Glu Lys Val Glu Phe
 660 665 670
 Leu Arg Ser Leu Arg Gln Met Lys Gln Lys Val Gln Ser Leu Tyr Gln
 675 680 685
 Glu Val Phe Gly Arg Leu Arg Asp Glu His Gly Arg Pro Tyr Ser Pro
 690 695 700
 Ser Gln Tyr Ala Leu Gln Tyr Ala Gly Asp Gly Ser Val Leu Leu Ile
 705 710 715 720

Asp Ser Asp Ser Ser Ser Glu Glu Glu Thr Pro Gln Thr Gln Lys Pro
 180 185 190
 Lys Ala Ala Val Ala Ala Lys Ala Gln Thr Lys Ala Glu Ala Lys Pro
 195 200 205
 Gly Thr Pro Ala Lys Ala Gln Pro Lys Val Ala Asn Gly Lys Ala Ala
 210 215 220
 Ala Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Asp Asp Ser Glu
 225 230 235 240
 Glu Glu Lys Lys Ala Ala Ala Pro Pro Lys Lys Thr Val Pro Lys Lys
 245 250 255
 Gln Val Val Ala Lys Ala Pro Val Lys Val Ala Ala Ala Pro Thr Gln
 260 265 270
 Lys Ser Ser Ser Ser Glu Asp Ser Ser Ser Glu Glu Glu Glu Gly Gln
 275 280 285
 Arg Gln Pro Met Lys Lys Lys Ala Gly Pro Tyr Ser Ser Val Pro Pro
 290 295 300
 Pro Ser Val Pro Leu Pro Lys Lys Ser Pro Gly Thr Gln Ala Pro Lys
 305 310 315 320
 Lys Ala Ala Ala Gln Thr Gln Pro Ala Asp Ser Ser Asp Asp Ser Ser
 325 330 335
 Asp Asp Ser Asp Ser Ser Ser Glu Glu Glu Lys Lys Pro Pro Ala Lys
 340 345 350
 Thr Val Val Ser Lys Thr Pro Ala Lys Ala Ala Pro Val Lys Lys Lys
 355 360 365
 Ala Glu Ser Ser Ser Asp Ser Ser Gly Asn Ala Ala Gln Ser Ser Gly
 370 375 380
 Leu Leu Gly Tyr Ser Leu Pro Trp Ala Ala Leu Thr Gly Leu Pro
 385 390 395

<210> 146
 <211> 180
 <212> PRT
 <213> Mus musculus

<400> 146

Met Asn Thr Val Leu Ser Arg Ala Asn Ser Leu Phe Ala Phe Ser Leu
1 5 10 15

Ser Val Met Ala Ala Leu Thr Phe Gly Cys Phe Ile Thr Thr Ala Phe
20 25 30

Lys Asp Arg Ser Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu
35 40 45

Lys Asn Val Glu Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly
50 55 60

Phe Ile Thr Phe Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp
65 70 75 80

Asn Val Lys Gln Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys
85 90 95

Asn Asn Ala Leu Asn Gln Val Val Leu Trp Asp Lys Ile Val Leu Arg
100 105 110

Gly Asp Asn Pro Lys Leu Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe
115 120 125

Phe Phe Asp Asp Gly Asn Gly Leu Lys Gly Asn Arg Asn Val Thr Leu
130 135 140

Thr Leu Ser Trp Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val
145 150 155 160

Thr Gly Ser Gly His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile
165 170 175

Thr Lys Ser Tyr
180

<210> 147

<211> 451

<212> PRT

<213> Mus musculus

<400> 147

Met Gly Leu Glu Pro Ser Trp Tyr Leu Leu Leu Cys Leu Ala Val Ser
1 5 10 15

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

Gly Ala Thr Leu Glu Pro Glu Glu Leu Leu Arg Ala Gly Asn Ala Ser
 260 265 270
 Leu Thr Leu Pro Asn Leu Thr Leu Lys Asp Glu Gly Thr Tyr Ile Cys
 275 280 285
 Gln Ile Ser Thr Ser Leu Tyr Gln Ala Gln Gln Ile Met Pro Leu Asn
 290 295 300
 Ile Leu Ala Pro Pro Lys Val Gln Leu His Leu Ala Asn Lys Asp Pro
 305 310 315 320
 Leu Pro Ser Leu Val Cys Ser Ile Ala Gly Tyr Tyr Pro Leu Asp Val
 325 330 335
 Gly Val Thr Trp Ile Arg Glu Glu Leu Gly Gly Ile Pro Ala Gln Val
 340 345 350
 Ser Gly Ala Ser Phe Ser Ser Leu Arg Gln Ser Thr Met Gly Thr Tyr
 355 360 365
 Ser Ile Ser Ser Thr Val Met Ala Asp Pro Gly Pro Thr Gly Ala Thr
 370 375 380
 Tyr Thr Cys Gln Val Ala His Val Ser Leu Glu Glu Pro Leu Thr Thr
 385 390 395 400
 Ser Met Arg Val Leu Pro Asn Pro Glu Gln Arg Gly Thr Leu Gly Val
 405 410 415
 Ile Phe Ala Ser Ile Ile Phe Leu Ser Ala Leu Leu Leu Phe Leu Gly
 420 425 430
 Leu His Arg Gln Gln Ala Ser Ser Ser Arg Ser Thr Arg Pro Met Arg
 435 440 445
 His Ser Gly
 450

<210> 148
 <211> 414
 <212> PRT
 <213> Mus musculus
 <400> 148

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

Lys Tyr Glu Asn Val Tyr Ile Thr Lys Gln Phe Val Arg Phe Asp Glu
245 250 255

Lys Glu Arg His Gln Gln Arg Pro Cys Val Leu Pro Leu Asn Lys Lys
260 265 270

Glu Arg Lys Lys Tyr Val Ile Val Pro Ser Leu Gln Leu Thr Pro Lys
275 280 285

Glu Lys Lys Thr Leu Gly Leu Phe Phe Leu Pro Val Leu Thr Tyr Leu
290 295 300

Tyr Met Trp Val Leu Phe Ala Ala Val Asp Tyr Leu Leu Tyr Arg Leu
305 310 315 320

Ile Ser Ser Met Asn Lys Gln Phe Gln Ser Leu Pro Gly Leu Glu Val
325 330 335

His Leu Lys Leu Arg Gly Glu Leu Lys Ile Leu Val Ser Val Ser Phe
340 345 350

Tyr Pro Lys Val Glu Arg Glu Arg Ile Glu Tyr Leu His Ala Lys Leu
355 360 365

Leu Glu Lys Arg Ser Lys Gln Pro Leu Arg Glu Ala Asp Gly Lys Pro
370 375 380

Ser Leu Tyr Phe Lys Lys Ile His Phe Trp Phe Pro Val Leu Lys Met
385 390 395 400

Ile Arg Lys Lys Gln Thr Ile Pro Ala Asn Glu Asp Asp Leu
405 410

<210> 149

<211> 412

<212> PRT

<213> Mus musculus

<400> 149

Met Glu Pro Trp Cys Gly Ala Glu Val Arg Gly Gln Gly Pro Gln Gly
1 5 10 15

Pro Arg Val Pro Gly Ala Ser Arg Ser Arg Ser Arg Ala Leu Leu Leu
20 25 30

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

Ser Lys Tyr Val Trp Pro Ile Cys Leu Pro Gly Leu Asp Tyr Met Val
 275 280 285
 Glu Asp Ser Ser Leu Cys Thr Val Thr Gly Trp Gly Tyr Pro Arg Ala
 290 295 300
 Asn Gly Asp Asn Trp Arg Ala Pro Gly Leu Leu Phe Arg Trp His Met
 305 310 315 320
 Val Pro Gly Gly Asn Asp Glu Leu Gly Pro Arg Leu Gln Glu Glu Arg
 325 330 335
 Gly Pro Thr His Leu Ser Ala Gly Leu Leu Leu Gln Ala Leu Asp Leu
 340 345 350
 Gly Pro Ala Gln Trp Gly Ala Pro Gly Pro Ser Ser Pro Ile Gln Asp
 355 360 365
 Leu Ala Pro Gly Phe Pro Ser Ala Pro His Pro Ser Gly His Thr Val
 370 375 380
 Thr Leu Pro Cys Leu Ser Phe Leu Pro Phe Leu Leu Ser Ala Ala Val
 385 390 395 400
 Gly Val Ala Leu Ser Leu Pro Glu Ala Gly Arg Ser
 405 410

<210> 150
 <211> 350
 <212> PRT
 <213> Homo sapiens

<400> 150

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

65	70								75								80			
Glu	Phe	Glu	Tyr	Phe ₈₅	Arg	Asn	His	Ser	Leu ₉₀	Glu	Pro	Leu	Ser	Thr ₉₅	Phe					
Leu	Thr	Tyr	Met ₁₀₀	Thr	Cys	Ser	Tyr	Met ₁₀₅	Ile	Asp	Asn	Val	Ile ₁₁₀	Leu	Leu					
Met	Asn	Gly ₁₁₅	Ala	Leu	Gln	Lys	Lys ₁₂₀	Ser	Val	Lys	Glu	Ile ₁₂₅	Leu	Gly	Lys					
Cys	His ₁₃₀	Pro	Leu	Gly	Arg	Phe ₁₃₅	Thr	Glu	Met	Glu	Ala ₁₄₀	Val	Asn	Ile	Ala					
Glu ₁₄₅	Thr	Pro	Ser	Asp	Leu ₁₅₀	Phe	Asn	Ala	Ile	Leu ₁₅₅	Ile	Glu	Thr	Pro	Leu ₁₆₀					
Ala	Pro	Phe	Phe	Gln ₁₆₅	Asp	Cys	Met	Ser	Glu ₁₇₀	Asn	Ala	Leu	Asp	Glu ₁₇₅	Leu					
Asn	Ile	Glu	Leu ₁₈₀	Leu	Arg	Asn	Lys	Leu ₁₈₅	Tyr	Lys	Ser	Tyr	Leu ₁₉₀	Glu	Ala					
Phe	Tyr	Lys ₁₉₅	Phe	Cys	Lys	Asn	His ₂₀₀	Gly	Asp	Val	Thr	Ala ₂₀₅	Glu	Val	Met					
Cys	Pro ₂₁₀	Ile	Leu	Glu	Phe	Glu ₂₁₅	Ala	Asp	Arg	Arg	Ala ₂₂₀	Phe	Ile	Ile	Thr					
Leu ₂₂₅	Asn	Ser	Phe	Gly	Thr ₂₃₀	Glu	Leu	Ser	Lys	Glu ₂₃₅	Asp	Arg	Glu	Thr	Leu ₂₄₀					
Tyr	Pro	Thr	Phe	Gly ₂₄₅	Lys	Leu	Tyr	Pro	Glu ₂₅₀	Gly	Leu	Arg	Leu	Leu ₂₅₅	Ala					
Gln	Ala	Glu	Asp ₂₆₀	Phe	Asp	Gln	Met	Lys ₂₆₅	Asn	Val	Ala	Asp	His ₂₇₀	Tyr	Gly					
Val	Tyr	Lys ₂₇₅	Pro	Leu	Phe	Glu	Ala ₂₈₀	Val	Gly	Gly	Ser	Gly ₂₈₅	Gly	Lys	Thr					
Leu	Glu ₂₉₀	Asp	Val	Phe	Tyr	Glu ₂₉₅	Arg	Glu	Val	Gln	Met ₃₀₀	Asn	Val	Leu	Ala					
Phe	Asn	Arg	Gln	Phe	His	Tyr	Gly	Val	Phe	Tyr	Ala	Tyr	Val	Lys	Leu					

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Asn Ile Glu Leu Leu Arg Asn Lys Leu Tyr Lys Ser Tyr Leu Glu Ala
180 185 190

Phe Tyr Lys Phe Cys Lys Asn His Gly Asp Val Thr Ala Glu Val Met
195 200 205

Cys Pro Ile Leu Glu Phe Glu Ala Asp Arg Arg Ala Phe Ile Ile Thr
210 215 220

Leu Asn Ser Phe Gly Thr Glu Leu Ser Lys Glu Asp Arg Glu Thr Leu
225 230 235 240

Tyr Pro Thr Phe Gly Lys Leu Tyr Pro Glu Gly Leu Arg Leu Leu Ala
245 250 255

Gln Ala Glu Asp Phe Asp Gln Met Lys Asn Val Ala Asp His Tyr Gly
260 265 270

Val Tyr Lys Pro Leu Phe Glu Ala Val Gly Gly Ser Gly Gly Lys Thr
275 280 285

Leu Glu Asp Val Phe Tyr Glu Arg Glu Val Gln Met Asn Val Leu Ala
290 295 300

Phe Asn Arg Gln Phe His Tyr Gly
305 310

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<212> PRT
<213> Mus musculus

<400> 152

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Phe Val Arg Ala Val Arg Ala Tyr Asn Gly Glu Asn Trp Arg Thr Ser
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Ile Ser Asp Met Glu Leu Ala Leu Pro Asp Phe Leu Lys Ala Phe Tyr
35 40 45

Glu Cys Leu Ala Ala Cys Glu Gly Ser Arg Glu Ile Lys Asp Phe Lys
50 55 60

Asp Phe Tyr Leu Ser Ile Ala Asp His Tyr Val Glu Val Leu Glu Cys
65 70 75 80

Lys Ile Arg Cys Glu Thr Leu Thr Pro Val Ile Gly Gly Tyr Pro
85 90 95

Val Glu Lys Phe Val Ala Thr Met Tyr His Tyr Leu Gln Phe Ala Tyr
100 105 110

Tyr Lys Leu Asn Asp Leu Lys Asn Ala Ala Pro Cys Ala Val Ser Tyr
115 120 125

Leu Leu Phe Asp Gln Ser Asp Arg Val Met Gln Gln Asn Leu Val Tyr
130 135 140

Tyr Gln Tyr His Arg Asp Lys Trp Gly Leu Ser Asp Glu His Phe Gln
145 150 155 160

Pro Arg Pro Glu Ala Val Gln Phe Phe Asn Val Thr Thr Leu Gln Lys
165 170 175

Glu Leu Tyr Asp Phe Ala Gln Glu His Leu Met Asp Asp Asp Glu Gly
180 185 190

Glu Val Val Glu Tyr Val Asp Asp Leu Leu Glu Thr Glu Glu Ser Ala
195 200 205

<210> 153

<211> 385

<212> PRT

<213> Homo sapiens

<400> 153

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Ser Ala Pro Ser Arg Ala Gly Ala Leu Leu Leu Leu Leu Leu Leu
20 25 30

Arg Ser Ala Gly Cys Trp Gly Ala Gly Glu Ala Pro Gly Ala Leu Ser
35 40 45

Thr Ala Asp Pro Ala Asp Gln Ser Val Gln Cys Val Pro Lys Ala Thr
50 55 60

Cys Pro Ser Ser Arg Pro Arg Leu Leu Trp Gln Thr Pro Thr Thr Gln
 65 70 75 80
 Thr Leu Pro Ser Thr Thr Met Glu Thr Gln Phe Pro Val Ser Glu Gly
 85 90 95
 Lys Val Asp Pro Tyr Arg Ser Cys Gly Phe Ser Tyr Glu Gln Asp Pro
 100 105 110
 Thr Leu Arg Asp Pro Glu Ala Val Ala Arg Arg Trp Pro Trp Met Val
 115 120 125
 Ser Val Arg Ala Asn Gly Thr His Ile Cys Ala Gly Thr Ile Ile Ala
 130 135 140
 Ser Gln Trp Val Leu Thr Val Ala His Cys Leu Ile Trp Arg Asp Val
 145 150 155 160
 Ile Tyr Ser Val Arg Val Gly Ser Pro Trp Ile Asp Gln Met Thr Gln
 165 170 175
 Thr Ala Ser Asp Val Pro Val Leu Gln Val Ile Met His Ser Arg Tyr
 180 185 190
 Arg Ala Gln Arg Phe Trp Ser Trp Val Gly Gln Ala Asn Asp Ile Gly
 195 200 205
 Leu Leu Lys Leu Lys Gln Glu Leu Lys Tyr Ser Asn Tyr Val Arg Pro
 210 215 220
 Ile Cys Leu Pro Gly Thr Asp Tyr Val Leu Lys Asp His Ser Arg Cys
 225 230 235 240
 Thr Val Thr Gly Trp Gly Leu Ser Lys Ala Asp Gly Met Trp Pro Gln
 245 250 255
 Phe Arg Thr Ile Gln Glu Lys Glu Val Ile Ile Leu Asn Asn Lys Glu
 260 265 270
 Cys Asp Asn Phe Tyr His Asn Phe Thr Lys Ile Pro Thr Leu Val Gln
 275 280 285
 Ile Ile Lys Ser Gln Met Met Cys Ala Glu Asp Thr His Arg Glu Lys
 290 295 300

Phe Cys Tyr Glu Leu Thr Gly Glu Pro Leu Val Cys Ser Met Glu Gly
305 310 315 320

Thr Trp Tyr Leu Val Gly Leu Val Ser Trp Gly Ala Gly Cys Gln Lys
325 330 335

Ser Glu Ala Pro Pro Ile Tyr Leu Gln Val Ser Ser Tyr Gln His Trp
340 345 350

Ile Trp Asp Cys Leu Asn Gly Gln Ala Leu Ala Leu Pro Ala Pro Ser
355 360 365

Arg Thr Leu Leu Leu Ala Leu Pro Leu Pro Leu Ser Leu Leu Ala Ala
370 375 380

Leu
385

<210> 154
<211> 350
<212> PRT
<213> Homo sapiens

<400> 154

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Glu Gly Leu Val Arg Gly Cys Lys Ala Ser Leu Leu Thr Gln Gln Asp
20 25 30

Tyr Ile Asn Leu Val Gln Cys Glu Thr Leu Glu Asp Leu Lys Ile His
35 40 45

Leu Gln Thr Thr Asp Tyr Gly Asn Phe Leu Ala Asn His Thr Asn Pro
50 55 60

Leu Thr Val Ser Lys Ile Asp Thr Glu Met Arg Lys Arg Leu Cys Gly
65 70 75 80

Glu Phe Glu Tyr Phe Arg Asn His Ser Leu Glu Pro Leu Ser Thr Phe
85 90 95

Leu Thr Tyr Met Thr Cys Ser Tyr Met Ile Asp Asn Val Ile Leu Leu
100 105 110

Met Asn Gly Ala Leu Gln Lys Lys Ser Val Lys Glu Ile Leu Gly Lys

115 120 125
 Cys His Pro Leu Gly Arg Phe Thr Glu Met Glu Ala Val Asn Ile Ala
 130 135 140
 Glu Thr Pro Ser Asp Leu Phe Asn Ala Ile Leu Ile Glu Thr Pro Leu
 145 150 155 160
 Ala Pro Phe Phe Gln Asp Cys Met Ser Glu Asn Ala Leu Asp Glu Leu
 165 170 175
 Asn Ile Glu Leu Leu Arg Asn Lys Leu Tyr Lys Ser Tyr Leu Glu Ala
 180 185 190
 Phe Tyr Lys Phe Cys Lys Asn His Gly Asp Val Thr Ala Glu Val Met
 195 200 205
 Cys Pro Ile Leu Glu Phe Glu Ala Asp Arg Arg Ala Phe Ile Ile Thr
 210 215 220
 Leu Asn Ser Phe Gly Thr Glu Leu Ser Lys Glu Asp Arg Glu Thr Leu
 225 230 235
 Tyr Pro Thr Phe Gly Lys Leu Tyr Pro Glu Gly Leu Arg Leu Leu Ala
 245 250 255
 Gln Ala Glu Asp Phe Asp Gln Met Lys Asn Val Ala Asp His Tyr Gly
 260 265 270
 Val Tyr Lys Pro Leu Phe Glu Ala Val Gly Gly Ser Gly Gly Lys Thr
 275 280 285
 Leu Glu Asp Val Phe Tyr Glu Arg Glu Val Gln Met Asn Val Leu Ala
 290 295 300
 Phe Asn Arg Gln Phe His Tyr Gly Val Phe Tyr Ala Tyr Val Lys Leu
 305 310 315 320
 Lys Glu Gln Glu Ile Arg Asn Ile Val Trp Ile Ala Glu Cys Ile Ser
 325 330 335
 Gln Arg His Arg Thr Lys Ile Asn Ser Tyr Ile Pro Ile Leu
 340 345 350

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<211> 312
 <212> PRT
 <213> Homo sapiens

<400> 155

Met Leu Glu Gly Ala Glu Leu Tyr Phe Asn Val Asp His Gly Tyr Leu
 1 5 10 15

Glu Gly Leu Val Arg Gly Cys Lys Ala Ser Leu Leu Thr Gln Gln Asp
 20 25 30

Tyr Ile Asn Leu Val Gln Cys Glu Thr Leu Glu Asp Leu Lys Ile His
 35 40 45

Leu Gln Thr Thr Asp Tyr Gly Asn Phe Leu Ala Asn His Thr Asn Pro
 50 55 60

Leu Thr Val Ser Lys Ile Asp Thr Glu Met Arg Lys Arg Leu Cys Gly
 65 70 75 80

Glu Phe Glu Tyr Phe Arg Asn His Ser Leu Glu Pro Leu Ser Thr Phe
 85 90 95

Leu Thr Tyr Met Thr Cys Ser Tyr Met Ile Gly Asn Val Ile Leu Leu
 100 105 110

Met Asn Gly Ala Leu Gln Lys Lys Ser Val Lys Glu Ile Leu Gly Lys
 115 120 125

Cys His Pro Leu Gly Arg Phe Thr Glu Met Glu Ala Val Asn Ile Ala
 130 135 140

Glu Thr Pro Ser Asp Leu Phe Asn Ala Ile Leu Ile Glu Thr Pro Leu
 145 150 155 160

Ala Pro Phe Phe Gln Asp Cys Met Ser Glu Asn Ala Leu Asp Glu Leu
 165 170 175

Asn Ile Glu Leu Leu Arg Asn Lys Leu Tyr Lys Ser Tyr Leu Glu Ala
 180 185 190

Phe Tyr Lys Phe Cys Lys Asn His Gly Asp Val Thr Ala Glu Val Met
 195 200 205

Cys Pro Ile Leu Glu Phe Glu Ala Asp Arg Arg Ala Phe Ile Ile Thr
 210 215 220

Leu Asn Ser Phe Gly Thr Glu Leu Ser Lys Glu Asp Arg Glu Thr Leu
225 230 235 240

Tyr Pro Thr Phe Gly Lys Leu Tyr Pro Glu Gly Leu Arg Leu Leu Ala
245 250 255

Gln Ala Glu Asp Phe Asp Gln Met Lys Asn Val Ala Asp His Tyr Gly
260 265 270

Val Tyr Lys Pro Leu Phe Glu Ala Val Gly Gly Ser Gly Gly Lys Thr
275 280 285

Leu Glu Asp Val Phe Tyr Glu Arg Glu Val Gln Met Asn Val Leu Ala
290 295 300

Phe Asn Arg Gln Phe His Tyr Gly
305 310